surface of the mucosa; 3 = ulcerations of generalized diffusion, involving two-thirds or more of the whole surface of the mucosa; 4 = perforated ulcers.

Statistics. Percent inhibitions were calculated by comparison to control values, and statistical evaluation was made according to Student's *t* method.[21]

Acute Lethal Toxicity. Approximate LD_{50} values were determined in CF-1 male mice (Charles River strain), weighing 20–23 g, arranged in groups of three at each dose (30, 100, 300, and 1000 mg/kg). The observation of lethality was continued over a period of 5 days.

Acknowledgment. The authors are grateful to E. Gerli for expert assistance in the synthetic work, to A. Depaoli for helpful discussions of NMR spectra, and to Dr. G. Tarzia for the revision of the manuscript. We also thank Dr. M. Croci for his valuable contribution as Project Manager of compound **35**.

Registry No. **2**, 131-91-9; **3a**, 32600-54-7; **3b**, 76145-86-3; **3c**, 88842-16-4; **3d**, 76145-77-2; **3e**, 39159-58-5; **3f**, 88842-17-5; **3g**, 39159-59-6; **3h**, 88842-18-6; **3i**, 88842-19-7; **3j**, 76145-85-2; **3k**, 81288-65-5; **3l**, 88842-20-0; **6a**, 88842-21-1; **6b**, 606-57-5; **7**, 76145-46-5; **8**, 76145-51-2; **9**, 76145-47-6; **10**, 10250-30-3; **11**, 76145-68-1; **12**, 76145-70-5; **13**, 76145-74-9; **13** (ethyl ester), 76145-73-8; **14**, 76145-72-7; **15**, 76145-48-7; **16**, 76145-50-1; **17**, 76145-49-8; **18**, 76145-59-0; **19**, 76145-60-3; **20**, 76145-65-8; **21**, 76145-67-0; **22**, 76145-58-9; **23**, 76145-64-7; **24**, 76145-62-5; **25**, 88842-22-2; **26**, 88842-23-3; **27**, 76145-57-8; **28**, 76145-56-7; **29**·HCl, 88842-24-4; **30**·2HCl, 88842-25-5; **31**, 76166-09-1; **32**, 88854-00-6; **33**, 76145-87-4; **34**, 88842-26-6; **35**, 76145-76-1; **36**, 76145-78-3; **37**, 88842-27-7; **38**, 88842-28-8; **39**, 88842-29-9; **40**, 88842-30-2; **41**, 88842-31-3; **42**·HCl, 88842-32-4; **43**, 81288-63-3; **44**, 88842-33-5; **45**, 81288-62-2; **46**, 88842-34-6; C_6H_5CHO, 100-52-7; 3-ClC_6H_4CHO, 587-04-2; 4-ClC_6H_4CHO, 104-88-1; 2-HOC_6H_4CHO, 90-02-8; 4-HOC_6H_4CHO, 123-08-0; 2-$CH_3OC_6H_4CHO$, 135-02-4; 3-$CH_3OC_6H_4CHO$, 591-31-1; 4-$CH_3OC_6H_4CHO$, 123-11-5; 4-$C_2H_5OC_6H_4CHO$, 10031-82-0; 4-$(CH_3)_2CHOC_6H_4CHO$, 18962-05-5; 4-$CH_3C_6H_4CHO$, 104-87-0; 4-$AcNHC_6H_4CHO$, 122-85-0; 4-$(CH_3)_2NC_6H_4CHO$, 100-10-7; 3-CH_3-4-$CH_3OC_6H_3CHO$, 32723-67-4; 3,4-$OCH_2OC_6H_3CHO$, 120-57-0; 3-CH_3-4-$(CH_3)_2NC_6H_3CHO$, 1424-69-7; 3,5-$(CH_3)_2$-4-$(CH_3)_2NC_6H_2CHO$, 76166-10-4; 2-$CH_3C_6H_4N(CH_3)_2$, 609-72-3; 2,6-$(CH_3)_2C_6H_3N(CH_3)_2$, 769-06-2; 2-chloro-1-nitronaphthalene, 4185-63-1; ethyl bromoacetate, 105-36-2; 3-(2-chloroethyl)-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazole, 81288-64-4; 3-(2-chloro-1-methylethyl)-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazole, 88842-35-7; 2-thiophenecarboxaldehyde, 98-03-3; 2-pyrrolecarboxaldehyde, 1003-29-8; 2-pyridinecarboxaldehyde, 1121-60-4; 3-pyridinecarboxaldehyde, 500-22-1; 4-pyridinecarboxaldehyde, 872-85-5.

(21) Herrington, M. *Biometrika* 1942, 32, 300.

Synthesis and Central Nervous System Properties of 2-[(Alkoxycarbonyl)amino]-4(5)-phenyl-2-imidazolines[1]

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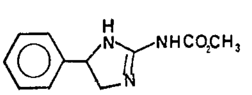
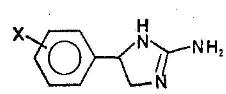
Institutes of Organic Chemistry and of Pharmacology and Metabolism, Syntex Research, Palo Alto, California 94304.
Received July 18, 1983

A series of 2-[(alkoxycarbonyl)amino]-4(5)-phenyl-2-imidazolines was prepared and evaluated for central nervous system (CNS) effects (antidepressant, anticonvulsant, muscle relaxant, and depressant) in animal models. Some separation of those CNS activities was achieved through substitutions on the phenyl and imidazoline moieties. Halo-substituted phenyl compounds were among the most potent antidepressants in this series, while imidazole N-alkylation produced compounds with increased depressant effects (loss of righting reflex, mouse behavior). Comparison of in vitro and in vivo data for pairs of 2-[(methoxycarbonyl)amino]-4(5)-phenyl-2-imidazolines and their parent, 2-amino-4(5)-phenyl-2-imidazolines, suggests that the title compounds were prodrugs for the 2-amino-4(5)-phenyl-2-imidazolines in inhibition of norepinephrine reuptake.

Through general screening in the mouse behavior assay we determined that 2-[(methoxycarbonyl)amino]-4-phenyl-2-imidazoline (1) demonstrated an antidepressant



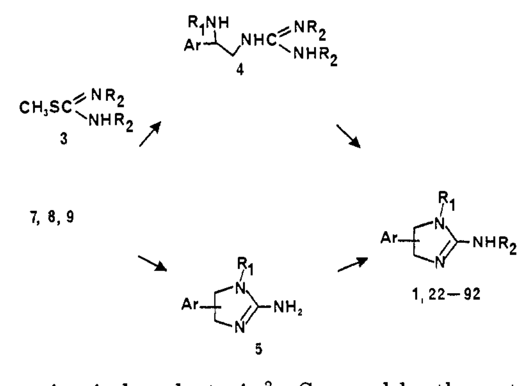
1



2

profile. Extensive pharmacological reports on compounds 1 and 49 have been published.[2ab] The parent 2-amino-4-aryl-2-imidazolines 2 had been reported as antihypertensive agents, and several members of that series also exhibited significant CNS activity through the prevention of reserpine-induced ptosis.[3] Spurred by the potential therapeutic utility implicit in the animal pharmacology of 1 and also by the structure–activity correlations that had been determined for the parent system 2, we decided to

Scheme I



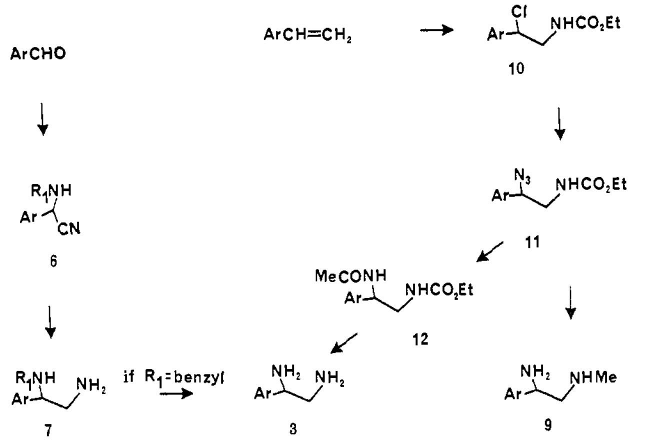
(1) Contribution no. 655 from the Institute of Organic Chemistry.

(2) (a) Wallach, M. B.; Roszkowski, A. P.; Waterbury, L. D. "Advances in Pharmacology and Therapeutics", Proceedings of the International Congress of Pharmacology, 7th, Paris, July 16–21, 1978; Pergamon Press: Oxford, 1979; Abstr 623, p 247. Pinder, R. M., *Annu. Rep. Med. Chem.* 1979, 14, 5–6. (b) Wallach, M. B.; Alps, B. J.; Roszkowski, A. P.; Waterbury, L. D. *Prog. Neuro-Psychopharmacol.* 1981, 4, 569. Bondinell, W. E.; Kaiser, C. *Annu. Rep. Med. Chem.* 1982, 17, 44.

(3) Matier, W. L.; Owens, D. A.; Comer, W. T.; Deitchman, D.; Ferguson, H. C.; Seidehamel, R. J.; Young, J. R. *J. Med. Chem.* 1973, 16, 901.

0022-2623/84/1827-0616$01.50/0

Scheme II



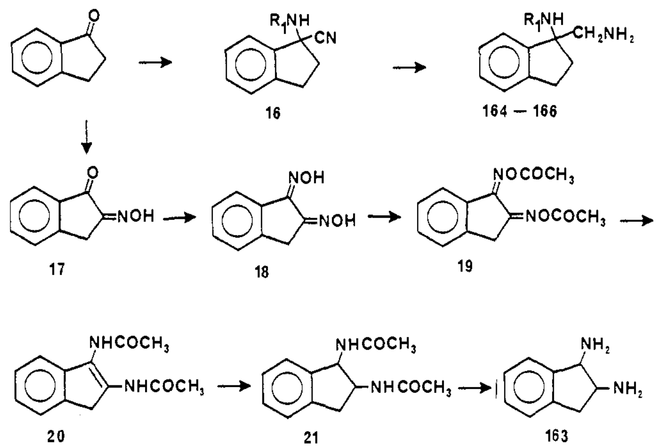
explore modifications of 1[4] in order to define a full range of substituent effects on biological activity in that system.

Chemistry. The 2-[(alkoxycarbonyl)amino]-4(5)-phenyl-2-imidazolines 1 and 22–102 (Table I) were prepared by condensation of the corresponding phenylethanediamines 7–9 with the bis(alkoxycarbonyl) derivatives of 2-methyl-2-thiopseudourea 3 (Scheme I). The uncyclized intermediates 4 were isolated only in the few cases (Table II, 160–162) for which the formation of imidazolines was apparently slowed by steric hindrance. Typically, the diamines as their dihydrochloride salts were dissolved in water, treated with sodium bicarbonate, and then combined with a solution of the cyclizing agents 3 in organic solvents and reacted either at room temperature for several days or at elevated temperatures for a few hours. The most convenient method for the preparations of compounds 1 and 22–53 (R_1 = H) was found to consist to simply combining solutions of the free amines and of the cyclizing agents in organic solvents (alcohols, ethers, etc.) and collecting the products, which crystallized from these solvents. The *N*-alkyl analogues 54–92 and 99–101 (R_1 = alkyl), which were much more soluble, required a more extensive workup. Those diamines that did not cyclize easily with 3 were reacted first with cyanogen bromide, and the resulting 2-amino-4(5)-phenylimidazolines 5 were then carbomethoxylated by reaction with dimethyl carbonate. Reaction of 1,2-diaminoindan (163) with cyanogen bromide led to mixtures, from which the product 95 could only be isolated with difficulty. The 2-amino indanoimidazoline 95 was better prepared by fusion of the indandiamine with the sulfate salt of 2-methyl-2-thiopseudousea. Phenolic imidazolines 43, 51, and 74 and the *N*-(2-hydroxyethyl) analogue 88 were prepared by hydrogenolysis of the *O*-benzyl-protected precursors 44, 52, 75, and 89, respectively.

Some additional functional group transformations of phenyl substituents were also carried out after the imidazoline moiety had been fully elaborated. The methylthio substituent of compounds 72 and 80 was oxidized to methylsulfinyl with sodium periodate. The hydroxymethyl group of 76 was oxidized to formyl with manganese dioxide. Further oxidation of the aldehyde function of 78 with manganese dioxide and sodium cyanide in methanol afforded the methyl benzoate 79. We were not successful in converting the aldehyde function of 78 to a nitrile by a number of known methods (dehydration of the oxime with Ac_2O; DCC; trimethyl orthoformate and DCC–Et_3N–$CuSO_4$).

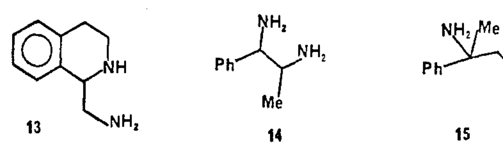
(4) Roszkowski, A. P.; Beard, C. C.; Dvorak, C.; Weinhardt, K. U.S. Patent 4088771, 1978.

Scheme III



The method of choice for the preparation of the intermediate primary 1-phenylethanediamines 8 was a Strecker synthesis of benzaldehydes with benzylamine, followed by LAH reduction of the α-amino nitriles 6 and hydrogenolysis of *N*-benzylamines as discussed by Matier.[3] Ammonium chloride was used instead of benzylamine in the Strecker synthesis of the 4-(benzyloxy)phenyl- and the 3,4-(methylenedioxy)phenyl-substituted ethanediamines. The *N*-benzyl group of compounds 7 was removed by hydrogenolysis over Pd/C. The hydroxyphenyl diamine 126 could be obtained by simultaneous O- and N-debenzylation of diamine 125. The diamine required for the synthesis of the benzylimidazole 102 was obtained via the same sequence of reactions, starting from phenylacetaldehyde.

When the *N*-alkyl-1-phenyl-1,2-ethanediamines 7 were required, the corresponding alkylamines were used in place of benzylamine in the Strecker synthesis. The same sequence of reactions was applied to the synthesis of 1-amino-1-(aminomethyl)indans 164–166, starting from 1-indanone. The synthesis of 1-amino-1-(aminomethyl)indan (165) by a slightly different route has been published.[5] 1,2-Diaminoindan (163) was also prepared from 1-indanone (Scheme III) and was obtained with ease as its dihydrochloride salt (hydrolysis of 21, the diacetyl derivative of 163), a finding at variance with the literature.[6] The 1-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline (13) was the

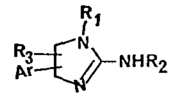


intermediate for the imidazolines 100 and 101 and was synthesized from isoquinoline according to Leonard and Leubner.[7] Two known phenyl-substituted propane-1,2-diamines, 14 and 15, were prepared by modifications of published procedures.[8,9]

Since the hydrogenolysis conditions that are used to effect N-debenzylation (Pd/C) were incompatible with aromatic chlorine and bromine substituents, diamines 8 with these substituents were prepared (Scheme II) starting

(5) Granger, R.; Techer, H. *C. R. Hebd. Seances Acad. Sci.* **1960**, *250*, 2581–3; *Chem. Abstr.* **1961**, *55*, 17593*i*.
(6) Veibel, S.; Nielsen, T. I. *K. Dan. Vidensk. Selsk. Mat.-Fys. Medd.* **1966**, *35*(6), 1–32; *Chem. Abstr.* **1967**, *67*, 21898*x*.
(7) Leonard, N. J.; Leubner, G. W. *J. Am. Chem. Soc.* **1949**, *71*, 3405.
(8) Moriguchi, S.; Ose, S.; Takamatsu, H. *Yakugaku Zasshi* **1962**, *82*, 1226–9; *Chem. Abstr.* **1963**, *59*, 594*e*.
(9) Granger, R.; Orzalesi, H.; Robe, Y. *Trav. Soc. Pharm. Montpellier* **1965**, *24*(4), 244–55; *Chem. Abstr.* **1966**, *64*, 14104*b*.

Table I. 2-Substituted 4(5)-Aryl-2-imidazolines



no.	Ar	position of Ar	R_1	R_2	R_3	formula (free base)	mp,[a] °C free base	mp,[a] °C salt[d]	crystn solvent[b] base	crystn solvent[b] salt	lipophilicity:[c] log k'
1	Ph	4(5)	H	CO_2CH_3	H	$C_{11}H_{13}N_3O_2$	210-211[e]	168	B	C	-0.19
22	Ph	4(5)	H	$COCH_2CH_3$	H	$C_{12}H_{15}N_3O_2$	210-211		B		0.17
23	Ph	4(5)	H	$CO_2CH_2CH(CH_3)_2$	H	$C_{14}H_{19}N_3O_2$	192-193		I		0.94[f]
24	2-CH_3Ph	4(5)	H	CO_2CH_3	H	$C_{12}H_{15}N_3O_2$	218-219	117-118[g]	D	BG	0.16
25	3-CH_3Ph	4(5)	H	CO_2CH_3	H	$C_{12}H_{15}N_3O_2$[e]	242-247	162-163	H	BG	0.26
26	4-CH_3Ph	4(5)	H	CO_2CH_3	H	$C_{12}H_{15}N_3O_2$	205-207	180-184	C	BG	0.30
27	2-FPh	4(5)	H	CO_2CH_3	H	$C_{11}H_{12}N_3O_2F$	203-204	144-146[e]	C	BG	-0.09
28	3-FPh	4(5)	H	CO_2CH_3	H	$C_{11}H_{12}N_3O_2F$	206-207	142-143[e,h]	D	tG	-0.10
29	2-ClPh	4(5)	H	CO_2CH_3	H	$C_{11}H_{12}N_3O_2Cl$	203-204[e]	160-162	D	BG	0.29
30	3-ClPh	4(5)	H	CO_2CH_3	H	$C_{11}H_{12}N_3O_2Cl$	197-198	163-164[i]	C	BG	0.40[f]
31	3-ClPh	4(5)	H	$CO_2CH(CH_3)_2$	H	$C_{13}H_{16}N_3O_2Cl$	194-196		C		0.95[f]
32	4-ClPh	4(5)	H	CO_2CH_3	H	$C_{11}H_{12}N_3O_2Cl$	220-222		C		0.31
33	4-ClPh	4(5)	H	$CO_2(CH_2)_5CH_3$	H	$C_{16}H_{22}N_3O_2Cl$	201-203		A		2.18[f]
34	2-BrPh	4(5)	H	CO_2CH_3	H	$C_{11}H_{12}N_3O_2Br$	203-204	156-159	C	BG	0.47
35	3-BrPh	4(5)	H	CO_2CH_3	H	$C_{11}H_{12}N_3O_2Br$	207-208	173-174	C	BG	0.50[f]
36	3-BrPh	4(5)	H	$CO_2CH_2CH_3$	H	$C_{12}H_{14}N_3O_2Br$	191-193		B		0.77[f]
37	4-$(CH_3)_2$CHPh	4(5)	H	CO_2CH_3	H	$C_{14}H_{19}N_3O_2$	213-215		C		0.99[f]
38	4-$(CH_3)_2$CHPh	4(5)	H	$CO_2CH_2CH_3$	H	$C_{15}H_{21}N_3O_2$	200-201[j]		D		1.30[f]
39	4-$CH_3(CH_2)_5$Ph	4(5)	H	CO_2CH_3	H	$C_{17}H_{25}N_3O_2$	188-189		J		2.28[f]
40	2-PhPh	4(5)	H	CO_2CH_3	H	$C_{17}H_{17}N_3O_2$	174-177		BC		1.06[f]
41	2-CH_3CH_2OPh	4(5)	H	CO_2CH_3	H	$C_{13}H_{17}N_3O_3$	209-211	155-156	I	BG	0.55
42	3-CH_3OPh	4(5)	H	CO_2CH_3	H	$C_{12}H_{15}N_3O_3$	176-177	110-112[g]	D	BG	-0.07
43	4-HOPh	4(5)	H	CO_2CH_3	H	$C_{11}H_{13}N_3O_3$	198-199	180-183	C	BG	-1.11[l]
44	4-$C_6H_5CH_2O$Ph	4(5)	H	CO_2CH_3	H	$C_{18}H_{19}N_3O_3$	221-223		BFI		
45	4-CF_3Ph	4(5)	H	CO_2CH_3	H	$C_{12}H_{12}N_3O_2F_3$	229-230		C		0.56
46	2,5-$(CH_3)_2$Ph	4(5)	H	CO_2CH_3	H	$C_{13}H_{17}N_3O_2$	220-222		D		0.58
47	2,5-$(CH_3)_2$Ph	4(5)	H	$CO_2CH_2CH_3$	H	$C_{14}H_{19}N_3O_2$	214-216[e]	177-178[k]	F	BG	0.88
48	2,5-F_2Ph	4(5)	H	CO_2CH_3	H	$C_{11}H_{11}N_3O_2F_2$	207-208	136-138	CH	BG	-0.08
49	2,6-Cl_2Ph	4(5)	H	CO_2CH_3	H	$C_{11}H_{11}N_3O_2Cl_2$	235-236	161-164[e,k]	A	BG	0.30
50	3,5-$(CH_3O)_2$Ph	4(5)	H	CO_2CH_3	H	$C_{13}H_{17}N_3O_4$	202-203		I		0.10
51	3,4-$(OH)_2$Ph	4(5)	H	CO_2CH_3	H	$C_{11}H_{13}N_3O_4$		178-179		CG	-1.51[l]
52	3,4-$(C_6H_5CH_2O)_2$Ph	4(5)	H	CO_2CH_3	H	$C_{25}H_{25}N_3O_4$	189-191	136-140	I	BG	
53	3,4-OCH_2OPh	4(5)	H	CO_2CH_3	H	$C_{12}H_{13}N_3O_4$	214-216	>130 dec[m]	C	C	-0.14
54	Ph	5	CH_3	CO_2CH_3	H	$C_{12}H_{15}N_3O_2$	145-147	147-149	M	BG	0.06
55	Ph	5	CH_3	$CO_2CH_2CH_3$	H	$C_{13}H_{17}N_3O_2$	135-138		J		0.41
56	Ph	5	CH_3	$CO_2CH_2CH(CH_3)_2$	H	$C_{15}H_{21}N_3O_2$	103-104		J		1.15[f]
57	Ph	5	CH_2CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_2$	115-115.5		J		0.39
58	2-CH_3Ph	5	CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_2$	158-160[e]	144-146	IK	BG	0.37
59	3-CH_3Ph	5	CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_2$	175-177		IK		0.49
60	2-FPh	5	CH_3	CO_2CH_3	H	$C_{12}H_{14}N_3O_2F$	178-180		IJ		0.14
61	2-FPh	5	CH_3	$CO_2(CH_2)_2CH_3$	H	$C_{14}H_{18}N_3O_2F$	98-101	151-154	J	BG	0.87
62	2-FPh	5	CH_3	$CO_2CH(CH_3)_2$	H	$C_{14}H_{18}N_3O_2F$	139-141	166-168	IJ	BG	0.77
63	3-FPh	5	CH_3	$CO_2CH_2CH_3$	H	$C_{13}H_{16}N_3O_2F$	152-154	153-155	J	BG	0.51
64	4-FPh	5	CH_3	$CO_2CH_2CH_3$	H	$C_{13}H_{16}N_3O_2F$	117-120[e]	139-141[n]	J	BG	0.48
65	2-ClPh	5	CH_3	CO_2CH_3	H	$C_{12}H_{14}N_3O_2Cl$	153-155		J		0.51
66	2-ClPh	5	CH_3	$CO_2CH_2CH_3$	H	$C_{13}H_{16}N_3O_2Cl$	117-118.5[o]	167-170	J	BG	0.82

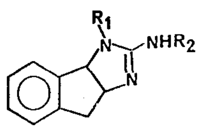
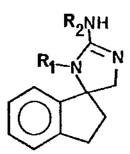
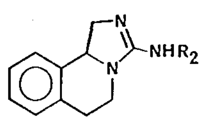
67	2-ClPh	5	CH_3	$CO_2CH(CH_3)_2$	H	$C_{14}H_{18}N_3O_2Cl$	124-125	170-172	J	BG	1.08
68	3-ClPh	5	CH_3	CO_2CH_3	H	$C_{12}H_{14}N_3O_2Cl$	181-182	144-147[h,p]	B	BG	0.53
69	3-ClPh	5	CH_3	$CO_2CH_2CH_3$	H	$C_{13}H_{16}N_3O_2Cl$	135-137	144-146	B	BG	0.78[f]
70	4-ClPh	5	CH_3	CO_2CH_3	H	$C_{12}H_{14}N_3O_2Cl$	184-186		I		0.54
71	3-CH_3OPh	5	CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_3$	137-138	130-133	IJ	BG	0.18
72	2-CH_3SPh	5	CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_2S$	122-123		J		0.63
73	2-CH_3S(O)Ph	5	CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_3S$	169-173		I		−0.87[l]
74	4-HOPH	5	$CH(CH_3)_2$	$CO_2CH_2CH_3$	H	$C_{15}H_{21}N_3O_3$		170-175[e]		BG	0.70
75	4-$C_6H_5CH_2$OPh	5	$CH(CH_3)_2$	$CO_2CH_2CH_2$	H	$C_{22}H_{27}N_3O_3$	149-150[e]		E		
76	4-$HOCH_2$Ph	5	CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_3$	174-175	140-141	D	BG	−0.76[l]
77	4-$HOCH_2$Ph	5	CH_3	$CO_2CH_2CH_3$	H	$C_{14}H_{19}N_3O_3$	185-187		D		−0.29
78	4-CHOPh	5	CH_3	CO_2CH_3	H	$C_{13}H_{15}N_3O_3$	198-201	144-147[e]	D	BG	−0.53
79	4-CH_3OCOPh	5	CH_3	CO_2CH_3	H	$C_{14}H_{17}N_3O_4$	151-152	>235 dec	CJ	AG	0.20
80	4-CH_3SPh	5	CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_2S$	149-151		D		0.61
81	4-CH_3S(O)Ph	5	CH_3	CO_2CH_3	H	$C_{13}H_{17}N_3O_3S$	173-175[q]		C		−1.03[l]
82	2,3-$(CH_3)_2$Ph	5	CH_3	$CO_2CH_2CH_3$	H	$C_{15}H_{21}N_3O_2$	147-148[e]	145-147[k]	J	BG	1.02
83	2,3-Cl_2Ph	5	CH_3	CO_2CH_3	H	$C_{12}H_{13}N_3O_2Cl_2$	184-186		J		0.91
84	3,5-Cl_2Ph	5	CH_3	CO_2CH_3	H	$C_{12}H_{13}N_3O_2Cl_2$	175-177[r]		N		
85	2,6-Cl_2Ph	5	CH_3	CO_2CH_3	H	$C_{12}H_{13}N_3O_2Cl_2$	180-182		A		
86	2,5-Br_2Ph	5	CH_3	CO_2CH_3	H	$C_{12}H_{13}N_3O_2Br_2$	196-198		AH_2O		0.98[f]
87	Ph	5	$C_6H_5CH_2$	CO_2CH_3	H	$C_{18}H_{19}N_3O_2$	161-162.5[s]		I		1.25[f]
88	Ph	5	$HOCH_2CH_2$	CO_2CH_3	H	$C_{13}H_{17}N_3O_3$	92-94[e]		M		
89	Ph	5	$C_6H_5CH_2OCH_2CH_2$	CO_2CH_3		$C_{20}H_{23}N_3O_2$	oil				
90	Ph	4	CH_3	CO_2CH_3	H	$C_{12}H_{15}N_3O_2$	119-120		EJ		
91	3-ClPh	4	CH_3	CO_2CH_3	H	$C_{12}H_{14}N_3O_2Cl$	134-137[e]	159-162	A	BG	0.86[f]
92	2,6-Cl_2Ph	4	CH_3	CO_2CH_3	H	$C_{12}H_{13}N_3O_2Cl_2$	155-156[e]	177-180[t]	N	C	0.54[f]
93	Ph	4(5)	H	CO_2CH_3	4(5)-CH_3	$C_{12}H_{15}N_3O_2$	184-187	142-144	A	BG	
94	Ph	4(5)	H	CO_2CH_3	5(4)-CH_3	$C_{12}H_{15}N_3O_2$	202-203[u]	148-150[e]	I	BG	0.15
95			H	H		$C_{10}H_{11}N_3$		315-320[k]		H_2O	
96			H	CO_2CH_3		$C_{12}H_{13}N_3O_2$	232-234		B	BG	−1.14[l]
97			CH_3	H		$C_{12}H_{15}N_3$		305-307[h]		B	
98			H	CO_2CH_3		$C_{13}H_{15}N_3O_2$	201-203	152-154[e,h]	C	BG	0.30[f]
99			CH_3	CO_2CH_3		$C_{14}H_{17}N_3O_2$	143-144	>205 dec	IJ	BG	0.48[f]
100				CO_2CH_3		$C_{13}H_{15}N_3O_2$	143-145		E		
101				$CO_2CH_2CH_3$		$C_{14}H_{17}N_3O_2$	139-40		E		
102	$PhCH_2$	4(5)	H	CO_2CH_3	H	$C_{12}H_{15}N_3O_2$	178.5-179		AO		0.12
103	2-ClPh	5	CH_3	H	H	$C_{10}H_{12}N_3Cl$		250-251[h]		C	−1.11[l]
104	2,6-Cl_2Ph	5	CH_3	H	H	$C_{10}H_{11}N_3Cl_2$		317-319[h]		B	
105	3-CH_3Ph	5	CH_3	H	H	$C_{11}H_{15}N_3$		268-269[h]		D	
106	Ph	5	$C_6H_5CH_2OCH_2CH_2$	H	H	$C_{18}H_{21}N_3O$		164-166[h]		D	
107	3-ClPh	4	CH_3	H	H	$C_{10}H_{12}N_3Cl$		164-166[h]		CG	

Table I (*Continued*)

no.	Ar	position of Ar	R_1	R_2	R_3	formula (free base)	mp,[a] °C: free base	mp,[a] °C: salt[d]	crystn solvent[b]: base	crystn solvent[b]: salt	lipophilicity:[c] log k'
108	2,6-Cl_2Ph	4(5)	H	H	H	$C_9H_9N_3Cl_2$		228–230[h,v]		BG	
109	Ph	4(5)	H	H	H	$C_9H_{11}N_3$		181–182[h,w]		C	−3.74[l]

[a] Satisfactory analyses (C, H, and N) for all compounds, except where otherwise noted. [b] A = MeOH; B = EtOH; C = *i*-PrOH; D = MeCN; E = acetone; F = EtOAc; G = Et_2O; H = toluene; I = benzene; J = cyclohexane; K = hexane; L = THF; M = precipitated by the addition of $NaHCO_3$ to acidic solution; N = chromatography; O = chloroform; t = triturated with hot solvent. [c] Log $[(t_x - t_0)/t_0]$, where t_x is retention time of sample and t_0 is retention time of DMF, unretained standard, on HPLC using 30%, w/w, MeOH in 0.001 M, pH 7.00, phosphate buffer on a C-18 Corasil, persilated, 50-cm column. [d] HCl salt, except where otherwise noted. [e] Satisfactory analysis was not obtained. [f] Determined with 40%, w/w, MeOH and extrapolated to 30%, w/w, MeOH by regression of standards common to both conditions. [g] HNO_3 salt. [h] HBr salt. [i] C: calcd, 45.54; found, 46.20. [j] C: calcd, 65.43; found, 64.74. [k] H_2SO_4 salt. [l] 15%, w/w, MeOH converted to 30%, w/w, MeOH by regression of standards common to both conditions. [m] Hemicitrate. [n] C: calcd, 51.75; found, 51.09. [o] C: calcd, 55.42; found, 54.75. [p] Phase change 144–147 °C, slow melting at >185 °C. [q] C: calcd, 52.87; found, 53.32. [r] C: calcd, 47.70; found, 46.77. [s] H: calcd, 6.19; found, 6.60. [t] C: calcd, 42.56; found, 43.08. [u] C: calcd, 61.78; found, 61.21. [v] Reported mp 233–235 °C. [w] Reported mp 181–182.5 °C.

from appropriately substituted styrenes, which were converted to β-chloroethyl carbamates **10** as described by Foglia and Swern.[10] The benzylic chlorine of **10** was either subjected to the Gabriel synthesis to yield, after hydrolysis, the primary diamines **8** in low yields or displaced by azide ion to yield the β-azidoethyl carbamates **11**. Reduction of the azido function with zinc dust in the presence of acetic anhydride afforded the β-acetamidoethyl carbamates **12**, which could be hydrolyzed to the damines **8**. The β-azidoethyl carbamates **11** were also utilized as precursors for the *N*-methyl-2-phenyl-1,2-diaminoethanes (**9**). This transformation was accomplished by simultaneous reduction of both functional groups with lithium aluminum hydride. As an alternate method, diamine **154** was also prepared by LAH reduction of the methyl amide of phenylglycine.

The bis(carbamate)s **3** were prepared either in situ or were isolated (sometimes admixed with varying amounts of the monocarbamates) by reactions of 2-methyl-2-thiopseudourea with the appropriate alkyl chloroformate and a base.[11]

Results and Discussion

The study of structure–activity relationships in our series was pursued by three types of structural changes. Phenyl substituents were varied to test for effects of position, bulk, electronic effects, and hydrogen bonding on biological responses.

Substitution on the imidazoline ring itself was changed by increasing the chain length of the carbamate (R_2) and by introduction of alkyl groups, on either one of both possible ring nitrogens (R_1) as well as on the adjacent carbons (R_3). Finally, rotation around the phenyl–imidazoline bond was constrained by introduction of methylene and ethylene bridges.

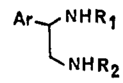
Since the physicochemical parameters are covariables in the set of compounds in Table I, and assignment of a single biological activity to a single variable would be tenuous at best. Nonetheless, it is possible to organize the results in Table III along broad generalizations drawn from the sensitivity of a given biological activity to a particular physicochemical variable.

Antidepressant activity, as measured by potency in antagonizing reserpine-induced hypothermia,[12] was found to be sensitive to the electronic nature of the aryl group (Ar), to the bulk of the carbamate and of the *p*-aryl substituent, and to lipophilicity. In the nor compounds (R_1 = H), there was generally an inverse relationship of potency to lipophilicity (log k'), whereas in the *N*-alkyl series, higher lipophilicity was tolerated. Halogen substitution overcame the negative effect of higher lipophilicity, as evidenced especially by comparing compounds **36**, **35**, and **30** with **25** and by comparing compounds **86** and **83** with **82**. Addition of one halogen to Ar generally led to the same or increased potency in the nor and *N*-alkyl series (**27–30**, **35**, **36**, **60–70**, and **52**, but not **32** and **34**). Addition of two halogens substituted in either the 2,6- or 2,5-positions of Ar led to increased potency (**48**, **49**, **85**, and **86**), whereas 2,3- and 3,5-disubstitution of halogen did not alter potency.

Alkyl substitution of Ar in the ortho and para positions led to decreased potency (**24**, **26**, **37–39**, and **58**); however, alkyl substitution in the meta position resulted in equiv-

(10) Foglia, T. A.; Swern, D. *J. Org. Chem.* **1966**, *31*, 3625.
(11) Klopping, H. L. U.S. Patent 2933504, 1960; *Chem. Abstr.* **1961**, 55, 9431*f*.
(12) Kaiser, C.; Setler, P. E. "Burgers Medicinal Chemistry"; 4th ed., Part III; Wolff, M. E., Ed., Wiley-Interscience: New York, 1981; p 1005.

Table II. Diamine Intermediates for 2-Imidazolines and Diamine Derivatives



no.	Ar	R_1	R_2	formula	mp or bp (mmHg),[a] °C	crystn solvent[b]
110	2-CH_3Ph	CH_2Ph	H	$C_{16}H_{20}N_2\cdot 2HCl$	263-267[c]	A
111	2-CH_3Ph	H	H	$C_9H_{14}N_2\cdot 2HCl$	281-287	tCG
112	2-FPh	CH_2Ph	H	$C_{15}H_{17}N_2F\cdot 2HCl$	226-229[c]	B
113	2-FPh	H	H	$C_8H_{11}N_2F\cdot 2HCl$	260-263	B
114	3-FPh	CH_2Ph	H	$C_{15}H_{17}N_2F\cdot 2HCl$	238-241[c]	BG
115	3-FPh	H	H	$C_8H_{11}N_2F\cdot 2HCl$	298-300	AG
116	2-BrPh	H	H	$C_8H_{11}N_2Br\cdot 2HCl$	295-299[c]	C
117	3-BrPh	H	H	$C_8H_{11}N_2Br\cdot 2HCl$	284-289	HCl
118	4-$(CH_3)_2$CHPh	CH_2Ph	H	$C_{18}H_{24}N_2\cdot 2HCl$	240-243[c]	BG
119	4-$(CH_3)_2$CHPh	H	H	$C_{11}H_{18}N_2\cdot 2HCl$	286-288	tG
120	4-$CH_3(CH_2)_5$Ph	CH_2Ph	H	$C_{21}H_{30}N_2\cdot 2HCl$	240-242[c]	C
121	4-$CH_3(CH_2)_5$Ph	H	H	$C_{14}H_{24}N_2\cdot 2HCl$	215-230	B
122	2-PhPh	H	H	$C_{14}H_{16}N_2\cdot 2HCl$	290-292[d]	B
123	2-CH_3CH_2OPh	CH_2Ph	H	$C_{17}H_{22}N_2O\cdot 2HCl$	155-160[c]	BG
124	2-CH_3CH_2OPh	H	H	$C_{10}H_{16}N_2O\cdot 2HCl$	199-200	ADG
125	4-PhCH_2OPh	CH_2Ph	H	$C_{22}H_{24}N_2O\cdot 2HCl$	213-216[c]	P
126	4-HOPh	H	H	$C_8H_{12}N_2O\cdot 2HCl$[e]	270 dec	A
127	2,5-$(CH_3)_2$Ph	CH_2Ph	H	$C_{17}H_{22}N_2\cdot 2HCl$	245-250[c]	P
128	2,5-$(CH_3)_2$Ph	H	H	$C_{10}H_{16}N_2\cdot 2HCl$	332-334	AC
129	2,5-F_2Ph	CH_2Ph	H	$C_{15}H_{16}N_2F_2\cdot 2HCl$	234-238[c]	BG
130	2,5-F_2Ph	H	H	$C_8H_{10}N_2F_2\cdot 2HCl$	298-302	B
131	3,5-$(CH_3O)_2$Ph	CH_2Ph	H	$C_{17}H_{22}N_2O_2\cdot 2HCl$	224-227[c]	P
132	3,5-$(CH_3O)_2$Ph	H	H	$C_{10}H_{16}N_2O_2\cdot 2HCl$	291-294	B
133	3,4-OCH_2OPh	H	H	$C_9H_{12}N_2O_2\cdot 2HCl$	285-288[f]	BG
134	Ph	CH_3	H	$C_9H_{14}N_2\cdot 2HCl$	242-244	B
135	Ph	CH_3CH_2	H	$C_{10}H_{16}N_2\cdot 2HCl$	226-229	AD
136	2-CH_3Ph	CH_3	H	$C_{10}H_{16}N_2$[g]	125-130 (25)[c]	
137	3-CH_3Ph	CH_3	H	$C_{10}H_{16}N_2\cdot 2HCl$	200-202	AC
138	2-FPh	CH_3	H	$C_9H_{13}N_2F\cdot 2HCl$	235-237	AG
139	3-FPh	CH_3	H	$C_9H_{13}N_2F\cdot 2HCl$	234-238	BC
140	4-FPh	CH_3	H	$C_9H_{13}N_2\cdot 2HCl$	199-203	B
141	2-ClPh	CH_3	H	$C_9H_{13}N_2Cl\cdot 2HCl$	258-262	B
142	3-ClPh	CH_3	H	$C_9H_{13}N_2Cl\cdot 2HCl$	204-207	B
143	4-ClPh	CH_3	H	$C_9H_{13}N_2Cl\cdot 2HCl$	250-253	B
144	3-CH_3OPh	CH_3	H	$C_{10}H_{16}N_2O\cdot 2HCl$	239-241	B
145	2-CH_3SPh	CH_3	H	$C_{10}H_{16}N_2S\cdot 2HCl$	177-180	D
146	4-CH_3SPh	CH_3	H	$C_{10}H_{16}N_2S\cdot 2HCl$	149-151	D
147	4-PhCH_2OPh	$(CH_3)_2$CH	H	$C_{18}H_{24}N_2O\cdot 2HCl$	233[h]	D
148	4-HOCH_2Ph	CH_3	H	$C_{10}H_{16}N_2O\cdot 2HCl$	205-206[i]	BD
149	2,3-$(CH_3)_2$Ph	CH_3	H	$C_{11}H_{18}N_2\cdot 2HCl$	278-281	B
150	2,3-Cl_2Ph	CH_3	H	$C_9H_{12}N_2Cl_2\cdot 2HCl$	272-275	B
151	3,5-Cl_2Ph	CH_3	H	$C_9H_{12}N_2Cl_2\cdot 2HCl$	246-249	B
152	2,6-Cl_2Ph	CH_3	H	$C_9H_{12}N_2Cl_2\cdot 2HCl$	267-269	B
153	Ph	Ph$CH_2OCH_2CH_2$	H	$C_{17}H_{22}N_2O\cdot 2HCl$	179-181	C
154	Ph	H	CH_3	$C_9H_{14}N_2\cdot 2HCl$	202-206	BG
155	3-ClPh	H	CH_3	$C_9H_{13}N_2Cl\cdot 2HCl$	190-194	AD
156	2,6-Cl_2Ph	H	CH_3	$C_9H_{12}N_2Cl_2\cdot 2HCl$	248-250[c]	D
157	3-ClPh	$COCH_3$	$CO_2CH_2CH_3$	$C_{13}H_{17}N_2O_3Cl$	148-149	F
158	3-BrPh	$COCH_3$	$CO_2CH_2CH_3$	$C_{13}H_{17}N_2O_3Br$	157-158[j]	tI
159	2,6-Cl_2Ph	$COCH_3$	$CO_2CH_2CH_3$	$C_{13}H_{16}N_2O_3Cl_2$	135-137	tH
160	4-PhCH_2OPh	PhCH_2	$C(=NCO_2CH_3)NHCO_2CH_3$	$C_{27}H_{30}N_4O_5$	114-116[k]	J
161	2,6-Cl_2Ph	CH_3	$C(=NCO_2CH_3)NHCO_2CH_3$	$C_{14}H_{18}N_4O_4Cl_2$	147-149[c]	A
162	Ph	Ph$CH_2OCH_2CH_2$	$C(=NCO_2CH_3)NHCO_2CH_3$	$C_{22}H_{28}N_4O_5\cdot HCl$	164-165	C

[a] A satisfactory C, H, and N analysis for all compounds, except where otherwise noted. [b] A = MeOH; B = EtOH; C = *i*-PrOH; D = MeCN; F = EtOAc; G = Et_2O; H = toluene; I = benzene; J = cyclohexane; HCl = constant-boiling HCl; P = precipitated by the addition of 2-propanol–concentrated HCl to the filtrate of the worked-up LAH reduction; t = tritiated with hot solvent. [c] Satisfactory analysis was not obtained. [d] The precursor *N*-benzylamine was not isolated. [e] Obtained by hydrogenolysis of 125. [f] N: calcd, 11.06; found, 10.65. [g] A salt was not prepared. [h] H: calcd, 6.27; found, 6.98. [i] N: calcd, 11.06; found, 10.47. [j] C: calcd, 47.47; found, 46.90. [k] C: calcd, 66.10; found, 66.52.

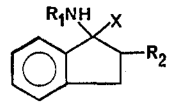
alent potency (**25** and **59**). The addition of a phenyl substituent resulted in a loss in potency (**40**). Para substitution of a hydroxymethyl or a carboxaldehyde group gave very active compounds (**76–78**). Addition of an oxygen or sulfur substituent to the aryl group resulted in a loss in activity (**41–44**, **50–53**, **71–74**, **80**, and **81**). No clear trend was evident in a comparison of *N*-alkyl compounds **54**, **68**, and **85** with their positional isomers **90–92** for any of the biological screens. Separation of aryl and imidazoline rings by CH_2 did not eliminate antidepressant activity (**102**).

Anticonvulsant activity, as measured by maximal electroshock antagonism,[13] and muscle-relaxant activity, as measured by antagonism of etonitazene-induced rigidity,[14]

(13) Reference 12, pp 834–835.

(14) Barnett, A.; Goldstein, J.; Fiedler, E.; Taber, R. *Eur. J. Pharmacol.* **1975**, *30*, 23–28.

Table III. Indandiamines



no.	X	R_1	R_2	formula	mp,[a] °C	crystn solvent[b]
163	H	H	NH_2	$C_9H_{12}N_2 \cdot 2HCl$	300-305	AB
164	NH_2CH_2	$PhCH_2$	H	$C_{17}H_{20}N_2 \cdot 2HCl$	210-212[c]	C
165	NH_2CH_2	H	H	$C_{10}H_{14}N_2 \cdot 2HCl$	218-220	C
166	NH_2CH_2	CH_3	H	$C_{11}H_{16}N_2 \cdot 2HCl$	217-218	B

[a] A satisfactory C, H, and N analysis for all compounds, except where otherwise noted. [b] A = MeOH; B = EtOH; C = *i*-PrOH. [c] C: calcd, 62.77; found, 63.48.

tended to follow many of the correlates of antidepressant activity. Thus, in the absence of overriding effects, there was an inverse relationship of anticonvulsant activity and lipophilicity. For the nor compounds, the optimal carbamate chain length was methoxy (except for 36), and for the *N*-methyl compounds, longer chains were tolerated. Relative to the standard compounds shown in Table IV, anticonvulsant and muscle-relaxant activity never reached high levels in this series.

Several types of substitution resulted in loss of anticonvulsant and muscle-relaxant activity. Introduction of substituents in the para position of Ar was deleterious for these activities. As had been observed in the antidepressent screen, oxygen and sulfur substitution of the aryl group had a deleterious effect on anticonvulsant activity; however, muscle-relaxant properties were not adversely affected as long as that substituent was not in the para position. The one exception was compound **73**, perhaps because of its highly hydrophilic methylsulfinyl substituent. Halophenyl- and alkylphenyl-substituted analogues showed no pattern.

The fused compounds **95–101**, which have the planes of the phenyl and imidazoline rings fixed relative to each other, were synthesized with the hope of gaining some insight into conformational requirements for biological activity. The lack of antidepressant activity with the indanoimidazoline **96** contrasts sharply with the good levels of activity shown by its closest relatives among the nonfused compounds **24**, **94**, and **1**. This result indicated that **79** might be fixed in an undesirable conformation for eliciting antidepressant activity. The isoquinolinoimidazoline **100**, on the other hand, was nearly as active as its closest nonfused relative, **58**. For the spiro compounds **98** and **99**, there were no really close relatives among the nonfused compounds; however, considering that **93**, the only other compound that was substituted in the benzylic position, was not highly active suggested that the relative conformation of the two rings in **98** and **99** was compatible with receptor requirements. The conformation of the two rings of spiro compounds **98** and **99** is similar to the least hindered rotamers of the highly active di-ortho-substituted analogues **49**, **85**, and **92** and the ortho-substituted *N*-methyl analogues **58** and **65**. It can also be seen from log k' values that differences in lipophilicity probably do not play a significant role for **98** and **99**.

If a compound was classified as a depressant in the mouse behavior assay, it was investigated further for its effects on the loss of righting reflex (LRR).[15] Several compounds were moderately active in this assay, and one of these, **82**, exhibited a very clean depressant profile. In general, compounds with higher lipophilicity possessed higher CNS-depressant and higher muscle-relaxant properties (**40**, **56**, **62**, **66**, **67**, **69**, **72**, **82**, and **83**). Exceptions to this are compounds where a single, large substituent was placed on either the imidazoline portion of the molecule (**23**, **33**, and **87**) or on the para position of the phenyl substituent (**37–39**). Here again, a larger carbamate side chain (R_2) was better tolerated in the *N*-alkyl (R_1) series. This becomes evident in a comparison of compounds **23** and **56**.

Tricyclic antidepresants (TCA's) and many newer non-TCA's are characterized by their ability to inhibit the uptake of 5-hydroxytryptamine (5-HT) and norepinephrine (NE).[12,16] This inhibition can be measured, for example, in brain slices in vitro[17] or in vivo in the mouse heart.[18]

Table V contains a comparison of in vivo and in vitro data for three pairs of 2-(alkoxycarbonyl)amino-substituted phenylimidazolines **1**, **49**, and **66** and their corresponding 2-amino parents **109**, **108**, and **103**. The dose responsiveness in either one of the two in vivo tests (reserpine hypothermia and inhibition of NE uptake in the mouse heart) within each pair differ by a factor of 5 at most. For the two in vitro reuptake assays, on the other hand, there is much greater difference between the members of each pair. This difference is more striking for NE reuptake than for 5-HT reuptake. These data suggested that the carbamates are hydrolyzed in vivo and thereafter exert their antidepressant activity through inhibition of NE uptake. Carbamates bearing varying alkyl chains on the same 2-aminoimidazoline (for example, **1**, **22**, and **23**) nevertheless may still show a widely different response in an oral antidepressant assay, perhaps due to different rates of hydrolyses and differing prehydrolysis distribution. It was also concluded by nearest-neighbor analysis that the carbamates were prodrugs (antidepressant activity) for the 2-aminoimidazolines.[25] However, we have not done any direct biotransformation studies, and there was no temporal trend in the reserpine hypothermia reversal.

However tempting it is to accept a prodrug explanation for how these carbamates might exert their antidepressant effect, one may not extend this explanation to cover the anticonvulsant and muscle-relaxant effects of these compounds. The difference observed between **1** and **109** and between **91** and **107** in maximal electroshock antagonism activity and between **91** and **107** in etonitazene-induced rigidity (the 2-carbamates are more active there than the

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2-amino parents) point to a different role for the (alkoxycarbonyl)amino group. We therefore conclude that the 2-(alkoxycarbonyl)amino-substituted arylimidazolines are not prodrugs for the 2-amino-4-arylimidazolines when it comes to manifesting anticonvulsant and muscle-relaxant activity.

Experimental Section

Pharmacology. Mouse Behavior Test.[19] Male Simonsen (ICR) fBR mice weighing 18–24 g were given a 3, 10, 30, 100, 300, or 1000 mg/kg ip dose of the compound and evaluated in groups of three. Test compounds were administered as aqueous solutions in all animal models.

Loss of Righting Test. Male Simonsen (ICR) fBR mice weighing 18–24 g were tested in groups of ten following administration of compound. Righting ability before (unaroused) and after (aroused) rapid rolling in the investigator's hands was determined. The ED_{50} values were calculated by the technique of Litchfield and Wilcoxon.[20] The aroused/unaroused ratio differentiates the nature of depressants. A ratio approaching unity suggests sedative hypnotic activity, while larger ratios (2–6) suggest anxiolytic and neuroleptic activities.[15]

LD_{50}. Male Simonsen (ICR) fBR mice weighing 18–24 g were tested in groups of ten to determine the LD_{50} and 95% confidence limit.[20] In many cases, the LD_{50} was also estimated from deaths up to 7 days after drug administration in the mouse behavior test.

Reserpine Hypothermia Antagonism.[21-23] Male HLa (ICR) BR mice weighing 18–24 g were dosed ip in groups in eight with 5 mg/kg of reserpine 2 h prior to oral compound administration. Rectal temperatures were determined hourly; 1–4-h thermia was determined by an analysis of variance.

Maximal Electroshock Antagonism.[24] Male HLa (ICR) BR mice in groups of eight to ten of were administered compound, ip, 15 min prior to a transcorneal electroshock (50 mA, 0.2 s). Abolition of the tonic hind-limb extension was used as the end point for a quantal analysis by the Litchfield and Wilcoxon[20] method for the ED_{50}.

Etonitazene-Rigidity Antagonism.[14] Male HLa (SD) BR rats weighing 70–100 g were tested in groups of ten. Compound was administered at 60 mg/kg, ip, 15 min prior to 0.0125 mg/kg of etonitazene, subcutaneously. At 5, 10, and 15 min after the etonitazene, rats were rated for trunk (3 points) and hind-limb (2 points) rigidity. ED_{50}s were determined when results at 60 mg/kg indicated a significant degree of activity. Results were quantalized by rating active, if the total score for each rat was reduced at least 60% as compared to etonitazene control animals.

Inhibition of [^{3}H]Norepinephrine (NE) Uptake into Mouse Heart.[13] Test compounds were administered ip prior to radioactive NE (iv, mice). At 3 h after the [^{3}H]NE, the hearts were removed, washed, weighed, and dissolved in Protosol. The samples were then counted, and the disintegrations per minute per milligram of tissue was determined. The dose–response curves were determined from linear regressions.

Inhibition of [^{3}H]Norepinephrine and [^{14}C]Serotonin (5-HT) Uptake by Rat Brain Slices in Vitro.[17] Rat cerebral cortex slices were incubated at 37 °C in Krebs–Henseleit buffer to produce a concentration of 5 mg of tissue per milliliter of buffer. Doses of test compound were added prior to the addition of either 0.2 μCi of [^{3}H]NE (3.8×10^{-8}M) or 0.005 μCi of [^{14}C]-5-HT (3.8×10^{-8} M). Control samples were incubated without dosing, while blanks were incubated at 4 °C. After 20 min the incubation was terminated by filtration, and radioactivity in the tissue slices was determined. The IC_{50}s were calculated from the linear regression of the inhibition of the uptake.

Chemistry. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. The structures of all compounds are supported by NMR spectroscopy (Varian A60 and HA 100). IR spectra were recorded (Perkin-Elmer 217B) for all compounds except diamines and their salts (**110–156** and **163–166**). Elemental analyses (C, H, and N) were obtained for all final products and their precursor diamines. The results are within ±0.4% of the theoretical values, except where noted (footnotes in Tables I–III). The lipophilicities were measured as described (footnotes in Table I).

***N*,*N*-Bis(methoxycarbonyl)-2-methyl-2-thiopseudourea (3, $R_2 = CO_2CH_3$).** A mixture containing 150 g of 2-methyl-2-thiopseudourea sulfate (0.54 mol), 215 mL of methyl chloroformate (2.77 mol), and 800 mL of water was stirred rapidly while external cooling from an ice–water bath was supplied. A solution of 172 g of sodium hydroxide (4.3 mol) in 800 mL of water was added at a rate sufficient to keep the reaction temperature between 15 and 22 °C. The pH was checked occasionally and was found to be mildly alkaline, except toward the end, when it became strongly basic. The addition took 2 h, and the product was extracted into two 400-mL portions of methylene chloride. The combined extracts were concentrated, and the product was recrystallized from 200 mL of MeOH, affording 115 g (52%) of the bis(carbamate): mp 98–101 °C (lit.[11] mp 100–102 °C); IR 1750, 1650, 1585 cm^{-1}.

2-Amino-1-(methylamino)-1-[4-(hydroxymethyl)phenyl]ethane Dihydrochloride (148). A mixture of 16.5 g (0.121 mol) of *p*-(hydroxymethyl)benzaldehyde, 10 mL of H_2O, 80 mL of MeCN, 10 g of NaCN (0.204 mol), and 14 g of methylamine hydrochloride (0.207 mol) was stirred for 20 h. The mixture was then concentrated to half volume under reduced pressure and below 30 °C. The solid was extracted with ether, and the combined extracts were concentrated to yield 19.5 g of the α-methyl amino nitrile, mp 51–54 °C. A sample was recrystallized from ether: mp 58–59 °C; IR 3260, 2220 cm^{-1}. A slurry of 8.4 g of LAH (0.221 mol) in 400 mL of ether was refluxed for 3 h and then cooled to −10 °C. To this was added under stirring a solution of the α-methyl amino nitrile in 120 mL of THF, while the reaction temperature was kept below −5 °C. The reaction was then stirred at 15 °C for 16 h and worked up by the careful addition of 40 mL of saturated sodium sulfate. The inorganic solids were filtered off, and the filtrate was concentrated. The residual oil was dissolved in 50 mL of EtOH and, under cooling and swirling, combined with a solution of 8 g of HCl (0.22 mol) in 120 mL of EtOH. The white crystals that separated on standing overnight were collected and dried under vacuum at 80 °C, affording 11.8 g (38%) of the *p*-(hydroxymethyl)phenyl-substituted diamine, dihydrochloride, mp 188–191 °C. A sample was recrystallized from MeOH, mp 204–205 °C.

Ethyl [2-Acetamido-2-(3-bromophenyl)ethyl]carbamate (158). Ethyl [2-azido-2-(3-bromophenyl)ethyl]carbamate (11, Ar = 3-BrPh) was prepared as described for the unsubstituted phenyl analogue. A solution consisting of 13.5 g of the azido compound (43 mmol), 13 mL of Ac_2O (137 mmol), 4 mL of AcOH (70 mmol), 70 mL of benzene, and 250 mL of THF was stirred mechanically. An excess of zinc dust (35 g) was added in portions over a period of 1 h, and stirring was continued for additional 2 h. The mixture was treated with 500 mL of EtOAc, 300 mL of water, and solid $NaHCO_3$ and then filtered after 1 h of stirring. The organic phase was separated, dried (K_2CO_3), and concentrated. The yellow solid was triturated with 100 mL of benzene, affording 7.0 g (49%) of pure, white product: mp 157–158 °C; IR 3320, 3290, 1690, 1645, 1550 cm^{-1}.

1-(3-Bromophenyl)-1,2-diaminoethane Dihydrochloride (117). A solution of 6.9 g of the acetamide **158** (21 mmol) in 50 mL of concentrated HCl was heated at reflux (135–140 °C, oil bath) for 16 h. Some product crystallized while the mixture was boiling. The crystallization was completed by cooling of the mixture in an ice bath. The crystals were collected, washed with 2-propanol–ether mixtures, and dried under vacuum at 100 °C. There was 5.9 g of pure product (98%), mp 284–289 °C.

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Table IV. In vivo CNS Activities of 2-Substituted 4(5)-Aryl-2-imidazolines

compd	mouse behavior act.[a]	loss of righting reflex[b] unaroused	loss of righting reflex[b] aroused	Ar/Unar LRR ratio	LD_{50},[b] mg/kg ip	HYPO[c]	MES ED_{50},[b,d] mg/kg ip	ED_{50},[b,d] mg/kg ip
1	ST-D wk				303 (231-396)	++	54 (49-63)	111 (76-207)
22	D wk				500[f]	(+)	75 (69-82)	+
23	D wk				700[f]	I	I	+
24	D	144 (105-175)	172 (156-187)	1.19	300[f]	+	~55	
25	D	100 (80-112)	157 (138-179)	1.57	500[f]	++V	~100	51 (38-65)
26	D wk				>1000[f]	(+)	I	+
27	D	210 (188-235)	234 (209-262)	1.11	255 (199-326)	+++	54 (46-66)	++
28	D				200[f]	++	70 (59-86)	36 (16-76)
29	D	200[f]			500[f]	++	~50	
30	D wk				300[f]	++	48 (36-61)	40 (26-53)
31						+	79 (64-97)	
32	ST wk				500[f]	+	~200	+
33	D wk				200[f]	I	I	I
34						+	62 (52-77)	49 (37-89)
35	D wk				300[f]	++	~68	28 (16-50)
36						+++	I	++
37	D wk				500[f]	I	I	
38	D wk				200[f]	I	I	+
39	D wk				200[f]	I	I	+
40	D	70[f]			200[f]	(+)		++
41	D	155 (132-181)	125 (118-143)	1.24	700[f]	I	I	++
42	D	182 (170-193)	197 (183-213)	1.08	700[f]	I	I	58 (37-117)
43	I				700[f]	+	I	
45	D wk				700[f]	(+)	I	I
46	D wk				700[f]	I	~100	
47							I	58 (38-98)
48	D wk				>300[f]	+++	49 (31-60)	++
49	D wk				300[f]	+++	I	++
50	D wk				300[f]	I	I	+
51	I				>1000[f]	(+)	I	
53	D wk				200[f]	I	I	++
54	ST-D				200[f]	++	107 (57-164)	P
55	ST-D	100[f]			200[f]	+++	78 (59-118)	P
56	D	41 (32-49)	76 (67-86)	1.85	247 (209-291)	(+)	70 (54-90)	31 (23-41)
57	D	84 (74-96)			117 (100-137)	++	66 (49-88)	+
58	D				200[f]	+	68 (58-78)	~82
59	D	90 (80-102)	149 (131-170)	1.65	475 (317-608)	++	89 (78-125)	++
60	D wk				254 (190-340)	++	74 (55-110)	I
61						+	23 (18-29)	+++
62	D-ST	11 (4-26)	55 (38-78)	5.2	700[f]	++	23 (18-30)	30 (14-74)
63						+++	I (30)	I
64	ST-D				200[f]	+++	~100	+
65	D	49 (44-54)	92 (83-102)	1.90	238 (207-274)	++	28 (24-34)	37 (23-63)
66	D	30 (27-34)	64 (58-71)	2.14	200[f]	+++	28 (26-35)	37 (24-50)
67	D-ST	46 (35-60)	67 (55-82)	1.45	700[f]	++V	35 (31-39)	29 (18-43)
68	D	200[f]			300[f]	++	~100	++
69	D	70[f]			300[f]	+++	74 (56-98)	59 (44-75)
70	D				200[f]	++	66 (49-88)	I
71	D	100 (89-112)	144 (116-179)	1.44	250[f]	(+)	128 (96-213)	60 (44-80)
72	D	70[f]			200[f]	I	I	++
73						+		I

74	ST-D wk				200[f]	I	I	+
76	I				>1000[f]	+++	I	I
77	I				500[f]	++	I	
78	D wk				>300[f]	+++	I	I
79	D wk				700[f]	I	I	I
80						I	~100	I
81	D wk				>1000[f]	I	I	I
82	D	41 (34-49)	66 (60-72)	1.63	300[f]	I	70 (53-87)	32 (20-46)
83						++	30 (23-37)	23 (16-31)
84						++	44 (38-49)	+++
85						+++		
86	D wk				500[f]	+++	45 (35-57)	++
87	D wk				200[f]	I	~100	58 (41-92)
88						++		
90	ST-D				200[f]	++	I	
91	D wk				200[f]	+++	31 (17-37)	58 (39-89)
92						++	22 (20-24)	
93						+	I	
94	ST wk				200[f]	++	~90	
96	D wk				700[f]	I	44 (34-52)	++
98	D	200[f]			700[f]	+	75 (65-84)	61 (40->100)
99	D wk				300[f]	+	I	I
100	D				200[f]	(+)		
101	ST-D				200[f]	I		
102						+		
103						+++		
104						++	I	++
107						++	I	+
108	ST wk				70[f]	+++	I	++
109	ST-D				300[f]	++	I	
amitriptyline	ST-D				70 (65-76)	+++	14 (10-18)	8 (5-14)
imipramine	ST-D				85 (70-99)	+++	15 (11-20)	6 (4-10)
doxepin	D	40 (37-43)	43 (41-51)	1.14	50 (33-75)	++	16 (11-22)	7 (5-9)
phenytoin	ST-D				700[f]	I	6 (4-8)	
viloxazine	ST-D				200[f]	++	17 (15-20)	++
diazepam	D	67 (49-81)	136 (121-168)	2.0	321 (206-502)		7 (5-9)	1 (1-3)
chlordiazepoxide	D	53 (44-64)	140 (114-172)	2.64	254 (223-290)	I		5 (3-9)
phenobarbital	D	60 (55-65)	107 (95-121)	1.78	222 (188-349)		15 (13-18)	22 (16-42)

[a] Mouse behavior test profiles: D = depressant; ST = stimulant; C = convulsant; wk = weak; I = inactive. [b] 95% confidence limits in parentheses. [c] Antagonism of reserpine-induced hypothermia. Minimum oral dose producing a significant reversal: (+) = >20 mg/kg; + = 5-20 mg/kg; ++ = 0.5-2.5 mg/kg; +++ = <0.5 mg/kg; V = excessive variability in data; I = inactive at highest dose tested (50 mg/kg). [d] Maximal electroshock antagonism (MES). [e] Antagonism of etonitazene-induced rigidity. ED_{50} or results at 60 mg/kg, ip, coded as follows: + = 10-30% reduction; ++ = 30-70% reduction; +++ = >70% reduction; P = rigidity was potentiated by compound. [f] Data estimated from mouse behavior experiment.

Table V. Comparative Biological Test Results of 2-[(Alkoxycarbonyl)amino]- and 2-Aminoimidazolines

compd	in vivo reserpine[a] hypothermia (po, mouse)	in vivo NE (mouse heart): ED_{50}, mg/kg, ip	in vitro, IC_{50},[b] $\times 10^{-7}$ M	
			NE	5-HT
1	1.25 (55)	1.3 (0.4–4.9)	1600	>1000
109	<10 (60)	0.3 (0.1–0.6)	1	310
49	0.15 (52)	14.2 (5.1–42)	>1000	>1000
108	0.15 (80)	6.5 (3.7–12)	1	78
66	0.15 (62)	34 (13–133)	300	1500
103	0.15 (57)	18.3 (5.1–73)	5	300
amitryptyline	0.15 (64)	4.4 (2.8–6.9)	25	85
imipramine	0.63 (44)	6.7 (3.1–15)	38	53

[a] Minimum active dose, milligrams per kilogram (percent reversal at 10 mg/kg). [b] Molar concentration that causes 50% inhibition of norepinephrine and 5-hydroxytryptamine uptake, respectively, in rat brain slices.

1-Amino-2-(methylamino)-1-phenylethane (154). A mixture of 6.1 g of ethyl (2-chloro-2-phenylethyl)carbamate (10, Ar = Ph) (27 mmol) and 2 g of NaN_3 (31 mmol) in 50 mL of Me_2SO was stirred at 70 °C for 16 h. The mixture was poured into water, and the organic material was extracted with benzene. The benzene was dried over K_2CO_3 and evaporated under vacuum to leave 5.7 g of ethyl(2-azido-2-phenylethyl)carbamate: IR (film) 2100, 1710, 1525, 1250 cm^{-1}. GLC analysis (3% SE-30) showed this product to be free of starting material. A slurry of 2 g of LAH (52 mmol) in 200 mL of ether was stirred in an ice bath, and the β-azidoethyl carbamate in 50 mL of ether was added dropwise. The mixture was refluxed overnight, cooled, and treated dropwise with 2 mL of H_2O, 2 mL 15% NaOH, and finally 3.6 mL of H_2O and stirred for an additional 2 h. The solids were removed by filtration, and the filtrate was concentrated and distilled, affording 2.1 g (52%) of 154: bp 70–73 °C (0.5 mm). A sample of 1 g of the diamine (6.7 mmol) was dissolved in 5 mL of ethanol that contained 0.5 g of HCl (14 mmol), and the dihydrochloride salt was precipitated by the addition of ether. There was 1.45 g of pure product, mp 202–206 °C.

***cis*-1,2-Indandiamine.** A solution of 3.95 g of *cis*-1,2-diacetamidoindan, mp 211–212 °C (lit.[6] mp 209–210 °C) (17 mmol) in 60 mL of concentrated HCl was refluxed for 15 h. A small amount of dark brown flakes was removed by filtration through a glass sintered funnel, and from the filtrate there was spontaneous crystallization of 2.52 g of the product dihydrochloride, mp 304–308 °C dec (darkening <280 °C). An additional 0.55 g, mp 298–303 °C dec, was obtained when the mother liquor was concentrated and the residue was treated with 2-propanol. The total yield was 3.07 g (82%). The free amine was liberated by treatment of the dihydrochloride salt in MeOH solution with 2 equiv of MeONa. The solution was filtered, the filtrate was concentrated, and the indandiamine was distilled, bp ~80 °C (0.01 mm). The distillate solidified, mp 43–47 °C (lit.[6] mp 153–154 °C) and turned green on storage.

2-Amino-5-(2,6-dichlorophenyl)-1-methyl-2-imidazoline Hydrobromide (104). 2-Amino-1-(methylamino)-1-(2,6-dichlorophenyl)ethane dihydrochloride (152; 5.56 g, 19.05 mmol) was dissolved in some water and then made alkaline with excess NaOH, and the free amine was extracted into toluene. The combined extracts were filtered, and the filtrate was concentrated. The residue was dissolved in 20 mL of MeOH, and 2.02 g of cyanogen bromide (19.07 mmol) was added. The clear solution was allowed to stand at 20 °C for 6 h, concentrated on a stirring hot plate to 25 mL, diluted with 100 mL of EtOH, and concentrated again to about 25 mL. The crystallization that had started while the mixture was still hot was allowed to continue by standing at 20 °C for 16 h. The crystalline 2-aminoimidazoline hydrobromide was collected, washed with ethanol, and dried to yield 5.1 g (82%): mp 317–319 °C; IR 1670, 1605 cm^{-1}.

5-(2,6-Dichlorophenyl)-2-[(methoxycarbonyl)amino]-1-methyl-2-imidazoline (85). A sample of 1 g of the 2-aminoimidazoline hydrobromide salt 104 (3.08 mmol) was converted into the free base (extracted from aqueous NaOH into toluene–methylene chloride; concentrated) and was refluxed with 20 mL of dimethyl carbonate for 1 h. After standing at 20 °C for 16 h, the mixture was concentrated and purified by column chromatography (silica gel 60; 2.5% MeOH in Et_2O) to afford 160 mg (17%) of the carbamate 85, mp 178–182 °C. A sample was recrystallized from MeOH: mp 180–182 °C; IR 1640, 1605 cm^{-1}.

2-Aminoindano[1,2-*d*]imidazoline (95). A mixture of 1.65 g of the indandiamine 163 (11 mmol) and 1.54 g of 2-methyl-2-thiopseudousea sulfate (5.5 mmol) in a small flask was immersed in a 230 °C oil bath and stirred magnetically. After a few minutes, there was some smoking and foaming, and the mixture solidified and was kept an additional 5 min at 230 °C. The solid was refluxed with 20 mL of MeOH, cooled, and collected. There was 1.58 g (64%) of the product as the sulfate salt: darkening at >300 °C and melting at 315–320 °C. The more water-soluble hydrochloride salt was prepared by stirring the sulfate in water with Amberlite ion-exchange resin CG-400, chloride form. The resin was removed by filtration, and the filtrate was concentrated to dryness. The product hydrochloride salt was trituated with 2-propanol, collected, and dried: mp 297–298 °C; IR 1675, 1600 cm^{-1}.

5-(2-Chlorophenyl)-2-[(ethoxycarbonyl)amino]-1-methyl-2-imidazoline (66). To a solution of 2.9 g of 2-amino-1-(methylamino)-1-(2-chlorophenyl)ethane dihydrochloride (141; 11.5 mmol) in some water was added saturated $NaHCO_3$ to a pH of about 7 and 80 mL of 2-propanol. This solution was combined with a solution of 2.8 g of the bis(ethoxycarbonyl) derivative of 2-methyl-2-thiopseudourea (12 mmol) in 50 mL of chloroform, and the mixture was stirred at 20 °C for 3 days and then concentrated to a small volume under reduced pressure. The addition of 50 mL of 1 N HCl resulted in a clear solution, which was washed several times with ether. The product was precipitated by the addition of saturated sodium bicarbonate to the acidic solution, collected, stirred with fresh water, and collected again to yield, after drying, 2.1 g, mp 104–107 °C. Recrystallization from 25 mL of cyclohexane afforded 1.93 g (60%) of pure carbamate: mp 117–118.5 °C; IR 1645, 1615 cm^{-1}.

The hydrochloride salt was obtained when 1.7 g (6.05 mmol) of the free amine was dissolved in 20 mL of EtOH that contained ~400 mg of HCl (~11 mmol), and the solution was diluted with ether until just barely cloudy (~200 mL). Scratching with a glass rod caused crystallization of the salt (1.5 g): mp 167–170 °C dec; IR 1745, 1625, 1605 cm^{-1}.

2-[(Isobutoxycarbonyl)amino]-4(5)-phenyl-2-imidazoline (23). The bis(isobutyl carbamate) of 2-methyl-2-thiopseudourea was prepared in situ by stirring a slurry of 2.5 g (9 mmol) of 2-methyl-2-thiopseudourea sulfate and 4 g (29 mmol) of isobutyl chloroformate in 8 mL of water in an ice bath for 2 h while adding 5.5 mL of 20% NaOH in three portions. The bis(carbamate) was extracted into chloroform (30 mL) and combined with a solution consisting of 3 g (14.3 mmol) of 1-phenylethane-1,2-diamine dihydrochloride, 12 mL of 10% NaOH, and 30 mL of 2-propanol. The mixture was stored for 10 days and then concentrated under vacuum, and the residue was dissolved in 100 mL of 0.5 N HCl. The solution was washed four times with ether and twice with toluene, and the product (1.84 g) was precipitated by the addition of saturated $NaHCO_3$, mp 184–187 °C. One recrystallization from 20 mL of benzene yielded 1.5 g (40%) of pure product, mp 192–193 °C; IR 3400, 1665, 1625 cm^{-1}.

2-[(Methoxycarbonyl)amino]indano[1,2-*d*]-2-imidazoline (96). Solutions of 2.28 g of the bis(methoxycarbonyl) derivative of 2-methyl-2-thiopseudourea (3, $R_2 = CO_2CH_3$; 11 mmol) in 200 mL of MeOH and 1.65 g of the indandiamine 163 (11 mmol) in 50 mL of EtOH were combined and stored at 20 °C for 16 h. The pure product that had crystallized was collected (1.51 g, mp 232–234 °C dec), and the mother liquor yielded an additional 0.41

g (mp 227–230 °C dec) when it was concentrated to 50 mL (total yield 1.92 g, 74%): IR 3360, 1630 cm^{-1}.

4(5)-(3,4-Dihydroxyphenyl)-2-[(methoxycarbonyl)amino]-2-imidazoline (51). A solution of 1.2 g of the HCl salt of the 3,4-bis(benzyloxy)phenyl-substituted imidazoline **52** in 50 mL of EtOH was hydrogenated at 40 lb of pressure over 0.5 g of 5% Pd/C overnight. The catalyst was removed by filtration, and the filtrate was concentrated to dryness. The solid was dissolved in 2-propanol, and the product was precipitated by the addition of ether, yielding 0.6 g (81.5% yield) of pure product as the hydrochloride salt, mp 178–179 °C dec; IR 1760, 1635, 1620 cm^{-1}.

Reaction of Diamine 125 with 3 (R_2 = CO_2Me). A solution of 4.6 g (11.4 mmol) of the diamine dihydrochloride in approximately 25 mL of water was treated with saturated $NaHCO_3$ to pH 8–9. This solution combined with a solution of 3.9 g (19 mmol) of *N,N'*-bis(methoxycarbonyl)-2-methyl-2-thiopseudourea in 70 mL of 2-propanol and 70 mL of chloroform. After standing at ambient temperature for 4 days, the mixture was concentrated to a small volume. The solid was collected and recrystallized once from 150 mL of 2-propanol and once from 200 mL of cyclohexane. There was 3.15 g (64%) of the noncyclized addition product **160**: IR 3330, 1740, 1630 cm^{-1}; the NMR spectrum exhibits two $COOCH_3$ signals.

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Registry No. 1, 69810-99-7; 1·HCl, 69811-37-6; 10 (Ar = Ph), 13800-04-9; 11 (Ar = Br-*m*-C_6H_4), 89145-13-1; **22**, 69811-33-2; **23**, 69811-32-1; 24, 69810-35-1; 24·HNO_3, 89145-14-2; **25**, 69811-02-5; **25**·HCl, 89145-15-3; **26**, 69811-00-3; **26**·HCl, 89145-16-4; **27**, 69811-12-7; **27**·HCl, 69811-13-8; **28**, 69811-11-6; **28**·HBr, 69811-24-1; **29**, 69811-14-9; **29**·HCl, 69811-15-0; **30**, 69811-17-2; **30**·HCl, 69811-18-3; **31**, 69811-36-5; **32**, 69811-16-1; **33**, 69811-34-3; **34**, 69811-19-4; **34**·HCl, 69811-20-7; **35**, 69811-22-9; **35**·HCl, 69811-23-0; **36**, 69811-35-4; **37**, 69810-98-6; **38**, 69811-04-7; **39**, 69811-03-6; **40**, 89145-17-5; **41**, 69811-08-1; **41**·HCl, 89145-18-6; **42**, 69811-05-8; **42**·HNO_3, 69811-10-5; **43**, 69811-09-2; **43**·HCl, 89145-19-7; **44**, 89145-20-0; **45**, 69811-21-8; **46**, 69811-26-3; **47**, 89145-21-1; **47**·H_2SO_4, 89145-22-2; **48**, 69811-29-6; **48**·HCl, 69828-14-4; **49**, 69811-30-9; **49**·H_2SO_4, 89145-23-3; **50**, 89145-24-4; **51**, 89145-25-5; **51**·HCl, 69811-28-5; **52**, 69811-39-8; **52**·HCl, 69811-40-1; **53**, 69811-25-2; **53** hemicitrate, 89164-62-5; **54**, 66308-18-7; **54**·HCl, 66308-19-8; **55**, 66308-21-2; **56**, 66308-22-3; **57**, 66308-23-4; **58**, 66308-16-5; **58**·HCl, 66308-17-6; **59**, 66308-20-1; **60**, 66308-26-7; **61**, 89145-26-6; **61**·HCl, 89145-27-7; **62**, 89145-28-8; **62**·HCl, 66308-31-4; **63**, 89145-29-9; **63**·HCl, 89145-30-2; **64**, 89145-31-3; **64**·HCl, 66308-32-5; **65**, 66308-27-8; **66**, 66308-29-0; **66**·HCl, 66308-30-3; **67**, 89145-32-4; **67**·HCl, 66308-34-7; **68**, 66308-33-6; **68**·HBr, 89145-33-5; **69**, 89145-34-6; **69**·HCl, 89145-35-7; **70**, 66308-28-9; **71**, 66308-24-5; **71**·HCl, 66308-25-6; **72**, 89145-36-8; **73**, 89145-37-9; **74**, 89145-38-0; **74**·HCl, 89145-39-1; **75**, 89145-40-4; **76**, 89145-41-5; **76**·HCl, 89145-42-6; **77**, 89145-43-7; **78**, 89145-44-8; **78**·HCl, 89145-45-9; **79**, 89145-46-0; **79**·HCl, 89145-47-1; **80**, 89145-48-2; **81**, 89145-49-3; **82**, 66308-35-8; **82**·H_2SO_4, 89145-50-6; **83**, 89145-51-7; **84**, 89145-52-8; **85**, 89145-53-9; **86**, 89145-54-0; **87**, 89145-55-1; **88**, 89145-56-2; **89**, 89164-63-6; **90**, 89145-57-3; **91**, 89145-58-4; **91**·HCl, 89145-59-5; **92**, 89277-77-0; **92**·HCl, 89145-60-8; **93**, 89145-61-9; **93**·HCl, 89145-62-0; **94**, 89145-63-1; **94**·HCl, 89145-64-2; **95**, 89145-65-3; **95**·H_2SO_4, 89145-66-4; **96**, 89145-67-5; **97**, 89145-68-6; **97**·HBr, 89164-64-7; **98**, 89145-69-7; **98**·HBr, 89145-70-0; **99**, 89145-71-1; **99**·HCl, 89145-72-2; **100**, 89145-73-3; **101**, 89145-74-4; **102**, 89145-75-5; **103**, 89145-76-6; **103**·HBr, 66308-15-4; **104**, 52157-32-1; **104**·HBr, 89145-77-7; **105**, 89145-78-8; **105**·HBr, 89145-79-9; **106**, 89145-80-2; **106**·HBr, 89145-81-3; **107**, 89145-82-4; **107**·HBr, 89145-83-5; **108**, 89145-84-6; **108**·HBr, 40658-99-9; **109**, 89145-85-7; **109**·HBr, 49703-82-4; **110**·2HCl, 89145-86-8; **111**·2HCl, 89145-87-9; **112**·2HCl, 89145-88-0; **113**·2HCl, 89145-89-1; **114**·2HCl, 69810-90-8; **115**·2HCl, 69810-91-9; **116**·2HCl, 89145-90-4; **117**·2HCl, 89145-91-5; **118**·2HCl, 69810-73-7; **119**·2HCl, 69810-74-8; **120**·2HCl, 89145-92-6; **121**·2HCl, 89145-93-7; **122**·2HCl, 89145-94-8; **123**·2HCl, 89145-95-9; **124**·2HCl, 89145-96-0; **125**·2HCl, 89145-97-1; **126**·2HCl, 89145-98-2; **127**·2HCl, 89145-99-3; **128**·2HCl, 89146-00-9; **129**·2HCl, 89146-01-0; **130**·2HCl, 89146-02-1; **131**·2HCl, 89146-03-2; **132**·2HCl, 89146-04-3; **133**·2HCl, 69810-88-4; **134**·2HCl, 89146-05-4; **135**·2HCl, 66308-13-2; **136**, 66308-10-9; **137**·2HCl, 66308-12-1; **138**·2HCl, 66308-08-5; **139**·2HCl, 89146-06-5; **140**·2HCl, 89164-65-8; **141**·2HCl, 66308-07-4; **142**·2HCl, 89146-07-6; **143**·2HCl, 66308-09-6; **144**·2HCl, 66308-11-0; **145**·2HCl, 89146-08-7; **146**·2HCl, 89146-09-8; **147**·2HCl, 89146-10-1; **148**·2HCl, 89146-11-2; **149**·2HCl, 89146-12-3; **150**·2HCl, 89146-13-4; **151**·2HCl, 89146-14-5; **152**·2HCl, 89146-15-6; **153**·2HCl, 89146-16-7; **154**·2HCl, 89146-17-8; **155**·2HCl, 89146-18-9; **156**·2HCl, 89146-19-0; **157**, 89164-66-9; **158**, 89146-20-3; **159**, 89146-21-4; **160**, 89146-22-5; **161**, 89146-23-6; **162**·HCl, 89146-24-7; **163**·2HCl, 64749-63-9; **164**·2HCl, 89146-25-8; **165**·2HCl, 89146-26-9; **166**·2HCl, 89146-27-0; *p*-(hydroxymethyl)benzaldehyde, 52010-97-6; 2-(methylamino)-*p*-(hydroxymethyl)benzeneacetonitrile, 89146-28-1; ethyl (2-azido-2-phenylethyl)carbamate, 89146-29-2; *cis*-1,2-diacetamidoindan, 89146-30-5; *cis*-1,2-indandiamine dihydrochloride, 89146-31-6; *cis*-1,2-indandiamine, 57432-87-8; 2-methyl-2-thiopseudourea hemisulfate, 867-44-7; 2-methyl-2-thiopseudourea [bis(ethoxycarbonyl) derivative], 89164-67-0; 2-methyl-2-thiopseudourea [bis(isobutyl carbamate) derivative], 89146-32-7; 2-methyl-2-thiopseudourea [bis(methoxycarbonyl) derivative], 34840-23-8; 1-indanone, 83-33-0; benzylamine, 100-46-9.