control group received the antagonists followed, after an appropriate time, by saline. The other control group received saline followed, after an appropriate time, by tryptamine or compound **7e**.

BOL. Six mice were treated with BOL (2 mg/kg ip). This dose of BOL shows no behavioral effects. After 20 min, the animals were given 25 mg/kg ip of tryptamine. Similar experiments were done with compound **7e** (25 mg/kg ip).

Methysergide. Six mice were treated with methysergide (10 mg/kg ip). At this dose of methysergide, the animals show a decrease in motor activity and fasciculations of the hind quarters. Sometimes these fasciculations are intense and resemble the clonic seizures shown by tryptamine and compound **7e**. When the animals appeared normal (40 min), 25 mg/kg ip of tryptamine was given. Similar experiments were done with compound **7e**. The interaction of tryptamine and compound **7e** was also studied using 5 and 20 mg/kg ip doses of methysergide.

Cyproheptadine. Six mice were treated with cyproheptadine (3 mg/kg ip). The behavioral effects observed at this dose of cyproheptadine are increased exploration and occasional tremors of hind legs. After 10 min, tryptamine (25 mg/kg ip) or compound **7e** (25 mg/kg ip) was given. In another experiment, the animals were given tryptamine or compound **7e** 40 min after cyproheptadine.

Acute Toxicity in Mice. The compounds were tested at 25, 50, 100, 200, and 300 mg/kg ip doses, four mice being used per dose. Saline was used as the vehicle. The dose at which two of the animals died in a 24-h period was taken as the approximate LD_{50}. If at a given dose only one or three of the animals died, then the LD_{50} was calculated by adding or subtracting, respectively, 25 mg/kg from this dose.

Drugs and Their Source. Pargyline hydrochloride [prepared from *N*-methylbenzylamine and propargyl bromide, mp 155 °C (lit.[27] 154–155 °C)], BOL tartrate (Department of Health & Welfare, Canada), methysergide bimaleate (Sandoz, Montreal), cyproheptadine hydrochloride (Merck, Montreal), and tryptamine hydrochloride (Sigma Chemical Co., St. Louis, Mo.) were used.

References and Notes

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Analgesic and Tranquilizing Activity of 5,8-Disubstituted 2-Aminomethyl-3,4-dihydronaphthalenes

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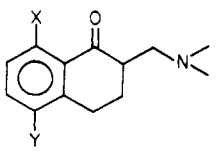
Interesting analgesic activity approaching that of meperidine and codeine was observed in standard animal models for 8-chloro-3,4-dihydro-5-methoxy-2-pyrrolidinomethylnaphthalene (compound **7**). This compound was orally effective and its analgesic activity was not reversed by the opiate antagonist, naloxone. A limited number of other 2-aminomethyl analogues displayed activity in neuroleptic screens.

An investigation of the structural requirements for analgesic and tranquilizing activity in a series of 5,8-disubstituted 1-tetralone Mannich bases I has recently been



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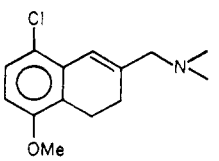

II

reported.[1] In an extension of this work we have found that the related 2-aminomethyl-3,4-dihydronaphthalene compounds II also exhibit interesting CNS activity. In this paper we wish to describe the synthesis and biological activity of a series of 2-aminomethyl-8-chloro-3,4-dihydro-5-methoxynaphthalenes together with a probe into the effect of substitution on the aromatic ring in the pyrrolidinomethyl series.

Chemistry. The 2-aminomethyl-3,4-dihydronaphthalene derivatives described in this paper were prepared by two main routes depending in part upon the nature of the desired amine substituent. The first route (Scheme I) was employed in cases where the amine substituent was not sensitive to hydride reducing agents. As indicated in Scheme I, the ethyl ester of 4-(2-methoxy-5-chlorophenyl)butyric acid[2] (III) was converted to the unstable hydroxymethylene derivative IV by means of sodium

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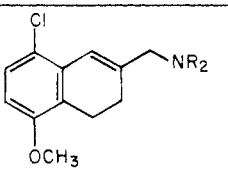
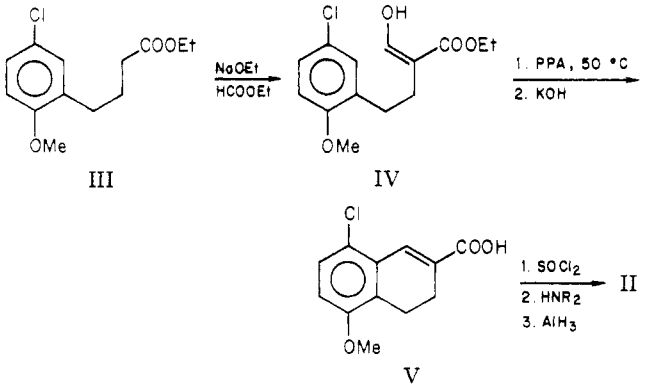
Table I. Analgesic Activity of 8-Chloro-3,4-dihydro-5-methoxy-2-aminomethylnaphthalenes



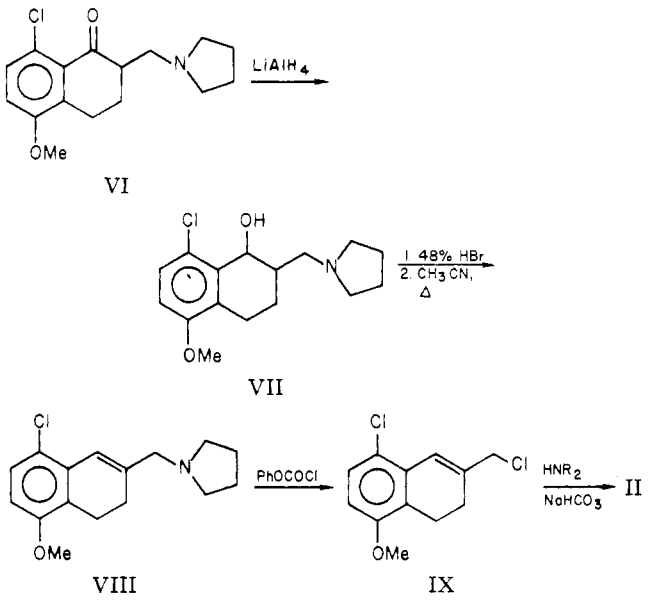
Compd	NR_2	Mp, °C	Formula[a]	% yield	Prep method	Hot plate (mouse), 100 mg/kg ip, % control[b] 0.5 h	Hot plate (mouse), 100 mg/kg ip, % control[b] 2 h	Tail flick (mouse), 100 mg/kg ip, % control[b] 0.5 h	Tail flick (mouse), 100 mg/kg ip, % control[b] 2 h
1	$NHCH_3$	184-186	$C_{13}H_{16}NOCl \cdot HCl$	67	A	139[c]	120[c]	163[c]	127[c]
2	$NHCH_2CH{=}CH_2$	213-216	$C_{15}H_{18}NOCl \cdot HCl$	45	A	158	115	131	108
3	$NHCH_2$-c-C_3H_5	185-187	$C_{16}H_{20}NOCl \cdot HCl$	36	A	224	171	203	162
4	$NHCH_2CH_2OCH_3$	168-171	$C_{15}H_{20}NO_2Cl \cdot HCl$	75	A	213	141	226	160
5	NH-c-C_6H_{11}	216-218	$C_{18}H_{24}NOCl \cdot HCl$	58	A	120[c]	102[c]	188[c]	141[c]
6	$N(CH_3)_2$	217-220	$C_{14}H_{18}NOCl \cdot HBr$	28	B	107	100	97	98
7	c-NC_4H_8	233-235	$C_{16}H_{20}NOCl \cdot HBr$	83	B	282	117	238	135
8	c-NC_5H_{10}	211-212	$C_{17}H_{22}NOCl \cdot HCl$	30	B	155	127	212	167
9	c-$N(CH_2CH_2)_2O$	>255	$C_{16}H_{20}NO_2Cl \cdot HBr$	51	B	95	90	136	125
Propoxyphene						139	138	169	146
Morphine[d]						300	276	300	295
Morphine[e]						244	200	261	229
Meperidine[f]						296	231	194	160

[a] All compounds were analyzed for C, H, and N. Except where noted, values agreed with calculated values within ±0.4%. [b] Increase in latency of response as defined in the Pharmacology Methods section. At least ten mice were exposed to each dose. [c] Values from 32 mg/kg dose. LD_{50} 32-100 mg/kg. [d] Morphine sulfate, 10 mg/kg ip. [e] Morphine sulfate, 3.2 mg/kg ip. [f] 56 mg/kg ip.

Scheme I



Scheme II



ethoxide–ethyl formate. Cyclization of IV in the presence of polyphosphoric acid[3] at 50 °C followed by hydrolysis afforded the dihydronaphthalenecarboxylic acid V, from which the desired aminomethyl compounds II were obtained by an aluminum hydride reduction of the corresponding carboxamides. The use of aluminum hydride was critical in that lithium aluminum hydride gave the corresponding tetrahydro derivative.

An alternate route, outlined in Scheme II, involved displacement upon the allyl chloride derivative IX by the requisite amine. The chloromethyl compound IX was obtained in good yield by phenyl chloroformate assisted deamination of dihydronaphthylmethylamine VIII which in turn was prepared from the previously described[1] tetralone Mannich base VI by the reduction–dehydration sequence illustrated. Compounds for which the corresponding Mannich bases were readily available could be prepared by this latter sequence as well.

Pharmacology. Compounds were evaluated for analgesic activity in the mouse hot-plate[4] and tail-flick[5] procedures and in the rat flinch–jump test.[6,7] Activity in these tests was determined by comparing test results for drug-treated animals with concurrent and historical control values. In the hot-plate and tail-flick procedures, elevation of response latencies to 200% of control values was taken as the lower bound of activity, whereas in the flinch–jump procedure, failure of the animal to respond to the 2.2-mA shock level was considered evidence of activity. These methods are discussed in more detail in the Pharmacology Methods section.

Activity in this series was generally observed only in hot-plate and tail-flick procedures. In the flinch–jump screen, with the exception of compounds 7 and 17, values from drug-treated animals were usually only marginally superior to control values and are, hence, not tabulated. Since hot-plate and tail-flick activity has been historically linked with narcotic properties,[18] the most active compounds from this series were subjected to a naloxone challenge test—a classical test for the detection of opiate-like analgesic activity.

Compound 7 (Table I) displayed the most interesting profile of activity in the above procedures and is an exception to the general lack of activity of the series in the flinch–jump test. The hot-plate and tail-flick data show that this compound is relatively short acting, with 100 mg/kg ip giving a response equivalent to 10 mg/kg sc of morphine at the 0.5-h test. In the flinch–jump assay, 32

mg/kg ip of **7** is roughly equivalent to 17.8 mg/kg of morphine administered sc at both 0.5 and 2 h. In the dog radiant heat procedure,[9] 3.2 mg/kg sc of **7** raised the response threshold (reflex fasciculations of the back muscles) by 50%, which approximated the effects seen with 1.5 mg/kg sc of morphine sulfate and 16 mg/kg sc of meperidine. Compound **7** was also active orally in the dog test, with 16.2 mg/kg being required to achieve a 50% threshold elevation.

The analgesic activity of **7** in mice in the hot-plate and tail-flick tests was not attenuated by naloxone, and tolerance did not develop to the analgesic activity of sequential doses of **7** (100 mg/kg ip bid) over a 4-day period. A second group of animals treated with morphine sulfate (10 mg/kg ip bid) during the same period showed clear signs of tolerance. When both groups of mice in this latter test were challenged with naloxone at the end of the procedure, the typical jumping response[10] was seen in the morphine-treated animals, whereas this response was absent in the animals receiving compound **7**.

Compound **17** was the most active of a number of substituted piperidine analogues (Table II) investigated. This compound was highly active in both the mouse and rat tests at 32 mg/kg at both 0.5 and 2 h. However, as could be anticipated from the nature of the prodine moiety, this compound elicited clear behavioral indications of narcotic-like activity (Straub tail[11]) and, consistent with this observation, its analgesic activity was clearly reversed by the opiate antagonist, naloxone.

Among a series of 4-carboxamidopiperidine derivatives, compound **21** displayed the most potent activity in hot-plate and tail-flick procedures, with compounds **22**, **24**, and **25** showing considerably less activity in these screens. Compound **21** was inactive in the radiant heat procedure[9] and, although it did not elicit clear Straub tail symptoms in mice or rats, naloxone blocked its activity in the hot-plate and tail-flick test.[5] The 3-carboxamido derivative **28** was essentially inactive in all these tests at the doses tested, and its *N,N*-diethyl derivative **29** was active only in the tail-flick procedure.

Of the 4-substituted piperazines prepared (Table III), the carboethoxy derivative **31**, the 4-methyl analogue **33**, and the 4-β-hydroxyethyl compound **35** possessed limited and short-lived activity. The 4-phenylpiperazine derivatives **36–38** were only weakly active at the doses tested.

In view of the apparent selectivity of compound **7**, structure–activity relationships in the aromatic ring were developed around this 2-pyrrolidinomethyl analogue. It will be noted from the results in Table IV, however, that alternative substitution in the aromatic ring did not enhance activity beyond that of the original 8-chloro-5-methoxy substitution pattern.

A number of the compounds above were tested for neuroleptic activity. Several exhibited the ability to enhance the accumulation of Dopa in decarboxylase-inhibited rat brain[12] and to antagonize amphetamine-induced stereotypy in rats.[13] These results are tabulated in Table V. It is of interest to note that the most active of these compounds (e.g., compounds **15** and **30**) are derived from piperidines known to be associated with neuroleptic activity[14] in the butyrophenone series. The enhanced activities of these compounds may be related to favorable allosteric binding capabilities of these respective structures and to the semirigid Janssen "S-shaped" configuration[15] incorporated into their structures.

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. UV spectra were recorded on a Cary Model 14 spectrophotometer. Low- and high-resolution mass spectra were obtained with Perkin-Elmer RMU-6E and AEI MS-30 mass spectrometers, respectively. Microanalyses were performed by the Pfizer Analytical Department.

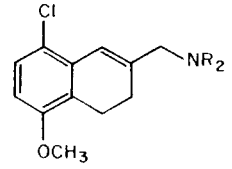
Ethyl 8-Chloro-3,4-dihydro-5-methoxynaphthalene-2-carboxylate. A solution of 100.8 g (0.44 mol) of 8-(2-methoxy-5-chlorophenyl)butyric acid[2] in 700 mL of absolute EtOH was saturated with HCl gas and allowed to stand overnight. After concentration, the residue was taken up into CH_2Cl_2, washed with aqueous $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent and distillation gave 106.4 g (94%) of III: bp 140–143 °C (1.5 mm); NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7 Hz), 1.60–2.75 (6 H, m), 3.77 (3 H, s), 4.12 (2 H, q, J = 7 Hz), 6.65–7.30 (3 H, m). A suspension of sodium ethoxide (0.82 mol) in Et_2O was prepared by addition of 47.6 mL (0.82 mol) of absolute EtOH to 34.5 g (0.82 mol, 57% mineral oil dispersion) of NaH in 300 mL of Et_2O. This suspension was cooled to −15 °C and a solution of III (97.3 g, 0.38 mol) and ethyl formate (59.2 g, 0.8 mol) in 200 mL of Et_2O was added over a period of 1.5 h. After stirring for 84 h at room temperature, the mixture was poured onto 1.5 L of ice-cold water and the resulting solution was extracted with Et_2O. Evaporation of the combined ethereal extracts gave recovered ester which could be recycled. Acidification of the aqueous phase to pH 2 with 5% H_2SO_4 followed by extraction with Et_2O gave, after drying ($MgSO_4$) and evaporation, 62.8 g (58%) of IV as an oil. This material was unstable upon storage and was therefore used directly in the next step. To 375 g of polyphosphoric acid was added 15.0 g (53 mmol) of the above hydroxymethylene ester IV and the mixture was then stirred at 50 °C for 1.75 h. The mixture was then poured onto 300 mL of ice and the resulting precipitate was collected by filtration. Recrystallization from CH_2Cl–hexane provided 12.4 g (88%) of the desired product, mp 88–90 °C. Anal. ($C_{14}H_{15}O_3Cl$) C, H.

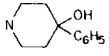
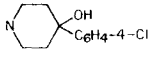
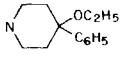
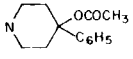
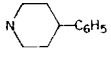
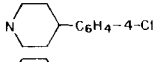
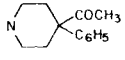
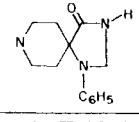
8-Chloro-3,4-dihydro-5-methoxynaphthalene-2-carboxylic Acid (V). A solution of the above ester (16.0 g, 0.06 mol) and NaOH (5.4 g, 0.135 mol) in 185 mL of 20% aqueous MeOH was heated at reflux for 2 h. The solvent was evaporated and the residue was decanted into 300 mL of 1 N HCl. The resulting precipitate was collected and recrystallized from MeOH to give 11.1 g (78%) of acid V, mp 228–230 °C. Anal. ($C_{14}H_{15}O_3Cl$) C, H.

General Procedure for the Preparation of 2-Aminomethyl-3,4-dihydronaphthalenes II by Reduction of the Corresponding Carboxamides (Preparative Method A). 8-Chloro-2-(*N*-cyclohexyl)aminomethyl-3,4-dihydro-5-methoxynaphthalene (6). To 5.0 g (0.21 mol) of acid V was added 35 mL of thionyl chloride, and the mixture was then heated at reflux for 1 h. Removal of the volatiles under reduced pressure left the solid acid chloride which was used directly in the acylation step. A stirred solution of this acid chloride in 50 mL of CH_2Cl_2 was treated dropwise with a solution of cyclohexylamine (4.18 g, 42.0 mmol) in 5 mL of CH_2Cl_2. After stirring overnight at room temperature the mixture was diluted with CH_2Cl_2 and extracted successively with 1 N NaOH and 1 N HCl and was then dried ($MgSO_4$). Evaporation of the solvent left the crystalline amide which was recrystallized from benzene to give 3.95 g (58%) of 8-chloro-3,4-dihydro-5-methoxynaphthalene-2-(*N*-cyclohexyl)-carboxamide, mp 193–194 °C. Anal. ($C_{18}H_{22}NO_2Cl$) C, H, N. To a slurry of $LiAlH_4$ (0.86 g, 22.5 mmol) in 50 mL of THF cooled to 0–5 °C was added 1.0 g (7.5 mmol) of $AlCl_3$. The resulting mixture was stirred for 0.5 h, and then a solution of the above carboxamide (3.0 g, 9.0 mmol) in 15 mL of THF was added dropwise over a period of 20 min. Stirring at 0–5 °C was continued for 2 h, and then the reaction mixture was decomposed by careful addition of water. The precipitated aluminum salts were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 and dried over $MgSO_4$. Removal of the solvent left an oil which was dissolved in dry Et_2O and converted to the hydrochloride salt **6** with HCl gas. There was obtained 1.9 g (58%) of pure product, mp 216–218 °C. Anal. ($C_{18}H_{24}NOCl$) C, H, N.

8-Chloro-1-hydroxy-5-methoxy-2-(pyrrolidinomethyl)-1,2,3,4-tetrahydronaphthalene. A suspension of 6.45 g (0.17

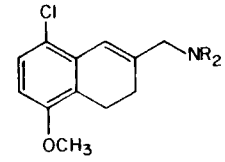
Table II. Substituted Piperidine Derivatives



Compd	NR_2	Mp, °C	Formula[a]	% yield	Prep method	Hot plate (mouse), 100 mg/kg ip, % control[b] 0.5 h	Hot plate (mouse), 100 mg/kg ip, % control[b] 2 h	Tail flick (mouse), 100 mg/kg ip, % control[b] 0.5 h	Tail flick (mouse), 100 mg/kg ip, % control[b] 2 h
10	c-NC_5H_9-4-CH_3	247–249	$C_{18}H_{24}NOCl \cdot HCl$	81	A	158[c]	135[c]	128[c]	115[c]
11	c-NC_5H_9-4-C_6H_5	94–97	$C_{23}H_{26}NOCl \cdot 0.5H_2O$	75	A	233	171	109	106
12	c-NC_5H_9-4-OH	73–75	$C_{17}H_{22}NO_2Cl \cdot HCl$	17	A	174	142	239	180
13	c-NC_5H_9-4-$OCOC_2H_5$	233–235	$C_{20}H_{26}NO_3Cl \cdot HCl$	46	C	95	101	237	179
14		242–244	$C_{23}H_{26}NO_2Cl \cdot HCl$	59	A	249	175	196	158
15		242–243	$C_{23}H_{25}NO_2Cl_2 \cdot 0.5H_2SO_4$	62	A	177	102	162	123
16		113–114	$C_{25}H_{30}NO_2Cl$	47	A	262	156	196	157
17		215–217	$C_{25}H_{28}NO_3Cl \cdot HCl \cdot 0.25H_2O$	74	C	315[c]	345[c]	317[c]	320[c]
18		125–126	$C_{23}H_{24}NOCl$	58	A	170	138	150	120
19		243–245	$C_{23}H_{23}NOCl_2$	35	A	123	109	156	125
20		226–232	$C_{25}H_{28}NO_2Cl \cdot HCl$	82	C	143	124	134	122
21	c-NC_5H_9-4-$CONH_2$	138–140	$C_{18}H_{23}N_2O_2Cl \cdot 0.5H_2O$	33	C	314	329	274	132
22	c-NC_5H_9-4-$CONHCH_3$	194–195	$C_{19}H_{25}N_2O_2Cl \cdot HCl \cdot H_2O$	25	C	221	167	208	166
23	c-NC_5H_9-4-CONH-c-C_6H_{11}	171–172	$C_{24}H_{33}N_2O_2Cl$	79	C	107	95	219	154
24	c-NC_5H_9-4-CO-c-NC_4H_8	128–133	$C_{22}H_{29}N_2O_2Cl \cdot HCl \cdot 0.5H_2O$	41	C	213	155	262	172
25	c-NC_5H_9-4-CO-c-NC_5H_{10}	129–132	$C_{23}H_{31}N_2O_2Cl \cdot HCl \cdot 1.25H_2O$	36	C	170	124	235	149
26	c-NC_5H_9-4-CO-c-$N(CH_2CH_2)_2O$	138–140	$C_{22}H_{29}N_2O_3Cl \cdot HCl$	55	C	107	95	162	133
27	c-NC_5H_9-4-CO-c-$N(CH_2CH_2)_2O$-4-CH_3	Amorph	$C_{23}H_{32}N_3O_2Cl$[d]	29	C	142	109	247	161
28	c-NC_5H_9-3-C(=O)NH_2	124–126	$C_{18}H_{23}N_2O_2Cl \cdot HCl$	46	C	197	170	91	106
29	c-NC_5H_9-3-C(=O)$N(C_2H_5)_2$	Amorph	$C_{22}H_{31}N_2O_2Cl \cdot HCl \cdot H_2O$	33	C	107	175	250	214
30		175–178	$C_{26}H_{30}N_3O_2Cl$	65	C	181	167	97	103

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I. Values for standards are included in Table I. [c] Values from 32 mg/kg dose. LD_{50} 32–100 mg/kg. [d] Not analyzed. One spot in more than one TLC system. Mol wt calcd for $C_{23}H_{32}N_3O_2Cl$, 417.2183; found, 417.2226.

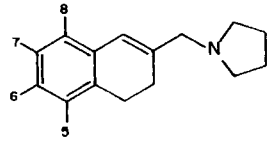
Table III. Substituted Piperazine Derivatives



Compd	NR_2	Mp, °C	Formula[a]	% yield	Prep method	Hot plate (mouse), 100 mg/kg ip, % control[b] 0.5 h	Hot plate (mouse), 100 mg/kg ip, % control[b] 2 h	Tail flick (mouse), 100 mg/kg ip, % control[b] 0.5 h	Tail flick (mouse), 100 mg/kg ip, % control[b] 2 h
31	c-$N(CH_2CH_2)_2N$-$COOC_2H_5$	206–208	$C_{19}H_{25}N_2O_3Cl \cdot HCl$	45	C	274	233	223	199
32	c-$N(CH_2CH_2)_2N$-SO_2NH_2	189–192	$C_{16}H_{22}N_3O_3SCl \cdot HCl$	26	C	123	109	104	88
33	c-$N(CH_2CH_2)_2N$-CH_3	73–74	$C_{17}H_{23}N_2OCl$	67	A	274	218	198	137
34	c-$N(CH_2CH_2)_2N$-$CH_2CH{=}CH_2$	258–259	$C_{19}H_{25}N_2OCl \cdot HCl$	55	A	164	127	159	137
35	c-$N(CH_2CH_2)_2N$-CH_2CH_2OH	108–109	$C_{18}H_{25}N_2O_2Cl$	50	A	249	236	187	191
36	c-$N(CH_2CH_2)_2N$-C_6H_4-4-Cl	122–123	$C_{22}H_{24}N_2OCl_2$	61	A	202	160	184	159
37	c-$N(CH_2CH_2)_2N$-C_6H_4-4-OCH_3	111–113	$C_{23}H_{27}N_2O_2Cl$	90	A	129	120	131	123
38	c-$N(CH_2CH_2)_2N$-C_6H_4-3-CF_3	73–76	$C_{23}H_{24}N_2OClF_3 \cdot 0.25H_2O$	95	A	167	149	119	118

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I. Values for standards are included in Table I.

Table IV. Structure–Activity Relationships in the Aromatic Ring



Compd	5	6	7	8	Mp, °C	Formula[a]	% yield	Prep method	Hot plate (mouse), 100 mg/kg ip, % control[b] 0.5 h	Hot plate (mouse), 100 mg/kg ip, % control[b] 2 h	Tail flick (mouse), 100 mg/kg ip, % control[b] 0.5 h	Tail flick (mouse), 100 mg/kg ip, % control[b] 2 h
39	OCH_3	H	H	F	235.0–236.5	$C_{16}H_{20}NOF \cdot HCl$	65	B	183[c]	149[c]	170[c]	141[c]
40	OCH_3	H	H	H	221–223	$C_{16}H_{21}NO \cdot HBr$	56	B	129[c]	103[c]	80[c]	90[c]
41	H	OCH_3	H	H	224–225	$C_{16}H_{21}NO \cdot HCl$	70	B	96	103	92	92
42	H	H	OCH_3	H	200–202	$C_{16}H_{21}NO$	27	B	114	98	149	129
43	OCH_3	H	H	OCH_3	184.0–185.5	$C_{17}H_{23}NO_2 \cdot HCl$	40	B	177[c]	132[c]	111[c]	99[c]
44	H	OCH_3	OCH_3	H	229–230	$C_{17}H_{23}NO_2 \cdot HCl$	76	B	173	135	101	95
45	OCH_3	H	H	CH_3	200.0–201.5	$C_{17}H_{23}NO \cdot HCl$	62	B	177[c]	145[c]	177[c]	135[c]
46	H	H	C_2H_5	H	220–222	$C_{17}H_{23}N \cdot HCl$	65	B	*d*	130	*d*	198
47	CH_3	H	CH_3	H	211–213	$C_{17}H_{23}N \cdot HCl$	84	B	126[c]	120[c]	124[c]	126[c]

[a] See footnote *a* in Table I. [b] See footnote *b* in Table I. Values for standards are included in Table I. [c] Values from 32 mg/kg dose. LD_{50} 32–100 mg/kg. [d] Loss of righting reflex at 0.5 h at 100 mg/kg.

Table V. Antiamphetamine and Dopa Accumulation Enhancing Properties of Selected Compounds

Compd	Antagonism of amphetamine (rat), ED_{50},[a] mg/kg	Enhancement of Dopa accumulation[b] (rat), % control (dose)
7	~32	288 (0.1 mmol/kg)
9	>32	243 (0.056 mmol/kg)
16	3.2-1.0	491 (0.001 mmol/kg)
19	0.32-1.0	NT
24	NT	332 (0.01 mmol/kg)
30	1.0-3.2	154 (0.01 mmol/kg)
Thiothixene	0.32-1.0	230 (0.002 mmol/kg)

[a] The dose required to reverse the stereotypy in rats caused by 5 mg/kg of amphetamine sulfate administered 1 h following ip administration of drug. [b] Reference 12.

mol) of $LiAlH_4$ in 150 mL of anhydrous Et_2O was heated at a gentle reflux while a solution of 10.0 g (34 mmol) of 8-chloro-3,4-dihydro-5-methoxy-2-(pyrrolidinomethyl)-1(2*H*)-naphthalenone was added portionwise so as to maintain a gentle reflux. After 20 min at reflux, the reaction mixture was cooled in an ice bath and decomposed with 26 mL of water and 6.5 mL of 15% aqueous NaOH. The precipitated solids were filtered off and washed with Et_2O, and then the filtrate was extracted with dilute HCl. The aqueous extracts were made basic with dilute NaOH and extracted with Et_2O. The combined ethereal extracts were then dried and evaporated to yield 7.1 g (71%) of the product as a colorless oil which subsequently crystallized, mp 101–103 °C. A portion of this material was converted to the HCl salt for analytical purposes: mp 176–181 °C. Anal. ($C_{16}H_{22}NO_2Cl$·HCl) C, H, N, Cl.

8-Chloro-3,4-dihydro-5-methoxy-2-(pyrrolidinomethyl)-naphthalene Hydrobromide (7) (Preparative Method B). A solution of 5.9 g (20.0 mmol) of compound VII in 25.0 mL of 48% HBr and 2.2 mL of water was stirred at room temperature for 3 h. The precipitated solids were then separated by filtration, washed with water, and air-dried. This material [which is the 1-bromo derivative [Anal. ($C_{16}H_{21}NOBrCl$·HBr) C, H, N, Br, Cl]] was dissolved in hot CH_3CN and then chilled overnight. The resulting crystals of the desired product weighed 6.07 g (85%) and melted at 248–251 °C. This salt could be converted to the hydrochloride salt in 83% yield by partitioning between Et_2O and 10% NaOH, drying the Et_2O layer, and adding HCl gas.

8-Chloro-2-(chloromethyl)-3,4-dihydro-5-methoxynaphthalene (IV). A solution of 5.04 g (18.2 mmol) of 8-chloro-3,4-dihydro-5-methoxy-2-(pyrrolidinomethyl)naphthalene (compound 7) in 100 mL of dry CH_2Cl_2 was mixed with a solution of 3.12 g (20.0 mmol) of phenyl chloroformate in 20 mL of CH_2Cl_2, and the resulting solution was stirred at room temperature for 24 h. The reaction mixture was then washed twice with water and dried, and the solvent was evaporated. The residual oil was chromatographed on a silica gel column using benzene as eluent. Fractions containing the desired product were combined and evaporated to yield a pale yellow oil which crystallized on standing to give 2.3 g (52%) of material melting at 57–58 °C. Anal. ($C_{12}H_{12}OCl_2$) C, H, Cl.

General Procedure for the Preparation of 2-Aminomethyl-3,4-dihydronaphthalenes II from the Allylic Chloride IX (Preparative Method C). 2-(4-Carboxamidopiperidino)methyl-8-chloro-3,4-dihydro-5-methoxynaphthalene (21). A mixture of 1.78 g (7.3 mmol) of 8-chloro-2-(chloromethyl)-3,4-dihydro-5-methoxynaphthalene, 2.0 g (14.6 mmol) of isonipecotamide, and 4.5 g (53.6 mmol) of $NaHCO_3$ in 50 mL of anhydrous EtOH was heated at reflux for 90 min. The solids were filtered from the cooled reaction mixture, and the filtrate was then evaporated to dryness. The residual yellow oil was dissolved in CH_2Cl_2 and extracted twice with dilute HCl. These extracts were combined and adjusted to pH 11.5 with dilute NaOH. The resulting aqueous solution was extracted with CH_2Cl_2, and the combined extracts were dried and evaporated to a colorless foam which crystallized from Et_2O to give 1.37 g (56%) of the product, mp 138–140 °C.

Pharmacology Methods. Mice were Charles River males, Swiss CD strain, weighing approximately 20 g. Rats were Charles River males, Sprague–Dawley CD strain, weighing 200–300 g. Dogs were male mongrels weighing 9–12 kg. Saline solutions or suspensions of experimental compounds were administered intraperitoneally unless otherwise noted. Injection volumes were usually 5 mL/kg.

Mouse Hot-Plate Analgesic Testing. The method used was modified after Woolfe and MacDonald.[4] 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 was begun 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. Averaged latencies of response divided by averaged control latencies times 100 gave "percent control" values.

Mouse Tail-Flick Analgesic Testing. Tail-flick testing in mice was modified after D'Amour and Smith,[5] 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. The cylinder was then 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 within 3–5 s after exposure to the lamp. The test was terminated after 10 s if there was no response. Each mouse was tested at 0.5 and 2 h after drug treatment. At least ten mice were exposed to each dose. Averaged latencies of response divided by averaged control latencies times 100 gave "percent control" values.

Flinch-Jump Analgesic Procedure. A modification of the flinch-jump procedure[6,7] was used for measuring pain thresholds. Rats were placed in a chamber and presented with repeated series of 1-s foot shocks of 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. The minimum shock intensity (mA's) required to elicit each behavior was recorded. 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 et al.[9] was adapted for use with dogs. Each animal was positioned in a harness such that a previously shaved and blackened (India ink) area of skin in the mid-back region was positioned beneath a concealed heat source. Control latencies were ascertained for each animal by noting the delay between onset of the thermal stimulus and the nociceptive response, which was defined as a "rippling" of the skin. Each animal was then tested 0.5 and 2 h postdrug and the end point expressed as a percent of the control latency.

Dopa Accumulation Procedure. The procedure of Koe[12] was used.

Rat Amphetamine Antagonism Studies. The procedure of Weissman[13] was used.

Acknowledgment. The authors are grateful to Dr. B. Kenneth Koe for the Dopa accumulation experiments, to Dr. Albert Weissman for the rat antiamphetamine results, to Dr. J. R. Tretter for valuable chemical discussions, and to Mrs. Gwendolyn Robinson and Messrs. R. B. Drolet, C. F. Ebbinghaus, J. W. Homiski, and R. L. Taylor for significant technical assistance.

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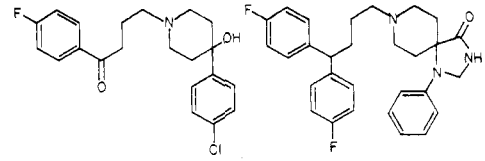
(14) For example, haloperidol (X) and fluspirilene (XI).



X XI

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Diazepines. 5. Synthesis and Biological Action of 6-Phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines[1-3]

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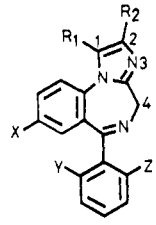
A series of 6-phenyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepines (**2**) has been prepared with 2-phthalimidomethylfurans (**12**) and 1-phthalimidoalkane-2,5-diones (**15**) or 2,5-dimethoxy-2-phthalimidomethyltetrahydrofurans (**16**) as the key intermediates and subsequently evaluated for CNS activity. The structure–activity data generated indicate that, in general, introduction of the methyl and/or ethyl group(s) in the pyrrole ring and a chlorine atom at the ortho position of the 6-phenyl group increases the activity and that substitution of the above chlorine atom for a fluorine atom decreases the activity. 8-Chloro-6-(2-chlorophenyl)-1,3-dimethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine (**2p**), the most potent among the compounds synthesized, was equipotent in taming and sedative activities to diazepam. The acute LD_{50} of **2p** in mice was larger than 3000 mg/kg po.

Previously we have observed that the introduction of an alkyl group (particularly the methyl and the ethyl group) at the 2 position of 6-phenyl-4*H*-imidazo[1,2-*a*][1,4]-benzodiazepines (**1**) greatly enhances the CNS activity of



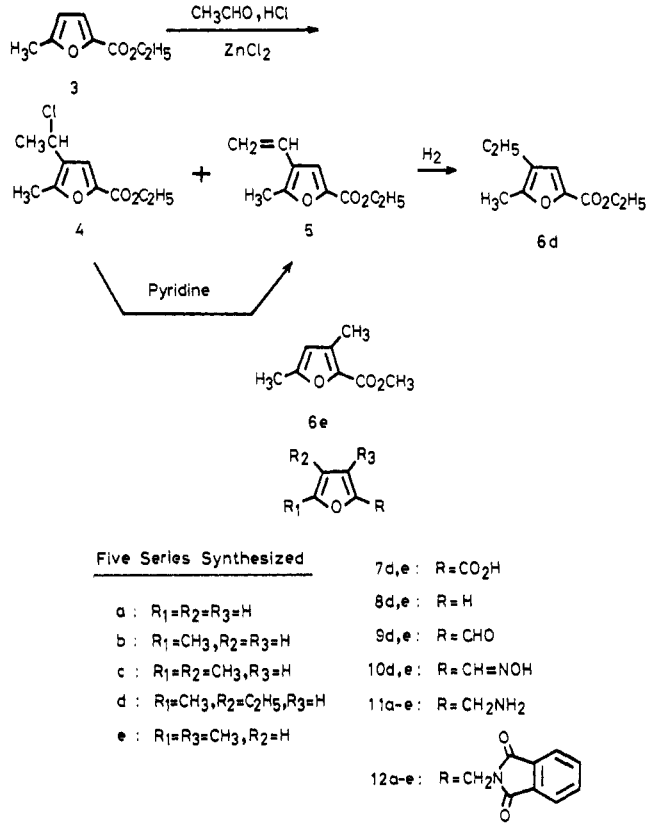
1

the compounds.[4] The present study was undertaken in order to synthesize 6-phenyl-4*H*-pyrrolo[1,2-*a*][1,4]-benzodiazepines[5] (**2**) by an efficient method and to investigate the CNS activity of the compounds particularly in terms of the effect of the alkyl group(s) on the pyrrole ring upon the pharmacological action. The potential effect of the introduction of an alkyl group at the 3 position is of interest, for compounds **1** cannot possess an alkyl group at this position.

Chemistry. The tricyclic diazepine compounds **2** were synthesized (Scheme III) with the furans **12** (Scheme I) and the 1,4-diketones **15** or the tetrahydrofurans **16** (Scheme II) as the key intermediates.

Phthalimidomethylfurans. Compound **4** obtained by distillation in the α-chloroethylation[7] of ethyl 5-methyl-2-furoate (**3**) using acetaldehyde and hydrogen chloride with zinc chloride as the catalyst was accompanied by the olefin **5**, apparently arising from the dehydrochlorination of the α-chloroethyl derivative **4** in the distillation flask. The mixture of **4** and **5** so obtained was heated with pyridine to yield pure **5**, which was then hydrogenated over Raney nickel to give ethyl 4-ethyl-5-methyl-2-furoate (**6d**). The ester **6d** was hydrolyzed to the acid **7d**, which was

Scheme I



decarboxylated[8] to **8d** by heating in an oil bath of 250–265 °C with copper powder and quinoline. The formylation of **8d** under Vilsmeier conditions[9] afforded the aldehyde **9d**. The phthalimidomethylfuran **12d** was prepared from **9d** via the oxime **10d** and the amine **11d** according to the

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