Journal of Medicinal Chemistry, 1977, Vol. 20, No. 5 699

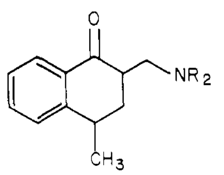
Analgesic and Tranquilizing Activity of 5,8-Disubstituted 1-Tetralone Mannich Bases

Willard M. Welch,* Charles A. Harbert, Reinhard Sarges, Wilford P. Stratten, and Albert Weissman

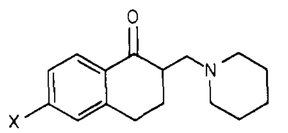
Pfizer Inc., Medical Research Laboratories, Groton, Connecticut 06340. *Received September 13, 1976*

5,8-Disubstituted 1-tetralone Mannich bases represent semirigid variants of classical (i.e., chlorpromazine) neuroleptic agents. 8-Chloro-5-methoxy-2-morpholinomethyl-1-tetralone exhibits neuroleptic potency in the thiothixene range in animal models. Of greater potential interest, however, is the analgesic potency of the 8-chloro-5-methoxy-2-pyrrolidinomethyl analogue which was in the morphine range. This compound did not induce tolerance nor was its activity reversed by naloxone. Structure–activity relationships of the series are discussed.

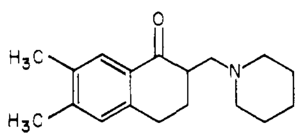
Mannich bases derived from 1-tetralones have been extensively investigated pharmacologically. For example, tranquilizing[1,2] and weak analgesic[3] activity have been reported for compounds derived from I and II, respectively, whereas the 6,7-dimethylpiperidinomethyltetralone Mannich base III was the most potent (~chlorpromazine) neuroleptic compound of a series of aryl-substituted



I



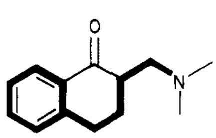
II



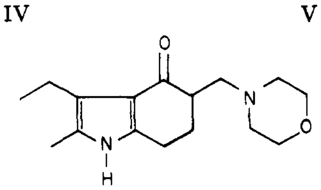
III

analogues.[4] The neuroleptic activity of compounds of this type may be readily rationalized in light of recent speculations of Janssen[5] postulating an "S-shaped" conformation IV as the active conformation of most neuroleptics (excluding only the Rauwolfia alkaloids). Compounds of general structure V can readily overlap such a configuration and, in view of the rigidity imposed by the tetralone moiety, might be expected to demonstrate advantages in

IV



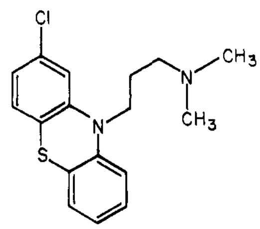
V



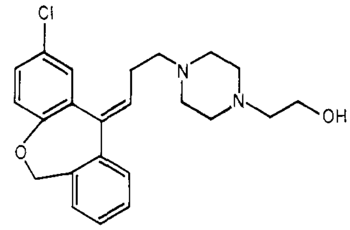
VI

binding to such a receptor over neuroleptics bearing more flexible side chains. Molindone (VI), which incorporates just such a semirigid structure, has been reported to demonstrate potent neuroleptic activity.[6]

Our interest in this area was stimulated by the observation that structure–activity relationships (SAR) of tricyclic neuroleptic agents [e.g., chlorpromazine (VII) and pinoxepin (VIII)] generally dictate the presence of an electron-withdrawing substituent at position 2 coupled with an electron-rich heteroatom at position 5. Application of this principle to the tetralone Mannich bases suggested that 5,8-disubstituted analogues might possess more potent neuroleptic activity than the unsubstituted or 6,7-disubstituted derivatives previously reported. Despite the



VII



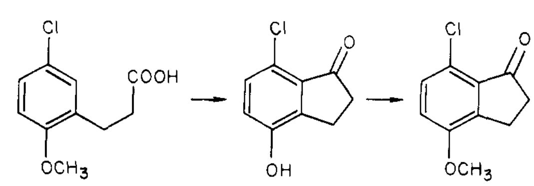
VIII

extensive prior pharmacological investigation of 1-tetralone Mannich bases, no examples incorporating such 5,8-disubstitution had been reported. The purpose of this paper is to report the synthesis and pharmacological evaluation of a number of these compounds.

Chemistry. The variously substituted 2-aminomethyltetralones tabulated in Tables I–V were prepared by standard Mannich reactions from the corresponding 1-tetralones which were available commercially or prepared according to published procedures. Cyclization of 3-(5-chloro-2-methoxyphenyl)propionic acid (IX) to afford the homologous indanone XI was best achieved through the slow addition of the acid to a molten eutectic mixture of $AlCl_3$–NaCl[7] followed by methylation of the resulting phenol X with dimethyl sulfate (Scheme I). 8-Chloro-5-ethoxy-1-tetralone was prepared by dealkylation of the corresponding methoxy derivative and realkylation with ethyl iodide–K_2CO_3. Compounds bearing methyl or phenyl substituents in the α position were prepared via Michael addition of the corresponding amine to the corresponding 2-ethylidene-[8] and 2-benzylidenetetralones[9] under base catalysis.[10]

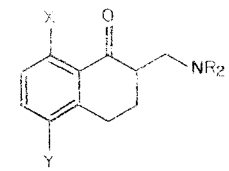
Pharmacology. The four 2-aminomethyl-8-chloro-5-methoxy-1-tetralones **1–4** were compared with their corresponding unsubstituted analogues **5**[1,2] and **6–8**[4] (Table I) in standardized neuroleptic tests—blockade of amphetamine-induced lethality[11] in mice and conditioned avoidance behavior (CAB)[11] in rats. Compounds **1** and **2** exhibited weak activity against amphetamine and, although this activity appeared to be superior to that of the corresponding unsubstituted analogues, no clear differentiation could be made. In the CAB assay, only compound **3** stood out as being clearly superior to the unsubstituted analogues, possessing an ED_{50} lower than that of thiothixene. Although **5** was reported to be equivalent

Scheme I



IX X XI

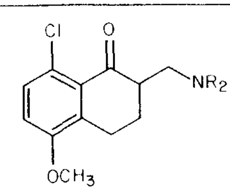
Table I. Neuroleptic and Analgesic Activity of 2-Aminomethyl-8-chloro-5-methoxy-1-tetralone Mannich Bases



Compd	X	Y	NR_2[a]	Amphetamine-induced mortality, mouse; ED_{50},[b] mg /kg ip	Conditioned avoidance, rat; ED_{50},[c] mg/kg ip	Flinch-jump analgesia, rat; jump component; mA,[d] 32 mg/kg ip	Radiant heat assay, dog; 10 mg/kg po, 2 h; % of control	Hot plate, mouse; 100 mg/kg ip, 2 h; % protection[e]	Tail flick, mouse; 100 mg/kg ip, 2 h; % protection[e]
1	Cl	OCH_3	c-NC_5H_{10}	10-32	32	>2.2 (2.2)[f]	110	0	0
2			c-NC_4H_8	10-32	>178	>2.2 (1.2)[f]	160	30	0
3			c-$N(CH_2CH_2)_2O$	32-100	0.32-1.0	2.2	140	0	20
4			$N(CH_3)_2$	32-100	>178	2.2	130	0	10
5	H	H	c-NC_5H_{10}	>100	>32	0.8	NT	0	0
6			c-NC_4H_8	32-100	>10	1.2	100	0	10
7			c-$N(CH_2CH_2)_2O$	32-100	>10	0.6	90	10	20
8			$N(CH_3)_2$	32-100	>10	1.2	79	10	0
Molindone				3.2-10	3.2-10				
Chlorpromazine				1.0-3.2	3.2-10				
Thiothixene				0.32-1.0	3.2-10				
Morphine					10-32	1.2 (17.8 mg/kg ip)	155 (1.62 mg/kg sc)	70 (10 mg/kg)	80 (10 mg/kg)
Propoxyphene					NT	1.2 (17.8 mg/kg po)	100 (5 mg/kg po)	30	70
Meperidine					10-32	1.2	150 (5 mg/kg ip)	50	70

[a] Physical data for compounds 1-8 are included in Table III. [b] Entries are an estimate of the ED_{50} for blocking amphetamine-induced mortality in groups of ten aggregated mice. At the higher dose shown, <5/10 died; at the lower dose >5/10 mice died. [c] Entries are an estimate of the ED_{50} of drug required for blocking discriminated jump-out avoidance behavior in rats 1 h postdrug.[10] At least five rats were exposed to each dose. [d] Median foot shock in mA required to elicit a "jump" response 2 h postdose as defined in the Pharmacology Methods section. The median control value was 0.8 mA. [e] The percentage of animals failing to react under the conditions and within the time limit as defined in the Pharmacology Methods section. Minimal activity is defined as the true probability of 20% response. With ten animals in a group, an observed activity of 45% or better yields a 90% lower bound on the true probability of response of 0.20 [see C. J. Clopper and E. S. Pearson, *Biometrika*, **26**, 404 (1934)]. [f] Unless otherwise indicated, numbers in parentheses were obtained following a dose of 10 mg/kg ip.

Table II. Variations of the Aminomethyl Substituent



Compd	NR_2	Mp, °C	Formula[a]	% yield	Flinch-jump analgesia rat; jump component; mA,[b] 32 mg/kg ip	Hot plate, mouse; 100 mg/kg ip, 2 h; % protection[c]	Tail flick, mouse; 100 mg/kg ip, 2 h; % protection[c]

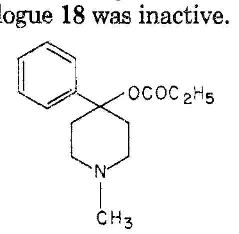
9	Methylamino	202-204	$C_{13}H_{16}O_2NCl\cdot HCl\cdot 0.5H_2O$	17	>2.2 (1.2)[d]	10	0
10	Ethylamino	188-190	$C_{14}H_{20}O_3NCl\cdot HCl\cdot 0.5H_2O$	45	>2.2 (2.2)[d]	40 (32 mg/kg)	0 (32 mg/kg)
11	Allylamino	180.0-181.5	$C_{15}H_{18}O_2NCl\cdot HCl$	17	>2.2 (2.2)[d]	0 (32 mg/kg)	0 (32 mg/kg)
12	Cyclohexylamino	200-202	$C_{18}H_{24}O_2NCl\cdot HCl$	49	>2.2 (1.2)[d]	40	0
4	Dimethylamino				2.2	0	10
13	Diethylamino	100-101	$C_{16}H_{22}O_2NCl\cdot C_4H_4O_4$[e]	46	0.6	20	0
2	Pyrrolidino				>2.2 (1.2)[d]	30	0
1	Piperidino				>2.2 (2.2)[d]	0	0
14	Hexamethylenimino	165-166	$C_{18}H_{24}O_2NCl\cdot HCl$	40	1.2	0	0
3	Morpholino				2.2	0	20
15	4-Carboethoxypiperazino	169-170	$C_{19}H_{25}O_4N_2Cl\cdot C_4H_4O_4$[e]	51	0.6	0	0
16	4-Phenylpiperidino	164-165	$C_{23}H_{26}O_2NCl\cdot HCl$	46	>2.2 (2.2)[d]	20	10
17	4-Hydroxy-4-phenylpiperidino	165-166	$C_{23}H_{26}O_3NCl\cdot HCl\cdot 1.5H_2O$[f]	27	>2.2 (1.2)[d]	60	0
18	4-Ethoxy-4-phenylpiperidino	183-184	$C_{25}H_{30}O_3NCl\cdot HCl$	35	1.2	0	0
19	4-Acetyl-4-phenylpiperidino	193-194	$C_{25}H_{28}O_3NCl\cdot HCl$	36	>2.2 (1.2)[d]	30	0
20	4-Phenyl-4-propionylpiperidino	182-183	$C_{26}H_{30}O_3NCl\cdot HCl$	20	>2.2 (1.2)[d]	0	0
21	4-Butyryl-4-phenylpiperidino	169.5-170.5	$C_{27}H_{32}O_3NCl\cdot HCl$	36	0.6	30	0

[a] All compounds were analyzed for C, H, and N. Except where noted, values agreed with calculated values ±0.4%. [b] See footnote d in Table I. [c] See footnote e in Table I. [d] See footnote f in Table I. [e] Maleate salt. [f] H: calcd, 6.53; found, 5.99.

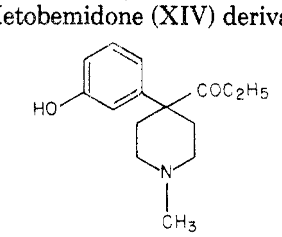
to chlorpromazine in antiamphetamine testing, no such neuroleptic activity was seen in this test or in CAB in our hands. The CAB activity of the 2-morpholinomethyl derivative **3** was interesting in light of its structural relationship to molindone; however, as will be illustrated below, the relationship of morpholine substitution to activity was not consistent throughout the series. No other compounds exhibited the potent neuroleptic activity expected for compounds capable of overlapping essential structural features of tricyclic neuroleptic agents in accordance with the speculations of Janssen.[5] These results suggest that neuroleptic activity is dependent upon other factors in addition to the "S-shaped" configuration IV.

Since literature precedent suggested that tetralone Mannich bases might also possess analgesic activity, the compounds in Table I were compared in various analgesic screens. In the rat flinch-jump procedure[12,13] and the dog radiant heat assay,[14] the 5,8-disubstituted analogues **1–4** demonstrated a substantial increment of activity over the unsubstituted compounds **5–8**. Interestingly, neither these compounds nor the unsubstituted analogues demonstrated marked activity in the mouse hot-plate[15] and tail-flick[16] procedures, tests classically sensitive to narcotic analgesics.[17] Comparison of the analgesic results for **1–4** with the values obtained for standard doses of morphine and propoxyphene (Table I) suggested that this series might include compounds with analgesic potency comparable to that of narcotic analgesics. Based on these initial findings, SAR were further elaborated as outlined below.

Variation of the amino substituent (Table II) led to a series of compounds which demonstrated excellent potency in the flinch–jump procedure but which largely lacked activity in the hot-plate and tail-flick procedures. This activity appeared to be independent of steric bulk and the activity of secondary amines (**9–12**) was comparable to or exceeded that of tertiary compounds. The 4-hydroxy-4-phenylpiperidine **17** demonstrated potent activity as expected for a prodine (XIII) derivative,[18] but the 4-ethoxy analogue **18** was inactive. Ketobemidone (XIV) derivative



XIII



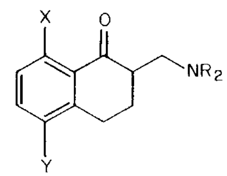
XIV

20 and its analogue **19** also demonstrated potent activity which was superior to that of the homologue **21**.[18]

The results presented in Table III show that analgesic activity was highly dependent on the type of aromatic substitution. Potent activity appears to be strongly dependent on the presence of the 8-chloro substituent, although limited activity was seen in the 8-methyl-5-methoxy series represented by **25** and **30**. Replacement of chlorine by fluorine led to limited hot-plate and tail-flick activity. Substitution at position 8 with hydrogen or exchange of 5-methoxy for 5-ethoxy led to a surprisingly abrupt reduction in potency. Comparison of indanone and tetralone analogues (Table IV) suggests that ring size and, hence, the relative positions of the aryl ring and amino nitrogen are critical to activity.

Alkyl and aryl groups were introduced into the 2, 4, and α position of the tetralone ring. Although the 4-methyl analogues **46** and **50** elevated the pain threshold slightly (Table V), this effect was not of sufficient magnitude to encourage further investigation. Substitution in the 2 and α positions abolished all analgesic activity, indicating again

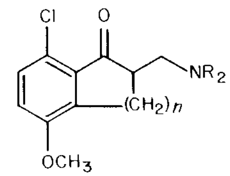
Table III. Effect of Variations in the 5,8-Substitution Pattern



Compd	X	Y	NR_2	Mp, °C	Formula[a]	% yield	Flinch-jump analgesia, rat; jump component; mA,[b] 32 mg/kg ip	Hot plate, mouse; 100 mg/kg ip, 2 h; % protection[c]	Tail flick, mouse; 100 mg/kg ip, 2 h; % protection[c]
5	H	H	c-NC_5H_{10}	173.0–174.5	$C_{16}H_{21}ON·HCl$	11	0.8	0	0
22	H	OCH_3	c-NC_5H_{10}	175–176	$C_{17}H_{23}O_2N·HCl$	62	0.8	NT	NT
1	Cl	OCH_3	c-NC_5H_{10}	179–180	$C_{17}H_{22}O_2NCl·HCl$	16	>2.2 (2.2)[d]	0	0
23	F	OCH_3	c-NC_5H_{10}	184–185	$C_{17}H_{22}O_2NF·HCl$	43	1.6	60 (32 mg/kg)	10 (32 mg/kg)
24	Cl	OC_2H_5	c-NC_5H_{10}	167–170	$C_{18}H_{24}O_2NCl·HCl$	80	0.6	33	33
25	CH_3	OCH_3	c-NC_5H_{10}	174.0–175.5	$C_{18}H_{25}O_2N·HCl$	61	>2.2 (2.2)[d]	40 (32 mg/kg)	30 (32 mg/kg)
26	OCH_3	OCH_3	c-NC_5H_{10}	172–174	$C_{18}H_{25}O_3N·HCl$	29	2.2	0	22
6	H	H	c-NC_4H_8	154–155	$C_{15}H_{19}ON·HCl$[e]	44	1.2	0	10
27	H	OCH_3	c-NC_4H_8	182.0–183.5	$C_{16}H_{22}O_2NCl·HCl$	10	0.8	0	0
2	Cl	OCH_3	c-NC_4H_8	180–181	$C_{16}H_{20}O_2NCl·HCl·H_2O$	90	>2.2 (1.2)[d]	30	0
28	F	OCH_3	c-NC_4H_8	187.0–188.0	$C_{16}H_{20}O_2NF·HCl·0.5H_2O$	32	1.2	50	0
29	Cl	OC_2H_5	c-NC_4H_8	164–166	$C_{17}H_{22}O_2NCl·HCl$	56	0.6	30	60
30	CH_3	OCH_3	c-NC_4H_8	155–156	$C_{17}H_{23}O_2N·HCl·H_2O$	14	2.2	12.5	50
31	OCH_3	OCH_3	c-NC_4H_8	150–152	$C_{17}H_{23}O_3N·HCl·H_2O$	30	1.2	0	0
7	H	H	c-$N(CH_2CH_2)_2O$	173–174	$C_{15}H_{19}O_2N·HCl$	68	0.6	10	20
32	H	OCH_3	c-$N(CH_2CH_2)_2O$	180–181	$C_{16}H_{21}O_3N·HCl$	28	0.6	NT	NT
3	Cl	OCH_3	c-$N(CH_2CH_2)_2O$	168–169	$C_{16}H_{20}O_3NCl·C_4H_4O_4$[f]	83	2.2	0	20
33	F	OCH_3	c-$N(CH_2CH_2)_2O$	178–179	$C_{16}H_{20}O_3NF·HCl$	49	1.2	30	10
34	Cl	OC_2H_5	c-$N(CH_2CH_2)_2O$	165.5–166.0	$C_{17}H_{22}O_3NCl·HCl·H_2O$[g]	81	2.2	10	20
35	CH_3	OCH_3	c-$N(CH_2CH_2)_2O$	172.5–173.5	$C_{17}H_{23}O_3N·HCl$	32	0.6	10	0
36	OCH_3	OCH_3	c-$N(CH_2CH_2)_2O$	179–181	$C_{17}H_{23}O_4N·HCl$	36	0.6	10	0
8	H	H	$N(CH_3)_2$	154.0–155.5	$C_{13}H_{17}ON·HCl$	52	1.2	10	0
37	H	OCH_3	$N(CH_3)_2$	204.0–205.5	$C_{14}H_{19}O_2N·HCl$	20	1.2	0	0
4	Cl	OCH_3	$N(CH_3)_2$	180–184	$C_{14}H_{18}O_2NCl·HCl$	25	2.2	0	10
38	F	OCH_3	$N(CH_3)_2$	191–192	$C_{14}H_{18}O_2NF·HCl$	31	0.6	50	0
39	Cl	OC_2H_5	$N(CH_3)_2$	193–195	$C_{15}H_{20}O_2NCl·HCl$	67	0.6	0	0
40	CH_3	OCH_3	$N(CH_3)_2$	179.5–181.0	$C_{15}H_{21}O_2N·HCl$	18	0.6	NT	NT
41	OCH_3	OCH_3	$N(CH_3)_2$	170–172	$C_{15}H_{21}O_3N·HCl$	51	0.6	10	0

[a] See footnote *a* in Table II. [b] See footnote *d* in Table I. [c] See footnote *e* in Table I. [d] See footnote *f* in Table I. [e] C: calcd, 67.77; found, 67.26. [f] Maleate salt. [g] H: calcd, 6.66; found, 6.02.

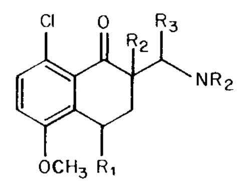
Table IV. Indanone Derivatives



Compd	n	NR_2	Mp, °C	Formula[a]	% yield	Flinch-jump analgesia, rat; jump component; mA,[b] 32 mg/kg ip	Hot plate, mouse; 100 mg/kg ip, 2 h; % protection[c]	Tail flick, mouse; 100 mg/kg ip, 2 h; % protection[c]
42	1	c-NC_5H_{10}	179 dec	$C_{16}H_{20}O_2NCl\cdot HCl$	57	0.6	0	0
1	2	c-NC_5H_{10}				>2.2 (2.2)[d]	0	0
43	1	c-NC_4H_8	179–181	$C_{15}H_{18}O_2NCl\cdot HCl$	52	0.6	0	0
2	2	c-NC_4H_8				>2.2 (1.2)[d]	30	0
44	1	c-$N(CH_2CH_2)_2O$	140–142	$C_{15}H_{18}O_3NCl\cdot HCl$[e]	61	0.6	0	0
3	2	c-$N(CH_2CH_2)_2O$				2.2	0	20
45	1	$N(CH_3)_2$	178–179	$C_{13}H_{16}O_2NCl\cdot HCl$	67	0.6	20	30
4	2	$N(CH_3)_2$				2.2	0	10

[a] See footnote *a* in Table II. [b] See footnote *d* in Table I. [c] See footnote *e* in Table I. [d] See footnote *f* in Table I. [e] C: calcd, 52.79; found, 52.08.

Table V. 2-, 4-, and Side-Chain-Substituted Derivatives



Compd	R_1	R_2	R_3	NR_2	Mp, °C	Formula[a]	% yield	Flinch-jump analgesia, rat; jump component; mA,[b] 32 mg/kg ip	Hot plate, mouse; 100 mg/kg ip, 2 h; % protection[c]	Tail flick, mouse; 100 mg/kg ip, 2 h; % protection[c]
46	CH_3	H	H	c-NC_5H_{10}	187–189	$C_{18}H_{24}O_2NCl\cdot HCl$	5	1.2	NT	NT
47	H	CH_3	H	c-NC_5H_{10}	177.5–178.5	$C_{18}H_{24}O_2NCl\cdot HCl\cdot 0.5H_2O$	10	0.6	NT	NT
48	H	H	CH_3	c-NC_5H_{10}	244–245	$C_{18}H_{24}O_2NCl\cdot HCl$	35	0.6	20	0
49	H	H	C_6H_5	c-NC_5H_{10}	160 dec	$C_{23}H_{26}O_2NCl\cdot HCl\cdot 0.5H_2O$	48	0.6	30	0
50	CH_3	H	H	c-$N(CH_2CH_2)_2O$	173.5–175.0	$C_{17}H_{22}O_3NCl\cdot HCl$	2	0.8	30	40
51	H	CH_3	H	c-$N(CH_2CH_2)_2O$	187.0–188.5	$C_{17}H_{22}O_3NCl\cdot HCl$	14	0.6	NT	NT
52	H	H	CH_3	c-$N(CH_2CH_2)_2O$	150–152	$C_{17}H_{22}O_3NCl\cdot HCl$	52	0.6	0	0
53	H	H	C_6H_5	c-$N(CH_2CH_2)_2O$	139–141	$C_{22}H_{24}O_3NCl\cdot HCl$	76	0.6	0	0

[a] See footnote *a* in Table II. [b] See footnote *d* in Table I. [c] See footnote *e* in Table I.

fairly strict steric requirements at the active site.

The clear dissociation of analgesic activity from neuroleptic activity seen for compound **2** led to its evaluation in narcotic dependence and tolerance studies. Compound **2** gave no indication of tolerance development to the analgesic response (flinch–jump method) under treatment protocols in which morphine produced clear tolerance. In addition, there was no evidence of cross tolerance to morphine and the analgesic activity of **2** was not reversed by naloxone.

Experimental Section

Melting points (uncorrected) were taken with a Thomas-Hoover capillary apparatus. NMR spectra were recorded on Varian A-60 and T-60 spectrometers with Me_4Si as an internal standard. IR spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. Mass spectra were obtained with a Perkin-Elmer RMU-6E mass spectrometer. Microanalyses were performed by the Pfizer Analytical Department.

General Procedure for Preparation of 1-Tetralone Mannich Bases. 8-Chloro-5-methoxy-2-pyrrolidinomethyl-1-tetralone Hydrochloride (2). A suspension of 8.34 g (39.6 mmol) of 8-chloro-5-methoxy-1-tetralone, 3.83 g (35.6 mmol) of pyrrolidine hydrochloride, 2.50 g (80 mmol) of paraformaldehyde, and 0.72 mL of saturated HCl–2-propanol solution in 25 mL of 2-propanol was heated at reflux for 24 h (solution occurred at about 70 °C). The solution was cooled yielding crystals which were collected and washed with 2-propanol and with ether to yield 10.40 g (79%) of the desired product, mp 180–181 °C.

General Procedure for Preparation of α-Methyl- and α-Phenyl-1-tetralone Mannich Bases. 8-Chloro-5-methoxy-2-(1-morpholinoethyl)-1-tetralone Hydrochloride (52). A solution of 1.0 g (4.2 mmol) of 8-chloro-2-ethylidene-5-methoxy-1-tetralone in 3.65 g (42.0 mmol) of morpholine was treated dropwise while stirring with 3.82 mL (25.2 mmol) of 37% aqueous KOH. The resulting mixture was stirred overnight at room temperature. Water was added causing the precipitation of a gum which was extracted into ether. The ethereal extracts were dried over Na_2SO_4 and concentrated to an oil. This oil was dissolved in 2-propanol, converted to the hydrochloride salt with HCl gas, and crystallized from 2-propanol to give 780 mg (46.5%) of the desired product, mp 150–152 °C.

3-(5-Chloro-2-methoxyphenyl)propionic Acid (IX). A solution of 25.15 g (0.14 mol) of 3-(2-methoxyphenyl)propionic acid in 300 mL of CCl_4 was cooled in an ice bath while a solution of 10.5 g (0.148 mol) of Cl_2 in 200 mL of CCl_4 was added over a period of 2 h. The temperature of the reaction mixture was maintained below 10 °C throughout the addition. After the addition was complete, the reaction mixture was allowed to warm to room temperature (30 min) and then the solvent was removed in vacuo. The resulting crystals were slurried in pentane and filtered, yielding 18.0 g (60%) of colorless needles, mp 85–89 °C. Anal. ($C_{10}H_{11}O_3Cl$) C, H.

7-Chloro-4-methoxy-1-indanone (XI). A mixture of 325 g of $AlCl_3$ and 81.5 g of NaCl was heated and stirred mechanically under N_2. After the pot temperature stabilized near 200 °C, 4.9 g (22.9 mmol) of 3-(5-chloro-2-methoxyphenyl)propionic acid was added via a Gooch rubber connecting tube (*caution*: methyl chloride is evolved). The pot temperature was maintained at 200 °C for 90 min and then the reaction mixture was poured over ice. The resulting cold aqueous suspension was extracted thoroughly with $CHCl_3$. The combined $CHCl_3$ extracts were then dried with $MgSO_4$ and evaporated to yield 3.5 g (85%) of tan solid. This solid (19.4 mmol) was dissolved in 160 mL of acetone and treated with 2.87 g (20.7 mmol) of K_2CO_3, 2.67 g (20.4 mmol) of dimethyl sulfate, and 1.19 g (21.2 mmol) of KOH (10% in CH_3OH). The resulting solution was stirred 3 h at room temperature and then filtered to remove a small amount of suspended solids. The filtrate was evaporated to dryness and the residue was taken up in ethyl acetate. This solution was washed with water, dried over $MgSO_4$, decolorized with 1.5 g of decolorizing carbon, and evaporated to give 3.5 g (93%) of a tan solid which was normally used without further purification. An analytical sample was recrystallized from ethyl acetate: mp 134–135 °C. Anal. ($C_{10}H_9O_2Cl$) C, H.

Pharmacology Methods. Antagonism of Amphetamine-Induced Mortality in Aggregated Mice. This procedure was described by Weissman.[11]

Conditioned Avoidance in Rats. The procedure of Weissman[11] was used.

Flinch–Jump Analgesic Procedure. A modification of the flinch–jump procedure[12,13] was used for measuring pain thresholds. Rats were placed in a chamber and presented with repeated series of 1-s foot shocks in increasing intensity. These intensities were 0.1, 0.2, 0.3, 0.4, 0.6, 0.8, 1.2, 1.6, and 2.2 mA. The shocks were presented at 30-s intervals; during and just after shock administration, each animal's behavior was rated for the presence of (a) flinch, obvious crouch, or startle, (b) squeak, and (c) jump or rapid movement forward. Single upward series of shock intensities were presented to each rat just prior to, and at 0.5 and 2 h subsequent to, intraperitoneal drug treatment. At least five rats were exposed to each dose.

Dog Radiant Heat Assay. The apparatus described by Hardy, Wolff, and Goodell[14] was adapted for use with dogs. Each animal was positioned in a harness such that a previously shaved area of skin in the mid-back region was positioned beneath the concealed heat source. Control values were ascertained for each animal by noting the delay between onset of the thermal stimulus and a response defined as a "rippling" of the skin. Each animal was then tested 0.5 and 2 h postdrug and the end point expressed as "% control".

Mouse Hot-Plate Analgesic Testing. The method used was modified after Woolfe and MacDonald.[15] A controlled heat stimulus was applied to the feet of mice on a $^1/_8$ in. thick aluminum plate. A 250-W reflector IR heat lamp was placed under the bottom of the aluminum plate; a thermal regulator, connected to thermistors on the plate surface, programmed the heat lamp to maintain a constant temperature of 57 °C. Each mouse was dropped into a 6.5 in. diameter glass cylinder resting on the hot plate, and timing began when the animal's feet touched the plate. The mouse was observed at 0.5 and 2 h after treatment for the first "flicking" movements of one or both hind feet or until 10 s elapsed without such movements. At least ten mice were exposed to each dose.

Mouse Tail Flick Analgesic Testing. Tail-flick testing in mice was modified after D'Amour and Smith,[16] using controlled high-intensity heat applied to the tail. Each mouse was placed in a snug-fitting metal cylinder, with the tail protruding through one end. This cylinder was arranged so that the tail lay flat over a concealed heat lamp. At the onset of testing, an aluminum flap over the lamp was drawn back, allowing the light beam to pass through the slit and focus onto the end of the tail. A timer was simultaneously activated. The latency of a sudden flick of the tail was ascertained. Untreated mice usually reacted from 3–5 s after exposure to the lamp. The end point was 10 s. Each mouse was tested at 0.5 and 2 h after drug treatment. At least ten mice were exposed to each dose.

Acknowledgment. The authors are grateful to Messrs. J. W. Homiski, W. H. Kappeler, F. W. Rusek, C. W. Scott, and R. L. Taylor, who rendered significant technical assistance.

References and Notes

(1) J. Knoll, *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.*, **236**, 92 (1959).
(2) J. Knoll, *Naunyn-Schmiedebergs Arch. Exp. Pathol. Pharmakol.*, **238**, 114 (1960).
(3) R. H. K. Foster and A. J. Carman, *J. Pharmacol. Exp. Ther.*, **91**, 195 (1947).
(4) J. Knoll, K. Nador, B. Knoll, J. Heidt, and J. G. Nievel, *Arch. Int. Pharmacodyn. Ther.*, **130**, 155 (1961).
(5) P. A. J. Janssen in "Modern Problems in Pharmacopsychiatry; The Neuroleptics", Vol. 5, D. P. Bobon, P. A. J. Janssen, and J. Bobon, Ed., S. Karger, Basel, 1970, p 33.
(6) D. M. Gallant and M. P. Bishop, *Curr. Ther. Res., Clin. Exp.*, **10**, 441 (1968).
(7) D. B. Bruce, A. J. S. Sorrie, and R. H. Thomson, *J. Chem. Soc.*, 2403 (1953).
(8) Prepared according to R. A. J. Smith and T. A. Spencer, *J. Org. Chem.*, **35**, 3220 (1970).
(9) Prepared according to A. Hassner and N. H. Cromwell, *J.*

Am. Chem. Soc., **80**, 893 (1958).
(10) K. Bruckner, K. Irmscher, F. W. Werder, K.-H. Bork, and H. Metz, *Chem. Ber.*, **94**, 2897 (1961).
(11) A. Weissman, *Psychopharmacologia*, **12**, 142 (1968).
(12) W. O. Evans, *Psychopharmacologia*, **2**, 318 (1961).
(13) S. S. Tenen, *Psychopharmacologia*, **12**, 278 (1968).
(14) J. D. Hardy, H. G. Wolff, and H. Goodell, "Pain Sensations and Reactions", Williams and Wilkins, Baltimore, Md., 1952, p 67.
(15) G. Woolfe and A. D. MacDonald, *J. Pharmacol. Exp. Ther.*, **80**, 300 (1944).
(16) F. E. D'Amour and D. I. Smith, *J. Pharmacol. Exp. Ther.*, **72**, 74 (1941).
(17) L. Grumbach in "Pain", R. S. Knighton and P. R. Dunke, Ed., Little, Brown and Co., Boston, Mass., 1966, p 163.
(18) R. A. Hardy, Jr., and M. G. Howell in "Analgetics", G. deStevens, Ed., Academic Press, New York, N.Y., 1965, p 179.

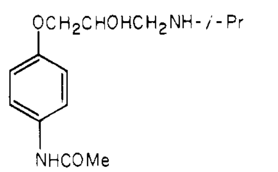
β-Adrenergic Blocking Agents. 15. 1-Substituted Ureidophenoxy-3-amino-2-propanols

L. H. Smith

Imperial Chemical Industries Limited, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England.
Received July 26, 1976

A series of 1-substituted ureidophenoxy-3-amino-2-propanols was synthesized and the compounds were screened as β-adrenergic receptor antagonists in cats. Many of the compounds are potent cardioselective β-blockers. Their structure–activity relationships and chemistry are discussed.

In paper 10, the syntheses and biological properties of the adrenergic β-receptor antagonist 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilide (practolol, 1) and several homologues were reported.[1] The cardioselective β-



1

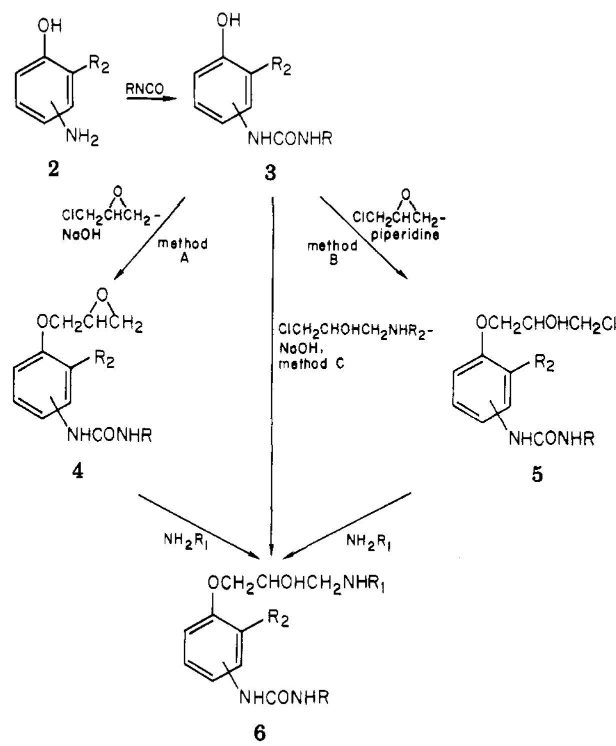
blocking property of practolol has since become established[2] and in the course of our synthetic program on cardioselective β-receptor antagonists we have now prepared a series of analogues of practolol in which the acylamino moiety in the aryl residue has been replaced by a ureido moiety.[3]

Many of the compounds described show a similar profile of activity to practolol in that they markedly inhibit the isoproterenol-induced tachycardia with only small effects on the isoproterenol depressor response. This finding is in accordance with other workers who have claimed selectivity of action for ureido-substituted aryloxypropanolamines.[4] This paper describes the synthesis and the structure–activity relationships within this series of homologues.

Chemistry. The compounds described in Tables I and II were prepared as shown in Scheme I. The above methods are analogous to those used for previously described 1-amino-3-aryloxy-2-propanols.[1,6] Of these, method A was preferred to methods B and C because of higher yield; therefore, the Experimental Section is limited to three brief descriptions of typical procedures. The epoxide intermediates (4) were used without further purification and their methods of synthesis are adequately described in previous papers. The synthesis of a typical ureidophenol is described and Table II lists those phenols that are novel and have been characterized. The aminophenols used as starting material are adequately described in the literature with the exception of 2-acetyl-4-aminophenol which is described in the Experimental Section.

Pharmacology. β-Adrenoceptor blocking potency was estimated in vivo using the previously described cat

Scheme I



preparation.[5] The results given in Tables I and II are expressed as the total dose, infused over a period of 30 min, causing a 50% inhibition of the tachycardia produced by a submaximal dose of isoproterenol (0.2 μg/kg dosed iv). The degree (%) of blockade of the vasodepressor response at that dose level is also given. The relative potencies of these two systems give some indication of selectivity for β-1 (cardiac) as opposed to β-2 (vascular) receptors. Statistical analysis of the results shows that the mean ED_{50} on the log scale for compounds with an average of two to three tests per compound was ±0.12 log unit (i.e., a mean error of approximately 30%).

Discussion of Results

Throughout the series many of the compounds have shown a selectivity of action similar to that found in