# New Bicyclic Antidepressant Agent. Synthesis and Activity of Napactadine and Related Compounds

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A number of N,N'-dialkylarylamidines were synthesized and evaluated for antidepressant activity. Several of these compounds were synthesized from the corresponding nitriles by a new method. Slight structural modification in the series caused a marked change in biological activity and led to compounds as active as imipramine. The arylacetamidine, N,N'-dimethyl-2-naphthaleneethanimidamide hydrochloride (33) (napactadine) was selected for clinical study. Forty-eight additional analogues of 33, including a number of N-alkylamidines, were prepared.

Depression is a complex and variable mental disorder that may be characterized by manic states as well as states of decreased motor activity. Tricyclic antidepressants are usually the drugs of choice for the treatment of depression.[1,2] However, these agents have a relatively slow onset of action,[1,2] and their use is often limited by the occurrence of undesirable side effects,[3] particularly anticholinergic[4] or cardiotoxic side effects.[5,6] We were interested in developing a novel nontricyclic antidepressant that has equal or greater potency, less undesirable side effects, and a more rapid onset of action than the tricyclics. The search for such a compound led us to prepare a series of aromatic N,N'-dialkylamidines. This was based on the promising activity that the imidazoline, fenmetozole (DL-524), was

fenmetozole
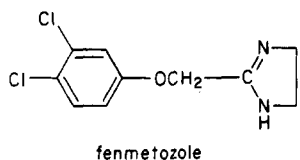
showing in depressed patients at the outset of this work[7] and the premise that an N,N'-dialkylamidine would serve as a suitable bioisostere for the imidazoline functional group. This report describes the synthesis and evaluation of several N,N'-dialkylamidines that began with the synthesis of 15, a potential bioisostere of fenmetozole, and culminated with the synthesis of N,N'-dimethyl-2-naphthaleneethanimidamide hydrochloride (33) (napactadine, DL-588),[8] a compound selected for clinical evaluation.

Chemistry. The compounds investigated, as part of this study, are listed in Tables I–III. Three procedures were used to prepare the N,N'-dialkylamidines, which are outlined in Chart I. The first route (method A) provided a new convenient procedure to prepare symmetrical $N,-$

Chart I
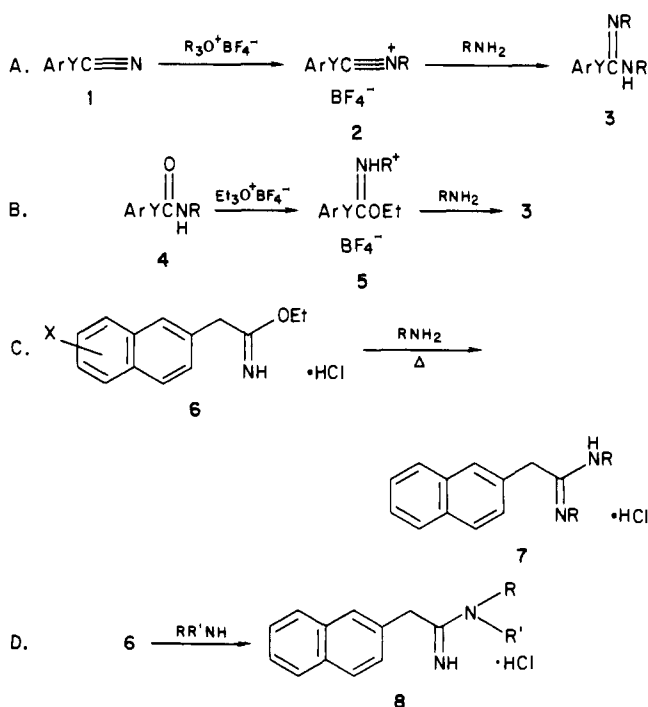
N'-dialkylamidines. The corresponding nitriles (1) were reacted with trimethyloxonium fluoroboate in nitromethane (40–45 °C) to form the methylnitrilium salts 2. The nitrilium salts were treated directly with anhydrous methylamine, to provide N,N'-dimethylamidines 3 (R = CH_3). Likewise, the N,N'-diethylamidines 3 (R = CH_2CH_3) were obtained with triethyloxonium fluoroborate in refluxing methylene chloride followed by ethylamine addition to the reaction mixture. There have been reports on the conversion of N-alkylnitrilium salts (2) to the corresponding N-alkylamides by treatment with water or to the imino derivatives by treatment with alcohol.[9] Borch[10] has reported the conversion of 2 to secondary amines by treatment with sodium borohydride. The reaction of an N-alkylnitrilium salt (2) with the corresponding alkylamine provides a facile synthetic route to N,N'-dialkylamidines. However, this procedure is limited to nitriles that lack an ethereal oxygen or presumably any nucleophilic functional group. The method of Weintraub and co-workers[11] (method B) was found to be useful for the synthesis of

† Medicinal Chemistry Department.
‡ Deceased Dec 12, 1984.
§ Pharmacology Department.
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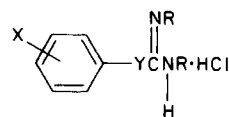(7) Chein, C. P.; Kaplan, R. M. *Curr. Ther. Res., Clin. Exp.* 1969, 11, 471.
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Table I. Antidepressant Agents: Effect of Aromatic Ring and Benzylic Substitution on Activity
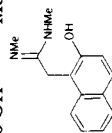

compd	X	Y	R	mp, °C	recryst[a] solvent	formula	method[b]	yield, %	ED$_{50}$,[c] mg/kg reserpine ptosis, ip[f]	ED$_{50}$,[c] mg/kg yohimbine potentiation, ip
9	H		Me	252–254 dec	A, B	C$_9$H$_{12}$N$_2$·HCl	B	33	0.8 (0.2–2.3)	4.0 (2.8–6.0)
10	4-Cl		Me	285–286	A	C$_9$H$_{11}$ClN$_2$·HCl	B	41	6.8 (2.8–17.7)	6.0 (3.2–11.1)
11	3,4-Cl$_2$		Me	320–321	A	C$_9$H$_{10}$Cl$_2$N$_2$·HCl	B	61	9.3 (6.4–13.5)	2.4 (1.4–3.9)
12	H	OCH$_2$	Me	212–213	A	C$_{10}$H$_{14}$N$_2$O·HCl	B	35	1.1 (0.4–2.1)	2.2 (1.1–3.5)
13	H	OCH$_2$	n-Pr	100–101	B	C$_{14}$H$_{22}$N$_2$O·HCl	B	37	NA	
14	2,4-Cl$_2$	OCH$_2$	Me	163–164	E	C$_{10}$H$_{12}$Cl$_2$N$_2$O·HCl	B	46	7.5 (3.1–12.1)[e]	
15	3,4-Cl$_2$	OCH$_2$	Et	170–171	B	C$_{12}$H$_{16}$Cl$_2$N$_2$O·HCl	B	36	3.3 (1.7–5.9)	3.5 (2.3–5.4)
16	2,4,5-Cl$_3$	OCH$_2$	Et	182–183	B	C$_{12}$H$_{15}$Cl$_3$N$_2$O·HCl	B	55	NA	
17	4-F	CH$_2$	Et	153–154	B	C$_{12}$H$_{17}$FN$_2$·HCl	A	6	NA	
18	4-Cl	CH$_2$	Me	242–243	A	C$_{10}$H$_{13}$ClN$_2$·HCl	B	17	2.3 (1.4–3.8)	15.0 (6.8–33.0)
19	4-Br	CH$_2$	Et	173–174	A	C$_{12}$H$_{17}$BrN$_2$·HCl	A	20	2.8 (0.1–4.7)	2.7 (1.3–4.5)
20	(4-ClC$_6$H$_4$)$_2$	CH	Me	145–146	F	C$_{23}$H$_{24}$Cl$_2$N$_2$O$_3$S[d]	B	26	2.4 (1.1–4.4)	27.2 (19.8–37.6)
21	2,4-Cl$_2$	CH$_2$	Et	218–219	A	C$_{12}$H$_{16}$Cl$_2$N$_2$·HCl	A	17	NA	
22	2,6-Cl$_2$	CH$_2$	Et	238–239	A	C$_{12}$H$_{16}$Cl$_2$N$_2$·HCl	A	14	NA	
23	3,4-Cl$_2$	CH$_2$	Et	231–232	A, C	C$_{12}$H$_{16}$Cl$_2$N$_2$·HCl	A	34	9.3 (5.7–15.0)	6.0 (3.2–11.1)
24	2,4,5-Cl$_3$	CH$_2$	Et	188–189	A	C$_{12}$H$_{15}$Cl$_3$N$_2$·HCl	A	18	NA	
25	2,3,6-Cl$_3$	CH$_2$	Et	195–196	B	C$_{12}$H$_{15}$Cl$_3$N$_2$·HCl	B	60	NA	
26	3-Me	CH$_2$	Et	145–146	B	C$_{13}$H$_{20}$N$_2$·HCl	A	12	NA	
27	4-Me	CH$_2$	Me	269–270	A	C$_{11}$H$_{16}$N$_2$·HCl	B	42	NA	
28	3-CF$_3$	CH$_2$	Et	167–168	A	C$_{13}$H$_{17}$F$_3$N$_2$·HCl	A	17	5.1 (3.3–7.3)	12.8 (8.5–23.0)
29	4-NO$_2$	CH$_2$	Me	248–249	A	C$_{10}$H$_{13}$N$_3$O$_2$·HCl	B	53	3.2 (2.1–4.9)	20 (9.1–44.0)
30	3,4-(OMe)$_2$	CH$_2$	Me	179–180	A, B	C$_{12}$H$_{18}$N$_2$O$_2$·HCl	B	50	NA	
31	4-C$_6$H$_5$	CH$_2$	Me	283–285	D	C$_{16}$H$_{18}$N$_2$·HCl	A	33	NA	
32			Et	233–234	A, B	C$_{16}$H$_{20}$N$_2$·HCl	A	24	NA	
33			Me	223–224	D	C$_{14}$H$_{16}$N$_2$·HCl	B	37	12.6 (7.8–20.5)	0.8 (0.3–2.2)
imipramine									13.0 (8.0–21.0)	0.7 (0.4–1.3)

[a] Key: A = 2-propanol; B = methyl ethyl ketone; C = acetone; D = ethanol; E = methanol; F = benzene. [b] Refers to route shown in Chart I. [c] For details, see the Experimental Section. The values in parentheses are 95% confidence intervals. [d] Isolated as the tosylate salt. [e] Tremors observed in mice: 1 out of 10 at 4.64 mg/kg; 3 in 10 at 10.0 mg/kg; 8 in 10 at 21 mg/kg. [f] NA = not active at 46 mg/kg.

Table II. Antidepressant Agents: Effect of Substituents on the Naphthalene Ring on Activity

compd	X	R	mp, °C	recryst[a] solvent	formula	method[b]	yield, %	reserpine ptosis, ip[e]	reserpine ptosis, po[f]	yohimbine potentiation, ip[e]
									ED$_{50}$,[c] mg/kg	
33	H	Me	223–224	B	C$_{14}$H$_{16}$N$_2$·HCl	B	37	12.6 (7.8–20.5)	17.1 (10.1–29.1)	0.8 (0.3–2.2)
34	H	Et	175–177	B, C	C$_{16}$H$_{20}$N$_2$·HCl	B	40	19.6 (10.0–36.0)	31.0 (23.0–59.0)	19.6 (12.2–31.4)
35	H	i-Pr	227–228	A	C$_{18}$H$_{24}$N$_2$·HCl	B	29	NA	NA	
36	1-Cl	Me	303–304.5 dec	B	C$_{14}$H$_{15}$ClN$_2$·HCl	C	68	11.0 (6.0–20.0)	15.0 (6.0–35.0)	26.1 (6.0–113)
37	1-Cl	Et	215–217	B, C	C$_{16}$H$_{19}$ClN$_2$·HCl·$^1/_2$H$_2$O	C	16	NA	41 (15.0–114)	31.6 (12.4–81.0)
38	6-OMe	Me	209–210	B	C$_{15}$H$_{18}$N$_2$O·HCl	C	62	19.0 (7.0–53.0)	23.7 (12.9–46.3)	NA
39	6-Me	Me	276–280 dec	B	C$_{15}$H$_{18}$N$_2$·HCl	C	69	19.6 (9.3–41.2)	31.6 (20.5–48.8)	NA
40	6-Me	Et	202–204	A, D	C$_{17}$H$_{22}$N$_2$·HCl	C	12	NA	NA	
41	3-Me	Me	310–315 dec	B	C$_{15}$H$_{18}$N$_2$·HCl	C	74	NA	26.1 (5.7–119)	
42	1-OH	Me	164–166	A	C$_{21}$H$_{24}$N$_2$O$_4$S[d]	C	47		23.7 (12.9–43.6)	
43	6-OH	Me	251–252 dec	B	C$_{14}$H$_{16}$N$_2$O·HCl	C	41.5		NA	
44	6-OH	Me	164.5–167	A	C$_{21}$H$_{24}$N$_2$O$_4$S·H$_2$O[d]	C	44			
imipramine								13.0 (8.0–21.0)	14.0 (5.8–33.6)	0.7 (0.4–1.3)

[a] Key: A = acetonitrile; B = ethanol; C = ether; D = ethyl acetate. [b] Refers to route shown in Chart I. [c] For details see the Experimental Section. The values in parentheses are 95% confidence intervals. [d] Tosylate salt. [e] NA = not active at 46 mg/kg. [f] NA = not active at 100 mg/kg.

(aryloxy)-N,N'-dialkylamidines. An N-alkylamide was treated with triethyloxonium fluoroborate, and the intermediate imidate fluoroborate (5) was reacted with the corresponding primary alkylamine.

A third procedure (method C) that was found to be convenient for the preparation of [^{13}C]-33[12] and for the scale-up of napactadine (33) utilized the imidate ester 6 as an intermediate. The intermediate (6) was prepared from the corresponding nitrile by the Pinner reaction.[13] Treatment of the imidate ester 6 with excess methylamine in warm ethanol led to the introduction of the first methylamino group instantaneously (to give 7, R = CH$_3$, R' = H) as determined by HPLC. Conversion of the N-methylamidine 7 to the N,N'-dimethylamidine 8 was a much slower process and was accomplished by heating the reaction at 50–55 °C until completion as indicated by HPLC. In addition, the reaction of 6 with ethylamine provided the N,N'-diethylamidines 8 (R = Et), albeit in much poorer yields.

It should be noted that three monohydroxy analogues of napactadine (33) (i.e., 42, 43, and 44) were prepared by method C for direct comparison with hydroxylated metabolites of 33 observed in rats and man. The starting materials for the preparation of these potential metabolites were the corresponding hydroxynaphthaleneacetonitriles. The synthesis of these prerequisite hydroxy nitriles was conveniently accomplished by treatment of the methyl ethers with sodium cyanide in Me$_2$SO. This demethylation procedure has been shown to be useful for a variety of aromatic methyl ethers.[14,15] One route to 2-hydroxy-1-naphthaleneacetonitrile was by way of a recently reported novel rearrangement.[16]

A number of N-substituted and N,N-disubstituted analogues of 33 (i.e., 8) were prepared by treatment of the imidate ester 6 with the appropriate amine at room temperature (method D, also outlined in Chart I).
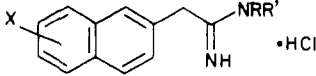
Results and Discussion

The N,N'-dialkylamidines initially prepared are listed in Table I. These compounds underwent primary evaluation for antidepressant activity by reserpine ptosis prevention in mice. While most clinically efficacious antidepressants have shown activity in this test,[17] secondary evaluation of active compounds by the potentiation of yohimbine lethality in mice[18] was carried out with the goal of avoiding false positives. Malick[19] found, with very few exceptions, antidepressants were the only agents that significantly enhanced the lethality induced by yohimbine.

The first compounds prepared were the (aryloxy)acetamidines 12–16. We were gratified to find the 3,4-dichloro analogue 15 active in both tests, supporting our hypothesis that N,N'-dialkylamidines could mimic the imidazoline ring. Unfortunately, this compound demonstrated undesirable central nervous system (CNS) effects at higher doses, particularly tremors. Substitution of 2,4-dichloro (14) for 3,4-dichloro exacerbated this problem, as noted

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Table III. Antidepressant Agents: Effect of Various Alkyl Groups on the Amidine Ring on Activity
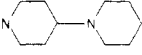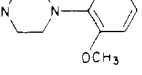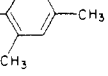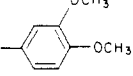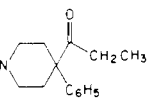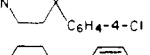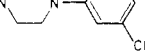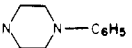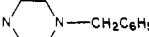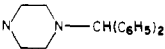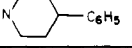

compd[a]	X	NRR'	mp, °C	recryst[b] solvent	formula	yield, %	ED$_{50}$, mg/kg: reserpine ptosis, po[g]
45	H	N(CH$_3$)CH$_2$CH$_2$OH	175–177	D	C$_{15}$H$_{18}$N$_2$O·HCl	18	19.6 (9.8–39.2)
46	H	(pyrrolidine)	233–234	D, F	C$_{16}$H$_{18}$N$_2$O·HCl	73	11.0 (6.9–17.7)
47	H	(N–CH$_3$ piperazine)	143–146	D	C$_{17}$H$_{21}$N$_3$·HCl·$^1/_2$H$_2$O	72	14.7 (6.2–35.0)
48	H	(piperidinyl-piperidine)	211–213 dec	D, F	C$_{22}$H$_{29}$N$_3$·HCl	70	40.8 (16.3–102)
49	H	(morpholine, O)	197	D*	C$_{16}$H$_{18}$N$_2$O·HCl	45	17.1 (10.5–27.8)
50	H	(azepane)	254–255	D*	C$_{18}$H$_{22}$N$_2$·HCl	67	11.0 (6.0–20.2)
51	H	(2,6-dimethylmorpholine CH$_3$, CH$_3$)	258–259	D*	C$_{18}$H$_{22}$N$_2$O·HCl	61	28.7 (15.4–53.6)
52	H	NH(CH$_2$)$_2$N(morpholine, O)	240–243	D	C$_{18}$H$_{23}$N$_3$O·2HCl	50	14.7 (8.6–25.0)
53	H	(4-phenylpiperidine C$_6$H$_5$)	179–184	D, E	C$_{23}$H$_{24}$N$_2$·HCl·$^1/_2$H$_2$O	25	14.7 (8.6–25.0)
54	H	(piperazine, 2-OCH$_3$ phenyl)	256–258	D*	C$_{23}$H$_{25}$N$_3$O·HCl	80	NA
55	H	(piperidine)	229–231	D*	C$_{17}$H$_{20}$N$_2$·HCl	79	11.0 (6.0–20.2)
56	H	NHCH$_2$-(CH$_3$, CH$_3$ phenyl)	161–163	B	C$_{21}$H$_{22}$N$_2$·HCl	64	NA
57	H	(N–C$_6$H$_5$ piperazine)	140–142	D*	C$_{22}$H$_{23}$N$_3$·HCl·$^1/_2$H$_2$O	68	NA
58	H	NH(CH$_2$)$_2$-(OCH$_3$, OCH$_3$ phenyl)	103–105	B	C$_{22}$H$_{24}$N$_2$O$_2$·HCl	68	NA
59	H	(piperidine CH$_2$C$_6$H$_5$, OH)	260–261	D*	C$_{24}$H$_{26}$N$_2$O·HCl	83	22.5 (12.6–35.5)
60	H	(piperidine C=O, CH$_2$CH$_3$, C$_6$H$_5$)	251–252.5	D*	C$_{26}$H$_{28}$N$_2$O·HCl	83	NA
61	H	NHCH(CH$_3$)$_2$	91–94	C	C$_{15}$H$_{18}$N$_2$·HCl·H$_2$O	45	NA
62	H	NHCH$_3$	145–147	B	C$_{20}$H$_{22}$N$_2$O$_3$S[d]	21	22.5 (12.6–35.5)[e]
63	1-Cl	(pyrrolidine)	>270 dec	D	C$_{16}$H$_{17}$ClN$_2$·HCl·H$_2$O	33	2.9 (1.5–5.7)
64	1-Cl	(morpholine, O)	230–232	D*	C$_{16}$H$_{17}$ClN$_2$O·HCl	53	15
65	1-Cl	NH(CH$_2$)$_3$N(morpholine, O)	228–231	A	C$_{19}$H$_{24}$ClN$_3$O·2HCl	34	3.2 (1.2–8.1)
66	1-Cl	(4-phenylpiperidine C$_6$H$_5$)	250 dec	D*	C$_{23}$H$_{23}$ClN$_2$·HCl	77	8.8 (3.5–22.0)
67	1-Cl	(piperidine OH, C$_6$H$_5$)	216–218	D	C$_{23}$H$_{23}$ClN$_2$O·HCl	73	24.5 (9.8–61.3)
68	1-Cl	(piperidine CH$_2$C$_6$H$_5$)	237–239	D	C$_{24}$H$_{25}$ClN$_2$·HCl	57	19.6 (9.3–41.2)
69	1-Cl	(piperidine OH, C$_6$H$_4$-4-Cl)	227–229	D*	C$_{23}$H$_{22}$Cl$_2$N$_2$O·HCl	34	10.8 (6.6–17.5)
70	1-Cl	(piperazine, 3-Cl phenyl)	240–243	D*	C$_{22}$H$_{21}$Cl$_2$N$_3$·HCl	63	16.2 (10.0–32.8)

Table III (Continued)

compd[a]	X	NRR'	mp, °C	recryst[b] solvent	formula	yield, %	ED$_{50}$, mg/kg: reserpine ptosis, po[g]
71	1-Cl		262–263	D*, A	C$_{22}$H$_{22}$ClN$_3$·HCl	83	16.2 (8.0–29.2)
72	1-Cl		214–215	D*	C$_{23}$H$_{24}$ClN$_3$·HCl	65	NA
73	1-Cl		100 dec	E	C$_{29}$H$_{27}$Cl$_2$N$_3$·HCl	67	NA
74	6-OMe		282–283	D*	C$_{17}$H$_{20}$N$_2$O·HCl	84	NA
75	6-OMe		210–213	D*	C$_{24}$H$_{26}$N$_2$O·HCl	66	NA

[a] All compounds were prepared by method D. [b] Key: A = 2-propanol; B = acetonitrile; C = water; D = ethanol, an asterisk indicates product crystallized directly from the ethanolic reaction mixture; E = ethyl acetate; F = ether. [c] For details see the Experimental Section. The values in parentheses are 95% confidence intervals. [d] Dihydrochloride salt. [e] Tosylate salt. [f] Ip dosage form. [g] NA = not active at 100 mg/kg.

in Table I, while 2,4,5-trichloro substitution resulted in the loss of activity in the reserpine ptosis test.

Extension of 3,4-dichloro substitution to a benzamidine series (11) and acetamidine series (23) led to additional classes of N,N'-dialkylamidines with activity in both tests.

The biological results listed in Table I indicate that slight modification of the series caused a marked change in activity in the reserpine ptosis test. Chloro, nitro, and trifluoromethyl groups on the aromatic ring generally provided active analogues, while methyl and methoxy substituents led to weakly active to inactive compounds. The exception to this trend was the introduction of a chlorine in the 2-position, which caused a decrease or loss of activity. Direct attachment of fluorine to the aromatic ring also resulted in the loss of activity (see 17). In general, N,N'-dimethylamidines were more active than the corresponding N,N'-diethyl analogues, whereas N,N'-diisopropyl substitution (see 35, Table II) caused complete loss of activity.

The compounds of most interest (10, 11, 18, 23, 29, and 33), which included a 3,4-dichloro-substituted benzamidine and acetamidine, were evaluated in greater detail. These compounds were selected for further evaluation because of their potency in inhibiting reserpine ptosis, for their potentiation of yohimbine lethality, and for their lack of tremors and other undesirable CNS side effects on acute administration to mice. None of these compounds potentiated tryptamine convulsions in rats, which indicated the lack of monoamine oxidase inhibition.[20] The intraperitoneal (ip) and oral (po) LD$_{50}$'s were determined for each of these compounds in mice, and therapeutic indices with respect to reserpine ptosis antagonism were obtained. In addition, the compounds were tested for their ability to block electric shock induced aggression in male mice; this test is indicative of anxiolytic activity.[21] Table IV presents a summary of this data.

As seen from the data in Table IV, 3,4-dichloro substitution on the aromatic ring in both the benzamidine series (11) and acetamidine series (23) gave compounds with the lowest therapeutic index. Eliminating the *m*-chloro group in the benzamidine series (i.e., 10) approximately doubled the therapeutic index, while the substitution of the 4-chlorobenzamidine nucleus by the corresponding acetamidine nucleus (18) quadrupled the oral therapeutic index. Moreover, substitution of 4-nitro (29)

for 4-chloro (18) approximately doubled the oral therapeutic index again. However, the 4-nitro group rendered the molecule inactive in blocking [^{14}C]norepinephrine uptake by rat cerebral cortex slices, whereas all the other compounds in Table IV were active in this test (data not shown).[22] Comparison of the biological data presented in Table IV for this series of compounds indicated that 18 and 33 (napactadine) were of the most interest. They potentiated yohimbine lethality, inhibited electric shock aggression, and prevented norepinephrine uptake.[22] Since mental depression may be due to abnormal levels of central monoamines,[23] these two compounds have a good potential as antidepressant agents. Further evaluation of both amidines in mice and dogs showed that 18 produced significant increases in mean arterial blood pressure when administered intravenously, while napactadine (33) had no effect. Therefore, the structure–activity relationship of analogues of 33 (napactadine) was studied in greater depth. Addition of substituents on the naphthalene ring decreased activity (see Table II). The monosubstituted N-methyl analogue (62) was less active than the parent compound as were the N,N'-diethyl- (34) and N,N'-diisopropyl- (35) amidines. The position of the N,N'-dimethylacetamidine group on the naphthalene ring was critical as seen from the inactivity of 1-substituted derivatives 32 and 44. A number of analogues of 33 (napactadine) were prepared by making additional changes on the amidine functional group (see Table III). The compounds in Table III that showed potential antidepressant activity had a heteroatom in the N-alkyl chain or had the N-alkyl chain as part of a heterocyclic ring. In this series, the 1-chloro-substituted derivatives were more active than the corresponding unsubstituted compounds. However, this substitution caused tremors in many cases. Substitution of a methoxy group in the 6-position of the naphthalene ring abolished activity in the reserpine ptosis test, as did a similar substitution in the phenylacetamidine series. Only three of the naphthalene series compounds, 46, 68, and 69, were active in the potentiation of yohimbine lethality.

Compound 33 (napactadine) was selected for clinical study. Preliminary unreported results indicated a marked improvement in depressive symptomalology within 7 days of treatment, as measured by the Hamilton depression scale. However, clinical studies were discontinued after

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Table IV. Summary of Pharmacological Activity of Selected N,N'-Dialkylamidines[a]

compd	LD50(mouse), mg/kg		antag of reserpine ptosis (mouse): ED50, mg/kg		ther index (mouse)		pot. of yohimbine lethality: ED50, ip mg/kg	elec shock aggression: ED50, mg/kg ip
	ip	po	ip	po	ip	po		
10	108 (74.1–155)	200 (137–291)	6.8 (2.6–17.7)	6.2 (3.1–12.5)	16	32	6.0 (3.2–11.1)	NA[b]
11	60	215 (134–344)	9.3 (6.4–13.5)	10.8 (6.7–17.5)	6	20	2.4 (1.4–3.9)	43 (26.5–69.8)
18	69.4 (58.4–108)	430 (265–698)	2.3 (1.4–3.8)	3.4 (1.5–7.8)	30	127	15.0 (6.8–33.0)	NA[b]
23	31.6 (20.5–48.8)	90 (60–153)	9.3 (5.7–15.0)	12.6 (7.8–20.5)	3	7		NA[b]
29	215 (138–336)	681 (441–1050)	3.2 (2.1–4.9)	3.2 (2.1–4.9)	67	213	20.0 (9.1–44.0)	12.6 (7.4–21.4)
33	68.1	584 (430–794)	12.6 (7.8–20.5)	17.1 (10.1–29.1)	5	34	0.8 (0.3–2.2)	23.0 (14.2–39.5)
imipramine	107 (52–222)	354 (183.8–8885)	13.0 (8–21)	14.0 (5.8–33.6)	8	25	0.7 (0.4–1.3)	

[a] For details see the Experimental Section. The values in parentheses are 95% confidence intervals. [b] No aggression blockade at 46.4 mg/kg.

chronic administration of napactadine (**33**) because an elevation in liver enzyme levels was observed in some patients. More detailed discussions of the pharmacology[24] and biochemistry[25] of **33** (napactadine) have been published.

Experimental Section

Chemistry. The amidines prepared are listed in Tables I–III. Examples of each general procedure (methods A–D) are given below. Elemental analyses were performed by Midwest Microlab or by Steve Konopnicki, Analytical Labs, The Dow Chemical Co., Midland, MI, and were satisfactory (±0.4%). All melting points are uncorrected. The IR spectra were recorded with a Perkin-Elmer Model 727 spectrophotometer. NMR spectra were determined with a Varian T-60 and a Perkin-Elmer R32 (90 MHz) instrument. Thin-layer chromatography (TLC) was run with Quantum Q1F silica gel plates.

N,N'-Diethyl-2-(3,4-dichlorophenyl)ethanimidamide Hydrochloride (23). Method A. A solution of 3,4-dichlorobenzeneacetonitrile (18.6 g, 0.1 mol) and triethyloxonium fluoroborate (21 g, 0.11 mol) in 150 mL of dry CH_2Cl_2 was heated at 35–45 °C (bath temperature) for 72 h. The light yellow solution was cooled in a dry-ice bath, 10 g (0.22 mol) of $EtNH_2$ was added, and the reaction was allowed to stand at room temperature overnight. The solution was evaporated, suspended in a small volume of ice water, made strongly alkaline with 20% aqueous NaOH, and extracted with EtOAc (5 × 20 mL). The combined organic layer was dried (Na_2SO_4) and acidified with HCl gas. The precipitated product was removed by filtration, and the filtrate was evaporated and triturated with acetone providing a second crop of product. The combined solids were crystallized from i-PrOH–acetone, yielding **23** as white crystals: 10.0 g (34%); mp 231–232 °C; NMR (Me_2SO-d_6) δ 1.14 (5 lines, 2 overlapping t, 6, J = 7 Hz, 2 CH_2CH_3), 3.4 (2 overlapping q, 4, 2 CH_2CH_3), 4.18 (s, 2, $C_6H_5CH_2$), 7.3–7.8 (ABX pattern, 3, aromatic H); IR (Nujol) 1660 (C=N), 875, 825 cm^{-1} (1,2,4-substituted benzene). Anal. ($C_{12}H_{16}Cl_2N_2$·HCl) C, H, N.

N,N'-Dimethyl-2-(4-biphenylyl)ethanimidamide Hydrochloride (31). Method A. A solution of 4-biphenylacetonitrile (19.3 g, 0.1 mol) and trimethyloxonium fluoroborate (15 g, 0.1 mol) in 75 mL of dry CH_3NO_2 (stored over 4A molecular sieves) (or a mixture in 75 mL of dry CH_2Cl_2) was stirred and heated at 40–45 °C (bath temperature) for 96 h. The reaction was cooled in a dry-ice bath, and 15 g (0.5 mol) of CH_3NH_2 was bubbled into the solution. After standing overnight at room temperature, the solution was evaporated, made strongly alkaline with cold 20% aqueous NaOH, extracted with EtOAc (5 × 20 mL), and dried over $MgSO_4$ for 24 h. The drying agent and a small amount of insoluble yellow material were removed by filtration, and the filtrate was acidified with HCl gas. The light yellow product (9.0 g, 33%) was collected by filtration. Recrystallization of a small amount of **31** from ethanol gave an analytically pure sample: mp 283–285 °C; NMR (Me_2SO-d_6-D_2O) δ 2.90 (s, 6, 2 CH_3), 4.0 (s, 2, CH_2), 7.1–7.6 (m, 9, aromatic); IR (Nujol) 1675 (C=N), 822 (para-substituted phenyl), 760 cm^{-1} (monosubstituted phenyl). Anal. ($C_{16}H_{12}N_2$·HCl) C, H, N.

N,N'-Diethyl-2-(2,4,5-trichlorophenoxy)ethanimidamide Hydrochloride (16). Method B. A mixtue of N-ethyl-2-(2,4,5-trichlorophenoxy)acetamide (14.1 g, 0.05 mol) (mp 115–117 °C, from benzene), triethyloxonium fluoroborate (19 g, 0.1 mol), anhydrous Na_2CO_3 (5 g), and dry CH_2Cl_2 (150 mL) was stirred at room temperature for 15 h. The reaction mixture was cooled in a dry-ice bath, 10 g (0.22 mol) of $EtNH_2$ was bubbled into the reaction, and the mixture was allowed to stand overnight at room temperature. The solvent was evaporated, and the resulting solid was suspended in a small volume of cold water, made strongly alkaline with 20% aqueous NaOH, and extracted with EtOAc (5 × 20 mL). The dried (Na_2SO_4) combined organic phase was acidified with HCl gas, and the resulting white solid was removed by filtration. The solid was crystallized from EtCOMe to yield **16** as fluffy white crystals: 9.5 g (55%); mp 182–183 °C; NMR

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(CDCl$_3$) δ 1.38 (2 t offset by 2 Hz, 6, J = 6 Hz, 2 CH$_2$C*H*$_3$), 3.67 (m, 4, 2 C*H*$_2$CH$_3$), 5.3 (s, 2, OCH$_2$), 7.45 and 7.57 (2 s, 2 aromatic H); IR (Nujol) 1675 (C=N), 878 cm^{-1} (isolated aromatic H). Anal. (C$_{12}$H$_{15}$Cl$_3$N$_2$O·HCl) C, H, N.

6-Hydroxy-*N*,*N*'-dimethyl-2-naphthaleneethanimidamide Hydrochloride (43). Method C. 6-Hydroxy-2-naphthalene-acetonitrile[14] (6.4 g, 0.035 mol) was added to a four-necked 500-mL round-bottom flask (previously dried at 140 °C) with overhead stirrer, gas addition tube, and N$_2$ bubbler. Anhydrous ether (200 mL) and absolute ethanol (1.9 g, 0.041 mol) were added, and the mixture was saturated with anhydrous HCl gas while keeping the inside temperature below 15 °C with an ice bath. The mixture was stirred with an overhead stirrer under a N$_2$ atmosphere. The reaction was monitored by TLC (chloroform), and after 3 days one spot was observed at the origin. The reaction was diluted with an equal volume of hexane, and the white crystals were collected on a sintered-glass Buchner funnel. The imidate ester was dissolved in 175 mL of absolute ethanol, and N$_2$ was bubbled through the light yellow solution for 20 min (to prevent quinone methide formation). The reaction was then saturated with methylamine gas, heated at 55 °C (bath temperature) for 24 h under a static N$_2$ atmosphere, and evaporated to dryness. The resulting light tan solid was triturated with ethyl acetate and recrystallized 2X from 50 mL of ethanol. The white crystals of the 6-hydroxy amidine 43 (3.85 g, 41.5%) were collected by filtration: mp 251–252 °C dec; IR (Nujol) 855, 800 cm^{-1}; NMR (Me$_2$SO-d_6) δ 2.87 (s, 3, CH$_3$), 2.95 (br s, 3, CH$_3$), 4.13 (s, 2, CH$_2$), 7.1–7.8 (m, 6), 9.2 (br s, 1, exchangeable H). Anal. (C$_{14}$H$_{16}$N$_2$O·HCl) C, H, N.

α-(2-Naphthalenylmethyl)-1-pyrrolidinemethanimine Hydrochloride (46). Method D. Ethyl 2-naphthaleneethanimidate hydrochloride (6, X = H) (10 g, 40 mmol) (prepared as 6, x = 6-OH in preparation of 43) and pyrrolidine (3.55 g, 50 mmol) were added to ethanol (100 mL), and the resulting solution was left at room temperature for 15 h. The colorless solution was evaporated to dryness, yielding a white solid that was triturated with ether and collected by filtration (11.0 g). Recrystallization from ethanol–ether (50–60 mL) gave white crystals of 46: 8.0 g (73%); mp 223–224 °C; IR (Nujol) 1680, 1630 cm^{-1}. Anal. (C$_{16}$H$_{18}$N$_2$·HCl) C, H, N.

Pharmacology. Acute Toxicities. Male albino mice (Swiss–Webster strain, Spartan Research Animals, Inc., Haslett, MI) weighing 20–24 g were used in this study. Mice were randomly divided into groups of five. Each group was injected intraperitoneally with a different dose of the test compound and placed in individual plastic observation cages. The volume of the dose administered was 10 mL/kg. After approximately 5 h, members of each group were housed together with food and water, ad libitum. The number of deaths were recorded at 1 and 24 h post-drug. Oral toxicity was determined similarly in mice, which were fasted 18 h, water ad libitum. All drugs were dissolved in saline 30 min before injection. The LD$_{50}$s were calculated according to the method of Litchfield and Wilcoxon.[26]

Reserpine Antagonism Test. Male mice (Swiss–Webster strain, Spartan Research Animals, Inc., Haslett, MI, or Harlan ICR strain, Harlan Sprague–Dawley Inc., Indianapolis, IN) were used throughout these studies. Test drugs were dissolved in saline and administered orally or intraperitoneally. Thirty minutes later, reserpine was administered (2.5 mg/kg, ip). The complete absence of ptosis 45 min after reserpine injection was recorded as a positive response. Five mice were used for each dose of drug. The ED$_{50}$s were calculated according to the method of either Litchfield and Wilcoxon[26] or Horn.[27]

Electric Shock Induced Aggression.[21] Two mice were put under an inverted beaker (1000 cm^3) and shocked via the floor grid (3 mA, 3 Hz) for 2 min to induce aggression. Mice were injected with experimental compounds (ip) 30 min before testing. Results were recorded on an all or none basis. The mean number of animals fighting in the drug-treated groups was compared to that of the saline treated group. Test compounds were considered to inhibit fighting if the mean number of attacks (X) was 1.5 times the standard deviation (SD) less than the mean of the vehicle treated groups (i.e., X – 1.5 SD).

Potentiation of Yohimbine Hydrochloride Lethality in Mice.[18] Male mice (Swiss–Webster Strain, Spartan Research Animals, Inc., Haslett, MI, or Harlan Sprague–Dawley Inc., Swiss ND/4, Indianapolis, IN) weighing 20–24 g were used in this study. Mice were divided at random into different groups (10 mice per group) and aggregated in plastic cages (4 in. × 4 in. × 5 in., five mice per cage). Test compounds were dissolved in saline and administered intraperitoneally; one group received saline and served as a control. Thirty minutes later, mice were injected with yohimbine hydrochloride (20 mg/kg, sc) and reaggregated. Two hours after yohimbine administration the number of deaths was recorded. If 20% or more of saline-pretreated group died, the experiment was discarded.

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