Table III. Urinary Excretion of Radioactivity from Rats[a] after Subcutaneous Administration of [^{3}H]Cyclazocine

Hours after injection	% of dose excreted (mean ± S.E.)
0–24	59.6 ± 0.3
24–48	9.0 ± 2.2
48–72	3.0 ± 0.8

[a] Three rats each received 2 mg of [^{3}H]cyclazocine hydrochloride dissolved in saline.

of tritiated water. Since no significant radioactivity was lost during lyophilization, it can be concluded that the tritium tag is metabolically stable.

Experiments *in Vitro*. A sample of the composite (sample F) (0.5–1.0 g) was sewn into a cheese-cloth sack and anchored under the water level of the sample holder 1 (Figure 5) of a 300-ml modified Raab extractor. [When the composite was in film form (sample B) the sample was placed as such in holder 1.] The cyclazocine was extracted with tepid (29 ± 3°) water as the solvent. At intervals of 6, 24, and 48 hr and then every 6 days the aqueous solution (av 150 ml) in the boiler (2) was collected and the volume recorded. The collected solutions were replaced at every sampling with distilled water. A sample of aqueous solutions (1 ml) was pipetted into 15 ml of scintillation solution and the radioactivity measured. The values of cyclazocine extracted in each interval of time are reported as per cent of dose initially present in the sample, calculated on the basis of disintegrations per minute.

At the end of the experiment the sample of composite left in the extractor was dissolved in dichloromethane and the radioactivity of the obtained solution measured. The total radioactivity of the extracted aqueous solution plus the radioactivity found in the sample after extraction checked with that present in the sample before extraction.

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Antihypertensive Agents. Synthesis and Biological Properties of 2-Amino-4-aryl-2-imidazolines†

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The synthesis and antihypertensive activity of a series of 2-amino-4-aryl-2-imidazolines are described. Although halogenated aryls and primary 2-amino or 2-methylamino groups are particularly suitable for good antihypertensive activity, an obvious correlation of physical parameters of the aryl substituents or amine groups with antihypertensive effects is not observed. Members of this series are potent adrenergic neuronal blocking agents; they also affect uptake and release of heart norepinephrine and prevent reserpine-induced ptosis. However, none of these biological effects correlate with antihypertensive activity in DOCA rats. One compound, 19, is particularly effective, after oral or subcutaneous administration, in several hypertensive models.

We have synthesized a series of 2-amino-4-aryl-2-imidazolines (V and VI) which incorporates the structural features of benzyl- and phenethylguanidines. These types of guanidines are believed to affect blood pressure by their actions at peripheral sympathetic nerve terminals.[1-3] This series of imidazolines is also chemically related to 2-(2,6-dichloroanilino)-2-imidazoline (catapres), a potent hypotensive agent, which appears to act mainly by a central mechanism.[4]

Many of the imidazolines (V and VI) are potent antihypertensive agents in hypertensive rat models, and we have attempted to relate some relevant biological actions and physical properties of these agents to their antihypertensive effects.

Chemistry. The 2-amino-4-aryl-2-imidazolines (Table I) were synthesized from β-aminophenethylamines III as shown in Scheme I. Primary amine derivatives V were obtained by cyclizing the β-aminophenethylamines with cyanogen bromide (method 10). The 2-substituted amino compounds VI were obtained by cyclizing the primary β-aminophenethylamines with carbon disulfide, followed by S-methylation with methyl iodide and displacement of methyl mercaptan with various amines (method 13). The hydrazones **37-40** were prepared by condensation of the hydrazine **36** with aldehydes or acetone (method 14).

Infrared spectra of the 2-amino-4-aryl-2-imidazolines are consistent with a delocalized guanidinium system. They exhibit strong NH absorption in the 3100-3400-cm^{-1} region rather than in the ammonium region. Their strong C=N absorption at 1680 and 1595 cm^{-1} is characteristic of the disubstituted guanidinium ion.[5]

The β-aminophenethylamine intermediates III (Table II) were prepared by several routes (A, B, and C) as shown in Scheme I. The unsubstituted diamine **51** and the 4-MeO de-

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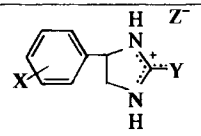
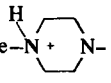
Table I. 4-Aryl-2-amino-2-imidazolines

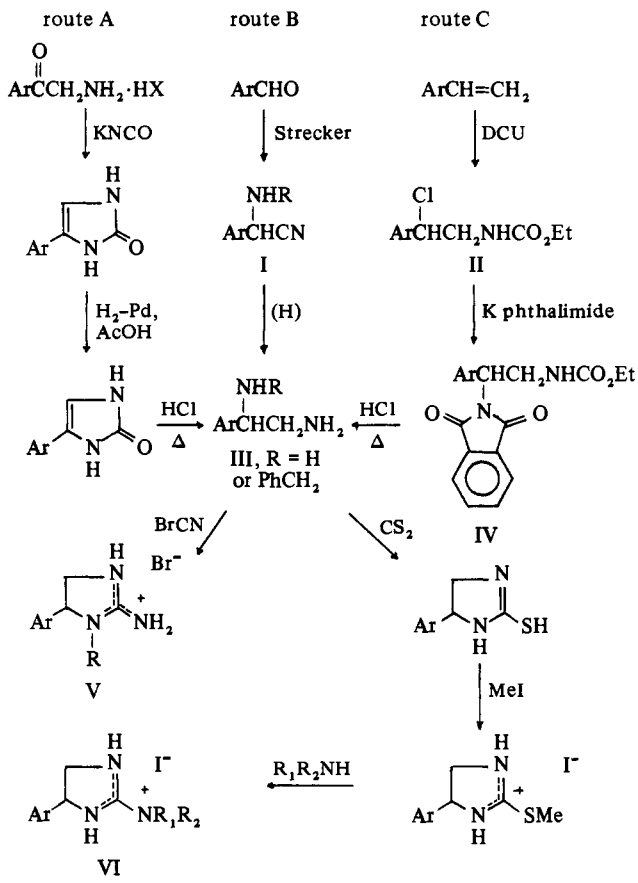


Compd no.	X	Y	Z[a]	Method	Crystn solvent[b]	Mp, °C[c]	Formula	Biological data: Neuronal block[d]	NE release,[d] % control	NE uptake,[d] % control	Prevention of ptosis,[d] ED_{50}, mg/kg po	Antihypertensive activity[d,e]
1	H	NH_2	A	10	AB	181–182.5[f]	$C_9H_{12}BrN_3$	0.03	74	9	0.65	0
2	4-Me	NH_2	A	10	GC	185–187.5	$C_{10}H_{14}BrN_3$	3.0	128	15	11	++
3	3-Me	NH_2	A	10	GB	148–149	$C_{10}H_{14}BrN_3$	0.43	67	21	8.3	++
4	4-Ph	NH_2	A	10	GC	256–258	$C_{15}H_{16}BrN_3$	0.60	185	85	24	++
5	4-CF_3	NH_2	A	10	GB	135.5–137.5	$C_{10}H_{11}BrF_3N_3$		43	29	>30	+
6	4-MeO	NH_2	A	10	AB	210.5–211	$C_{10}H_{14}BrN_3O$	1.0	146	66	5.9	+
7	3-MeO	NH_2	A	10	GB	150–151.5	$C_{10}H_{14}BrN_3O$		49	18	22	+
8	3,4-$(MeO)_2$	NH_2	A	10	DB	158.5–159.5	$C_{11}H_{16}BrN_3O_2$	0.003	99	113	>25	++
9	4-$PhCH_2O$	NH_2	A	10	AB	219.5–224.5	$C_{16}H_{18}BrN_3O$	0.75	107	70	>10	0
10	3-$PhCH_2O$	NH_2	A	10	HC	178.5–180.5	$C_{16}H_{18}BrN_3O$		64	58	>30	++
11	3,4-$(PhCH_2O)_2$	NH_2	A	10	AB	196.5–198.5	$C_{23}H_{24}BrN_3O_2$	<0.3	110	115	>25	0
12	4-HO	NH_2	A	11	AB	176.0–178.0	$C_9H_{12}BrN_3O$	<0.003	72	41	>25	0
13	3-HO	NH_2	A	11	G	119.5–122.5	$C_9H_{12}BrN_3O$		35	7	47	+++
14	3,4-$(HO)_2$	NH_2	A	11	GC	167.5–169.5	$C_9H_{12}BrN_3O_2$	<0.03	30	14	>25	+++
15	4-F	NH_2	A	10	GC	199–200.5	$C_9H_{11}BrFN_3$		52	22	0.6	0
16	4-Cl	NH_2	A	10	AB	241–242	$C_9H_{11}BrClN_3$	2.0	59[g]	24[g]	4.4	++
17	3-Cl	NH_2	A	10	GC	168.5–170.5	$C_9H_{11}BrClN_3$	0.03	45	17	1.4	+
18	2-Cl	NH_2	A	10	AB	213.5–215.5	$C_9H_{11}BrClN_3$	4.3	135[g]	51[g]	0.13	
d-18[h]	2-Cl	NH_2	A	10	AB	162–163	$C_9H_{11}BrClN_3$	3.8	113[g]	52[g]	0.07	++
l-18[i]	2-Cl	NH_2	A	10	AB	160–162.5	$C_9H_{11}BrClN_3$	3.0	103[g]	37[g]	0.78	+
19	3,4-Cl_2	NH_2	A	10	AB	217.5–219.5	$C_9H_{10}BrCl_2N_3$	1.5	15	5	14	++++
20	2,4-Cl_2	NH_2	A	10	GC	198.5–200.5	$C_9H_{10}BrCl_2N_3$	3.0	101	34	3	+++
21	2,6-Cl_2	NH_2	A	10	AB	233–235	$C_9H_{10}BrCl_2N_3$	3.0	135	49	0.18	+++
22	4-Br	NH_2	A	10	GC	239–240.5	$C_9H_{11}Br_2N_3$	0.6	48	16	19.5	++
23	H	$PhCH_2NH$-	D	13	CB	203–204	$C_{18}H_{19}N_3O_2$	0.15	95	99	>25	++
24	H	4-Cl-$C_6H_4CH_2NH$-	D	13	DB	180.5–182.5	$C_{18}H_{18}ClN_3O_2$	<0.3	94	105	>10	+++
25	H	MeNH-	E	13[j]	CB	186–186.5	$C_{13}H_{18}N_3O_4$	0.1	110	9	0.21	0
26	H	$Me_2\overset{+}{N}H(CH_2)_3NH$-	2B	13	AB	208–210	$C_{14}H_{24}Cl_2N_4$	<0.003	84	82	>25	+
27	H		2B	13	AB	257.5–259.5	$C_{14}H_{22}Cl_2N_4$	0.003	108	85	>25	+
28	H	Me_2N-	B	13	CB	199.5–201	$C_{11}H_{16}ClN_3$	0.008	106	72	20.8	0
29[k]	H	NH_2-	A	10	CB	242.5–244.5	$C_{16}H_{18}BrN_3$	0.075	88	84		0
30	H	HS-	F	12	AF	191–193.5[l]	$C_9H_{10}N_2S$					
31	H	MeS-	C	12	AB	136.5–137.5	$C_{10}H_{13}IN_2S$	<0.003			>25	0
32[m]	2-Cl	NH_2	A	10	CB	221.5–223.5	$C_{16}H_{17}BrClN_3$	0.15	105	113	>25	0
33	2-Cl	$PhCH_2NH$-	C	13	AB	147–149	$C_{16}H_{17}ClIN_3$	0.3	113	99	>25	0
34	2-Cl	HS-	F	12	AF	193–203						
35	2-Cl	MeS-	C	12	EB	168.5–170.5	$C_{10}H_{12}ClIN_2S$					
36	2-Cl	NH_2NH-	C	13	EB	198.5–200.5	$C_9H_{12}ClIN_4$	10.0	192	23	3.6	++
37	2-Cl	$Me_2C{=}NNH$-	C	14	AB	207.5–209.5	$C_{12}H_{16}ClIN_4$	10.0	178	59	1.2	++
38	2-Cl	$PhCH{=}NNH$-	C	14	GB	220–222	$C_{16}H_{16}ClIN_4$	<0.3	189	138	>25	0
39	2-Cl	2,4,6-Me_3-C_6H_2-$CH{=}NNH$-	CG	14	GB	183–185	$C_{19}H_{24}Cl_2N_4$	<0.3	140	138	>30	0

40	2-Cl	2,6-$Cl_2C_6H_3CH$=NNH-	C	14	GB	209.5–210.5	$C_{16}H_{14}Cl_3IN_4$	<0.003	115	127	>30	++
41	2-Cl	HONH-	B	13[j]	GC	175.5–177.5	$C_9H_{11}Cl_2N_3O$	1.5	104	26	0.18	+
42	4-Cl	HS-	F	12	AF	213.5–218	$C_9H_9ClN_2S$					
43	4-Cl	MeS-	C	12	E	178.5–181.5	$C_{10}H_{12}ClIN_2S$					
44	4-Cl	MeNH-	E	13[j]	CB	179.5–180.5	$C_{13}H_{17}ClN_3O_4$	0.075	54	27	>30	+++
45	4-Cl	NH_2NH-	B	13	HC	155.5–157.5	$C_9H_{12}Cl_2N_4$		85	9	5.0	++
46	4-Cl	4-Cl-$C_6H_4CH_2NH$-	C	13	CB	155–157.5	$C_{16}H_{16}Cl_4IN_3$					+
47	3,4-Cl_2	CH_2=$CHCH_2NH$-	C	13	HC	103–105	$C_{12}H_{14}Cl_2IN_3$					++
48	3,4-Cl_2	4-Cl-$C_6H_4CH_2NH$-	C	13	EB	116–119	$C_{16}H_{15}Cl_3IN_3$					0
49	3,4-Cl_2	MeNH-	C	13	HC	199–201	$C_{10}H_{12}Cl_3N_3$					+++
Guanethidine sulfate								1.0	26	37[n]	>25	+++
Bethanidine sulfate[o]								1.0	73[p]		>25	++
Catapres hydrochloride[q]								0.015	167	126	0.025[r]	++[s]

[a] A = Br, B = Cl, C = I, D = fumarate, E = hemimucate, F = free base, G = hydrate. [b] A = absolute EtOH, B = *i*-Pr_2O, C = MeOH, D = Me_2CO, E = *i*-PrOH, F = H_2O, G = MeCN, H = EtOAc. [c] Corrected melting point. [d] See biological section for explanation. [e] Relative activity was determined by the area under a time *vs.* % Δ (blood pressure) curve: 0 = inactive (<100 units), + = slightly active (100–300 units), ++ = active (300–500 units), +++ = very active (500–1000 units), and ++++ = extremely active (>1000 units). [f] H. Wollweber, R. Hiltmann, K. Stoepel, and G. Kroneberg, *Med. Chem., Abh. Med. Chem. Forschungsstaetten Farbwerke Hoechst A. G.*, 7, 248 (1963), report mp 177°. [g] At a dose of 10 mg/kg sc. [h] $[\alpha]^{25}D$ +94.6° (*c* 1, H_2O); prepared from *l*-β-amino-2-chlorophenethylamine (*l*-73). [i] $[\alpha]^{25}D$ −94.6° (*c* 1, H_2O); prepared from *d*-β-amino-2-chlorophenethylamine (*d*-73). [j] The amine HCl salt was allowed to react with the 2-methylthio-4-aryl-2-imidazoline base. [k] 1-Benzyl-5-phenyl-2-amino-2-imidazoline. [l] F. Feist, *Ber.*, 28, 3172 (1895), reports mp 192°. [m] 1-Benzyl-5-(2-chlorophenyl)-2-amino-2-imidazoline. [n] At a dose of 2 mg/kg sc. [o] *N',N''*-Dimethyl-*N*-benzylguanidine. [p] Value obtained after 3 hr: J. W. Daly, C. R. Creveling, and B. Witkop, *J. Med. Chem.*, 9, 280 (1966). [q] 2-(2,6-Dichloroanilino)-2-imidazoline. [r] Also reverses an established ptosis, ED_{50} = 0.022 mg/kg po. [s] At a daily dose of 50 μg/kg sc.

Scheme I

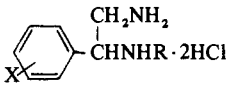


rivative **60** were obtained by the method of Duschinsky, *et al.*,[6] in good overall yield from the corresponding α-amino ketones (route A, method 8). However, difficulty in hydrogenating other imidazolone derivatives limits the use of this reaction sequence. The diamines III may also be synthesized from styrenes (route C, method 9). In the conversion of the β-chlorocarbamate II to the β-phthalimide IV, at least 2 equiv of K phthalimide are required. With 1 equiv, intramolecular displacement of Cl occurs to afford an aziridine which opens in the presence of excess K phthalimide. Both the phthalimide group and the carbamate function are hydrolyzed in one step with boiling concentrated HCl. The preferred route to the diamines (III) is through a Strecker reaction on the aldehyde, followed by reduction of the α-aminonitrile I (route B).

Various methods of performing the Strecker reaction have been tried,[7] but yields of primary α-aminophenylacetonitriles I (Table III) are generally <30%. Little difference in yields was noted whether the bisulfite adduct of the aldehyde was treated with NH_4OH and NaCN (method 1) or the free aldehyde was treated with NH_4Cl and NaCN (method 2). Use of MeCN or DMSO instead of aqueous MeOH gave higher yields in some cases; this may be due to better solubility of the aldehyde in these solvents. In the preparation of α-amino-2-chlorophenylacetonitrile (**97**) from the aldehyde bisulfite adduct, a significant amount (25%) of Schiff base was formed, presumably from reaction of starting aldehyde with the α-aminonitrile. This side reaction may account for the low yields of primary α-aminonitriles. Use of benzylamine hydrochloride instead of NH_4Cl in the Strecker reaction avoids this side reaction, and high yields of α-benzylaminophenylacetonitriles were obtained (method 3).

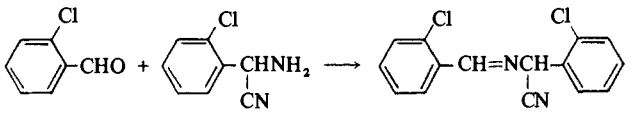
The α-benzylamino- and α-aminonitriles were reduced to

Table II. β-Aminophenethylamines



Compd no.	X	R	Method	Reaction solvent	Yield, %	Crystn solvent[a,b]	Mp, °C	Formula
50	H	$PhCH_2$	5	Et_2O	80	A	248-251	
51	H	H	7	MeOH	100	C	307-309[c]	
	H	H	8		72[d]	A		
52	4-Me	$PhCH_2$	5	Et_2O	61	T	244-247	$C_{16}H_{22}Cl_2N_2$
53	4-Me	H	6	MeOH	94		312-315	$C_9H_{16}Cl_2N_2$
54	3-Me	$PhCH_2$	5	Et_2O	70	T	205-210	
55	3-Me	H	7	MeOH	90	T	238-243	$C_9H_{16}Cl_2N_2$
56	4-Ph	$PhCH_2$	5	Et_2O	45	CG	257-259	$C_{21}H_{24}Cl_2N_2$
57	4-Ph	H	7	MeOH	72	T	325-327	
58	4-CF_3	$PhCH_2$	6	PhH	86	NR	242.5-245	$C_{16}H_{19}Cl_2F_3N_2$
59	4-CF_3	H	7	MeOH	82	T	250-260	$C_9H_{13}Cl_2F_3N_2$
60	4-MeO	H	8		35[d]	T	264-266[e]	$C_9H_{16}Cl_2N_2O$
61	3-MeO	$PhCH_2$	5	Et_2O	73	T	228-232	$C_{16}H_{23}Cl_2N_2O$
62	3-MeO	H	7	H_2O-MeOH	69	T	245-250	$C_9H_{16}Cl_2N_2O$
63	3,4-$(MeO)_2$	$PhCH_2$	5	Et_2O	68	T	227-229	$C_{17}H_{24}Cl_2N_2O_2$
64	3,4-$(MeO)_2$	H	7	H_2O-MeOH	77	T	258-261[f]	$C_{10}H_{18}Cl_2N_2$
	3,4-$(MeO)_2$	H	4	THF	75	AB		
65	4-$PhCH_2O$	H	4[g]	THF	35	NR	205-210	
	4-$PhCH_2O$	H	4	THF	65			
66	3-$PhCH_2O$	H	5	Et_2O-THF	43	NR	225-235	$C_{15}H_{20}Cl_2N_2O$
67	3,4-$(PhCH_2O)_2$	H	5	Et_2O	70	CB	241-243	$C_{22}H_{26}Cl_2N_2O_2$
68	4-F	$PhCH_2$	5	Et_2O	72	T	229-232	$C_{15}H_{19}Cl_2FN_2$
69	4-F	H	7	H_2O-MeOH	93	T	255-265	
70	4-Cl	$PhCH_2$	5	Et_2O	68	AB	239-242	$C_{15}H_{19}Cl_3N_2$
71	4-Cl	H	7[h]	MeOH	80	CB	285-288	$C_8H_{13}Cl_3N_2$
	4-Cl	H	4	THF	70			
	4-Cl	H	9		41[d]			
72	3-Cl	H	5[i,j]	THF	75	HC	280-283	$C_8H_{13}Cl_3N_2$
73	2-Cl	$PhCH_2$	5[i]	THF	48	A	218-223	$C_{15}H_{19}Cl_3N_2$
	2-Cl	$PhCH_2$	5	Et_2O	97			
74	2-Cl	H	7[h]	MeOH	87	CB	298.5-300.5[k]	$C_8H_{13}Cl_3N_2$
	2-Cl	H	4[g]	THF	51	E		
l-74	*l*-2-Cl	H				A	302.5-304.5[k]	$C_8H_{13}Cl_3N_2$
l-74[l]	*l*-2-Cl	H				A	245.5-249.5[k]	$C_{28}H_{43}ClN_2O_8S_2$
d-74	*d*-2-Cl	H				CB	297.5-300.5[k]	$C_8H_{13}Cl_3N_2$
d-74[m]	*d*-2-Cl	H				AF	205.5-207.5[k]	$C_{12}H_{17}ClN_2O_6$
75	3,4-Cl_2	H	5	Et_2O	82	T	283-285	$C_8H_{12}Cl_4N_2$
76	2,4-Cl_2	$PhCH_2$	5	Et_2O	76	T	239-241	$C_{15}H_{14}Cl_4N_2$
77	2,4-Cl_2	H	7[h]	MeOH	91	T	305-310	$C_8H_{12}Cl_4N_2$
78	2,6-Cl_2	H	4	THF	68	AB	329-331	
79	4-Br	H	4[g]	THF	66	T	300-305	$C_8H_{12}BrClN_2$

[a]See footnote *b*, Table I. [b]NR = not recrystallized; T = triturated with *i*-PrOH. [c]L. Arpesella, A. LaManna, and M. Grassi, *Gazz. Chim. Ital.*, 85, 1354 (1955), report mp 285-286°. [d]Overall yield for three steps. [e]E. Zalay, *Vegyip. Kut. Intez. Kozlem.*, 4, 101 (1954); melting point not given. [f]S. I. Kaneuskaya and D. S. Yaskina, *Zh. Obshch. Khim.*, 27, 68 (1957), and *J. Gen. Chem. USSR*, 27, 77 (1954); melting point not given. [g]The aminonitrile HCl was reduced. [h]Deactivated catalyst was used; see Experimental Section. [i]The reaction mixture was refluxed overnight. [j]The α-aminophenylacetamide was reduced. [k]Corrected melting point. [l]Di(*d*-camphorsulfonate) salt. [m]*l*-Tartrate salt.



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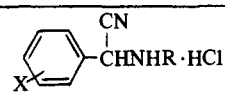
β-aminophenethylamines with $LiAlH_4$ (method 5) or diborane (method 4). Previous reports[8,9] have shown that α-aminonitriles readily lose the CN- group on attempted reduction. However, we have found that the use of $LiAlH_4$ at 0° in ether solution affords diamine in good yield with little hydrogenolysis. At elevated temperatures, the yield of diamine is much lower (see Table II, compound **73**). The diborane method affords the desired product in good yield in some cases, but in other cases little diamine is formed; higher yields are obtained using the α-aminonitrile free bases than the hydrochloride salts (see Table II, compound **65**). In the reduction of the 4-CF_3- compound **85** with $LiAlH_4$, none of the desired diamine **58** was isolated. However, use of diisobutylaluminum hydride (DIBAL) (method 6), in benzene solution at 0-5°, afforded **58** in good yield.

The best route to many of the primary diamines is by formation of β-benzylaminophenethylamines and catalytic debenzylation using a Pd/C catalyst (method 7). This procedure is particularly successful for compounds that do not contain Cl or Br substituents in the aromatic ring. These halogen derivatives undergo dehalogenation as well as debenzylation in agreement with the work of Freifelder[10,11] on the hydrogenolysis of *N*-benzylchlorophenylalkylamines. Surprisingly, we found that selective debenzylation of our chlorinated derivatives can be accomplished with 10% Pd/C catalyst if the catalyst is allowed to burn briefly during the "wetting process" with anhydrous MeOH. Extensive dechlorination occurs if the catalyst is not deactivated in this way or if water is present in the reaction mixture.

Biology. Groups of five rats (with DOCA-induced hypertension), each having a systolic blood pressure of 170

Table III. α-Aminophenylacetonitriles



Compd no.	X	R	Method	Reaction solvent	Yield, %	Crystn solvent[a,b]	Mp, °C	Formula
80	H	$PhCH_2$	3	H_2O–MeOH (1:1)	95	A	161–164[c]	$C_{15}H_{15}ClN_2$
81	H	H	1	H_2O	50	AB	171–173[d]	
	H	H	2	H_2O–DMSO (1:9)	28			
82	4-Me	$PhCH_2$	3	H_2O–MeOH (1:1)	95	NR	129–132	
83	3-Me	$PhCH_2$	3	H_2O–MeOH (1:1)	93	NR	166–170	$C_{16}H_{17}ClN_2$
84	4-Ph	$PhCH_2$	3	H_2O–MeOH (1:1)	95	NR	150–152	
85	4-CF_3	$PhCH_2$	3	H_2O–MeOH (1:1)	91	NR	153–158	$C_{16}H_{14}ClF_3N_2$
86	3-MeO	$PhCH_2$	3	H_2O–MeOH (1:1)	95	NR	155–158	$C_{16}H_{17}ClN_2O$
87	3,4-$(MeO)_2$	$PhCH_2$	3	H_2O–MeOH (1:1)	91	NR	114–116	$C_{17}H_{19}ClN_2O_2$
88	3,4-$(MeO)_2$	H	1	H_2O	30	AB	176–178[e]	$C_{10}H_{13}ClN_2O_2$
	3,4-$(MeO)_2$	H	2	H_2O–DMSO (1:19)	23			
89	4-$PhCH_2O$	H	1	H_2O–MeOH (1:1)	18	AB	178–179	$C_{15}H_{15}ClN_2O$
	4-$PhCH_2O$	H	2	H_2O–MeCN (1:1)	53		108–112[f]	
90	3-$PhCH_2O$	H	2	H_2O–DMSO (1:20)	43	T	167–168	$C_{15}H_{15}ClN_2O$
91	3,4-$(PhCH_2O)_2$	H	2	H_2O–MeOH–MeCN (1:1:1)	7	DB	168–171	$C_{22}H_{21}ClN_2O_2$
	3,4-$(PhCH_2O)_2$	H	2	H_2O–DMSO (1:24)	68			
92	4-F	$PhCH_2$	3	H_2O–MeOH (1:1)	92	NR	127–130	$C_{15}H_{14}ClFN_2$
93	4-Cl	$PhCH_2$	3	H_2O–MeOH (1:1)	92	G	132–134	$C_{15}H_{14}Cl_2N_2$
94	4-Cl	H	1	H_2O	16	AB	174–175	$C_8H_8Cl_2N_2$
95	3-Cl	H	2	H_2O–MeOH (1:1)	9	NR	253–256[g]	$C_8H_{10}Cl_2N_2O$
96	2-Cl	$PhCH_2$	3	H_2O–MeOH (1:1)	84	EB	153–155	$C_{15}H_{14}Cl_2N_2$
97	2-Cl	H	1	H_2O–MeOH (1:1)	24	EB	148.5–149	$C_8H_8Cl_2N_2$
	2-Cl	H	2	H_2O	30[h]			
98	3,4-Cl_2	H	2	H_2O–DMSO (1:20)	56	NR	184–185	$C_8H_7Cl_3N_2$
99	2,4-Cl_2	$PhCH_2$	3	H_2O–MeOH (1:1)	91	NR	138–144	$C_{15}H_{13}Cl_3N_2$
100	2,6-Cl_2	H	2	H_2O–MeOH (1:1)	27	AB	199–201	$C_8H_7Cl_3N_2$
101	4-Br	H	2	H_2O–MeOH (1:1)	27	NR	180–182	
	4-Br	H	2	H_2O–DMSO (1:20)	23			

[a] See footnote *b*, Table I. [b] NR = not recrystallized; T = triturated with *i*-PrOH. [c] L. E. Kholodov and V. G. Yashungskii, *J. Org. Chem. USSR*, **1**, 2103 (1965), report mp 143–145°. [d] G. Ruggeri and G. Rigoli, *Gazz. Chim. Ital.*, **54**, 550 (1924), report mp 173° dec. [e] J. Klosa, *J. Prakt. Chem.*, **12**, 258 (1961); melting point not given. [f] Isolated as the free base. [g] Isolated as the α-aminoacetamide; hydrolysis occurred during work-up. [h] The Schiff base **102**, mp 80–81°, was also isolated in 25% yield. *Anal.* Calcd for $C_{15}H_{10}Cl_2N_2$: C, 62.30; H, 3.48; N, 9.69. Found: C, 62.44; H, 3.56; N, 9.64.

mm or greater, received subcutaneously 5 mg/kg doses of each compound at 0 and 24 hr. Systolic blood pressure was determined by the tail-cuff method at 0 (immediately prior to dosing), 4, 24 (immediately prior to dosing), 28, and 48 hr.

The data‡ in Table I indicate that many of these imidazoline compounds effectively reduce the elevated pressure in the DOCA-hypertensive rat. Compound **19** is also orally active in DOCA rats, as well as in spontaneously hypertensive rats and in mecamylamine-induced hypertensive dogs.

The neuronal blocking potencies were determined on sympathetic nerves innervating the rabbit jejunum in an *in vitro* preparation similar to that described by Finkelman.[12] The values in Table I represent potency comparisons relative to bethanidine and are derived from the molar concentration of compound, estimated from log dose–response lines, that reduces the effect of nerve stimulation by 50% at 20 min.

The effects of test compounds on norepinephrine (NE) release from, and uptake into, mouse cardiac stores were measured by a modification of the methods of Daly[13] and of Lippmann and Wishnick,[14] and the results are shown in Table I. The test as conducted in this study consisted of two parts.

1. Mice were injected iv with DL-NE-7-^3H. After 4 hr, 20 mg/kg of the test compound was administered sc. Later (20 hr), the radioactivity of an extract of the mouse heart was measured and expressed as a percentage of the control value. Values greater than 100 indicate decreased release, whereas values less than 100 indicate increased release of NE.

2. After dosing (1 hr) the mice sc with 20 mg/kg of the test compound, they were injected iv with DL-NE-7-^3H. Later (3 hr), the radioactivity of an extract of the heart was measured and expressed as a percentage of the control value. Values less than 100 indicate inhibiton of uptake and/or increased release of NE.

The imidazolines were evaluated for their ability to both prevent reserpine-induced ptosis and reverse an established reserpine-induced ptosis in mice (Table I). Reserpine (2 mg/kg) was injected iv 1 hr after oral administration of the test compound. Later (1 hr) the extent of ptosis was estimated. Ptosis was deemed significant if the palpebral opening was not greater than 50% of normal. Conversely, the reserpine effect was significantly modified if the palpebral opening was *greater* than 50% of normal. In reversal tests, reserpine was injected first, followed 2 hr later by the test compound. At both 0.5- and 1-hr intervals after test drug the mice were examined for ptosis.

Representative imidazolines were tested *in vitro* for α-adrenergic receptor activity on the isolated rat seminal vesicle and β-adrenergic receptor activity on the isolated guinea pig trachea. No significant adrenergic receptor activity was observed. However, rapid iv injection of the primary 2-aminoimidazolines to anesthetized normotensive dogs in-

‡ The assays in the DOCA-hypertensive rats were conducted at Pharmakon Laboratories, Scranton, Pa., 18510, under the supervision of Dr. Richard J. Matthews.

creases blood pressure, heart rate, and myocardial contractile force. These responses appear to be due to an indirect action of the compounds that is both reflex in nature and dependent upon release of catechol amines. In general, compounds with substituted amino functions in the 2 position of the imidazoline ring cause weaker pressor, or else depressor, responses in the dog than do their primary 2-amino congeners. Only depressor responses have been observed in rabbits after iv or oral administration of selected primary 2-aminoimidazolines.

Several imidazolines were tested *in vitro* for inhibition of monoamine oxidase (MAO) in rat liver. The compounds were only weakly active, causing 50% inhibition of the enzyme at approximately 10^{-4} *M* concentrations.

Structure-Activity Relationships (SAR). Antihypertensive Activity. The 3,4-dichlorophenyl derivative **19** is more effective in lowering the blood pressure of DOCA-hypertensive rats than guanethidine or bethanidine or any other member of this series. The dichloro compounds **20** and **21** and the 3-HO and 3,4-$(HO)_2$ derivatives **13** and **14** are also very active antihypertensive agents. Among the chloro compounds, activity is in the order 3,4 > 2,6 > 2,4 > 4 ~ *d*-2 > *l*-2 ~ 3. In general, 4-substituted phenylimidazolines are more active than 3-substituted compounds. Exceptions to this are the 3-HO and 3-$PhCH_2O$ compounds **13** and **10**. The *d* enantiomer of **18** was slightly more effective than *l*-**18**.

Antihypertensive activity is retained by replacing the 2-amino group of the imidazoline ring by -NHMe, $-NHCH_2CH{=}CH_2$, $-NHNH_2$, or $-NHN{=}CMe_2$. Surprisingly, the 2,6-Cl_2 substituted hydrazone **40** is active, whereas the aryl hydrazones **38** and **39** are inactive. In the unsubstituted phenyl series, the only compounds with more than slight activity are the 2-benzylamino derivatives **23** and **24**. However, in the chlorophenyl series, the 2-benzylamino derivatives **33**, **46**, and **48** demonstrate only slight activity or are inactive. Compounds **29** and **32**, with a benzyl group on a ring N atom, are also inactive. Although we have been unable to observe any obvious correlation between physical parameters (π, σ, E_S) for the aryl substituents of these imidazolines and their antihypertensive activity, there does appear to be an optimum lipophilicity for the 2-amino substituent in each of the 4-aryl groups illustrated.

Adrenergic Neuronal Blocking Potency. For good neuronal blocking potency, the 2-amino-4-aryl-2-imidazolines require a substituent in the aromatic ring. In a series of para-substituted congeners with a 2-NH_2 group in the imidazoline ring, the potency order is Me > Cl > MeO > $PhCH_2O$ > Br ~ Ph ≫ H > HO. The methyl derivative **2** is three times as potent as guanethidine, whereas the unsubstituted compound **1** is relatively weak (0.03 times guanethidine). Best potency is found in compounds with chloro and methyl substituents in the ortho and/or para position of the aromatic ring; meta substituents are less effective in promoting neuronal blocking potency. The 4-Me compound **2** is seven times as potent as the 3-Me derivative **3** and, in a series of chlorinated compounds, the potency order is 2 > 2,6 ~ 2,4 > 4 > 3,4 ≫ 3. Little difference in potency was observed for the two enantiomers of compound **18**.

Variation of the substituent in the 2 position of the imidazoline ring has a great effect on neuronal blocking potency. In the 2-Cl series, the 2-NH_2 compound **18** is 4.3 times as potent as guanethidine, the 2-NHOH analog (**41**) is less potent, whereas the 2-hydrazine **36** is one of the two most potent compounds of the series (10 times guanethidine). This potency is retained in the acetone hydrazone **37**, but hydrazones from aromatic aldehydes have little potency. Compounds with other substituents in the 2 position of the imidazoline ring have little neuronal blocking potency; even the 2-$NHCH_3$ (**44**) is only $^1/_{27}$ as potent as the 2-NH_2 (**16**).

Uptake and Release of Norepinephrine (NE). In contrast to the SAR for neuronal blocking action, the most potent NE releasing agents in this series have meta and/or para substituents in the aromatic ring. The 3,4-dichloro derivative **19** causes a 50% increase in release of NE at a dose of 0.25 mg/kg sc, whereas a 2 mg/kg sc dose of guanethidine is required to achieve the same result. Compounds substituted in the ortho position with a chlorine atom do not deplete NE stores. Halogen, hydroxy, and trifluoromethyl substituents in the aromatic ring are most effective in promoting NE depletion. Replacement of the 2-NH_2 group of **16** with $NHCH_3$ (**44**) or $NHNH_2$ (**45**) decreases the NE releasing action.

Most of the imidazolines with 2-NH_2 substituents in the imidazoline ring decrease uptake of NE into nerve endings, and the potency order parallels that for NE release. Exceptions to this are the unsubstituted compound **1** and the 4-Me derivative **2**, which are potent inhibitors of NE uptake but only weak depletors of NE stores. For chloro-substituted derivatives, the order of potency is 3,4 > 3 ~ 4 > 2,4 > 2,6 ~ 2. The differences in activity in this series of chloro derivatives probably reflect the NE-releasing abilities of these compounds. The *type* of substituent in the aromatic ring, therefore, seems to be more important than its *position* for determining the inhibitory effect of the compound on the uptake process. In general, replacement of the 2-NH_2 group with substituted amino functions leads to compounds that are poor inhibitors of the NE uptake process. Exceptions to this are the 2-NHMe derivative **25**, which is as potent as the primary amine **1**, and the hydrazines **36** and **45** and 2-NHOH (**41**), which are more potent inhibitors than the primary amine.

Discussion

The blood pressure lowering action of antihypertensive agents of the guanethidine type is considered to be due to inhibiton of the sympathetic nervous system.[1-3] This is accomplished by (a) inhibiting impulse-dependent release of NE stored in sympathetic nerve endngs (*i.e.*, neuronal block), (b) promoting the depletion of NE stored in peripheral nerve terminals, and (c) blocking the NE uptake and/or binding mechanism in sympathetic nerve endings. In this series of imidazolines, we observed some, or all, of these actions in individual compounds (Table I). However, there is no clear-cut correlation between any single biological effect and the observed antihypertensive activity.

The unsubstituted compound **1** and its $NHCH_3$ analog **25** are potent inhibitors of NE uptake in the mouse heart, but they have little potency as neuronal blockers or as depletors of NE stores. They do not lower the blood pressure of DOCA-hypertensive rats. Among the compounds that are potent neuronal blocking agents, but do not deplete tissue stores of NE, antihypertensive activity ranges from inactive (**9**) to very active (**21**). The latter compound is a less potent neuronal blocker than **36** and **37**, but it is a more active antihypertensive agent than either **36** or **37**. Three compounds, **14**, **17**, and **44**, are depletors[§] of NE stores, with

[§] Data indicating release of NE may be due to increase in turnover rather than depletion of stores, and one cannot interpret them strictly as such without a measurement of actual levels.

little neuronal blocking action. Again, antihypertensive activity ranges from weakly active to very active. The derivative 8 is inactive, both as a depletor of NE stores and as a neuronal blocking agent, but it does lower the blood pressure of hypertensive rats.

Other biological effects, besides those described above, that might contribute to the antihypertensive activity of these imidazolines, have been studied. Many imidazolines are potent α-adrenergic receptor blocking agents,[1,15] but only weak α-blocking activity has been found in this series. Also, these agents are only weak inhibitors of MAO. Reserpine-induced ptosis might be considered evidence of peripheral sympathetic blockade or central depression. Prevention of reserpine-induced ptosis, unaccompanied by reversal of an established reserpine-induced ptosis, is characteristic of several pharmacologic classes of compound (*e.g.*, antidepressants, some MAO inhibitors, some antihistaminics, and some neuronal blocking agents). Some members of this series prevent, but do not reverse, reserpine-induced ptosis, whereas both guanethidine and bethanidine are inactive in this test system. Catapres differs in that it both prevents and reverses reserpine-induced ptosis (Table I). In our series some of the most active compounds (1, 15, and 25) in preventing ptosis exhibited no antihypertensive activity. Conversely, several compounds (*e.g.*, 13, 14, 44, and even 19) with good antiypertensive activity essentially lacked any antireserpine property. Thus, it does not appear that reserpine antagonism plays any obvious role in the antihypertensive activity of these compounds, at least in this DOCA-rat model.

Thus, although the biological profile of many members of this series of imidazolines is more like the peripherally acting guanidines, such as guanethidine, than the centrally acting catapres, their underlying mechanism(s) of action is (are) unclear at this time.

Experimental Section#

α-Aminophenylacetonitriles. See Table III for additional data and other compounds prepared by these methods.

Method 1. A solution of PhCHO (53 g, 0.5 mol) and $NaHSO_3$ (52 g, 0.5 mol) in H_2O (250 ml) was stirred at 25° for 20 min. NH_4OH (15 *N*, 33.3 ml) was then added rapidly and stirring was continued for 30 min. The mixture was cooled in an ice bath and a solution of NaCN (24.5 g, 0.5 mol) in H_2O (75 ml) was added slowly over 15 min and stirred for another 3 hr at room temperature. Insoluble product was extracted with Et_2O, washed with H_2O, and dried (K_2CO_3). Addition of 5.6 *N* EtOH–HCl precipitated 29.5 g (50%) of **α-aminophenylacetonitrile hydrochloride (81).**

Method 2. To a slurry of NaCN (32 g, 0.65 mol) and NH_4Cl (35 g, 0.65 mol) in 200 ml of DMSO–H_2O (9 : 1), 3,4-dibenzyloxybenzaldehyde (100 g, 0.325 mol) in DMSO (350 ml) was added in one lot and the mixture was stirred overnight at room temperature. The mixture was poured into H_2O (2 l.), and the insoluble oil was extracted into Et_2O, washed with H_2O, and dried (K_2CO_3). Addition of 5.6 *N* EtOH–HCl (45 ml) to the Et_2O solution precipitated 84 g (68%) of **α-amino-3,4-dibenzyloxyphenylacetonitrile hydrochloride (91).**

Method 3. To a stirred solution of NaCN (54 g, 1.1 mol) and $PhCH_2NH_2 \cdot HCl$ (158 g, 1.1 mol) in H_2O (400 ml) was added 2-chlorobenzaldehyde (154.3 g, 1.1 mol) in MeOH (400 ml) in one lot. After stirring the mixture at room temperature for 5 hr, it was diluted with H_2O (1 l.). The precipitated oil was extracted with Et_2O (2 l.) and dried (K_2CO_3). Addition of 5 *N* EtOH–HCl (280 ml) precipitated 268.7 g (84%) of **α-benzylamino-2-chlorophenylacetonitrile hydrochloride (96).**

β-Aminophenethylamines. See Table II for additional data and other compounds prepared by these methods.

Method 4. α-Amino-2,6-dichlorophenylacetonitrile hydrochloride (100) (24 g, 0.1 mol) was converted to its free base with 10% NaOH. To this oil (20 g, 0.1 mol) in THF (350 ml) under N_2, 225 ml of 1 *M* B_2H_6 in THF was added dropwise over 30 min. The temperature increased from 25 to 43°. After cooling, H_2O (100 ml) was added until H_2 evolution ceased and solvent was removed under reduced pressure to afford an oil which evolved gas vigorously on treatment with 5.6 *N* EtOH–HCl (36 ml, 0.2 mol). The acidic EtOH solution was evaporated under reduced pressure and converted to the free amine with 10% NaOH. The free base was extracted with $CHCl_3$ and dried (K_2CO_3) and the solvent removed to give an oil (15 g) which was treated with 5.6 *N* EtOH–HCl (27 ml, 0.15 mol). Dilution of the EtOH solution with an equal volume of *i*-Pr_2O yielded 19.0 g (68%) of **β-amino-2,6-dichlorophenethylamine dihydrochloride (78).**

Method 5. To a stirred suspension of $LiAlH_4$ (38 g, 1 mol) in Et_2O (1 l.) under N_2 was added dropwise, over 0.5 hr, a solution of the free base α-benzylamino-2-chlorophenylacetonitrile (96) (64.2 g, 0.25 mol) in Et_2O (500 ml) at 0°. The mixture was stirred at this temperature for 5 hr and at room temperature overnight. H_2O (38 ml) was then added, followed by 15% NaOH (38 ml), and finally another 70 ml of H_2O. Inorganic material was removed by filtration, and addition of 5 *N* EtOH–HCl (130 ml, 0.65 mol) precipitated 82 g (96%) of **β-benzylamino-2-chlorophenethylamine dihydrochloride (73).**

Method 6. To a stirred solution of α-benzylamino-4-trifluoromethylphenylacetonitrile (85) (24.7 g, 0.085 mol) in PhH (500 ml) under N_2 was added dropwise 228 ml of DIBAL (0.34 mol) solution at 0–5°; then the solution was allowed to react overnight at room temperature. MeOH (60 ml) was added dropwise at 0–5°, followed by H_2O (150 ml). Inorganic material was removed by filtration and the organic layer was separated. The aqueous layer was extracted three times with PhH and the extracts were combined with the organic layer. This solution was dried (K_2CO_3) and addition of 5 *N* EtOH–HCl precipitated 26.7 g (86%) of **β-benzylamino-4-trifluoromethylphenethylamine dihydrochloride (58).**

Method 7. A solution of β-benzylamino-2-chlorophenethylamine dihydrochloride (73) (105 g, 0.315 mol) in anhydrous MeOH (500 ml) was hydrogenated in a Brown apparatus at 25° and atmospheric pressure over a 10% Pd/C catalyst which had been treated as indicated below. H_2 was generated externally from 1 *M* aqueous $NaBH_4$ and AcOH. The reaction stopped after 1 equiv of H_2 had been consumed. Removal of the catalyst, evaporation of the solvent under reduced pressure, and trituration of the crude product with *i*-PrOH afforded 70.8 g (92%) of **β-amino-2-chlorophenethylamine dihydrochloride (74).**

Treatment of the Catalyst. Anhydrous MeOH is added dropwise to 2 g of 10% Pd/C in a 50-ml beaker, being careful to smother the resulting small fires with a watch glass. After several additions of solvent, the catalyst is "wet" and will no longer ignite. It is then washed into the hydrogenation flask with anhydrous MeOH. For hydrogenolysis of nonhalogen-containing compounds, the catalyst was "wet" with H_2O and did not ignite.

Method 8 (Route A in Scheme I). A solution of α-aminoacetophenone HCl (41.9 g, 0.245 mol) in H_2O (250 ml) and KOCN (39.7 g, 0.49 mol) in H_2O (250 ml) were mixed and stirred with heating to reflux. Filtration of the cooled mixture gave 38.2 g (98%) of 4-phenyl-2-imidazolone[6] (103), mp 300–320°.

A solution of the imidazolone 103 (38.2 g, 0.24 mol) in AcOH (250 ml) was hydrogenated on a Parr apparatus at 50 psi over a 10% Pd/C catalyst at 45°. After removal of catalyst and evaporation of solvent, trituration of the resulting solid with cold EtOH afforded 34.1 g (88%) of 4-phenyl-2-imidazolidone (104), mp 161–163° (lit.[16] mp 160–161°).

This compound (104) (34.1 g, 0.2 mol) was taken up in concentrated HCl (60 ml) and refluxed 1.5 hr. Removal of the HCl under reduced pressure left a solid that crystallized from 95% EtOH to give 36.5 g (82.5%) of **β-aminophenethylamine dihydrochloride (51).**

Similarly, β-amino-4-methoxyacetophenone hydrobromide converted to 4-(4-methoxyphenyl)-2-imidazolone (105), mp 310–315°, in 87% yield. Hydrogenation of 105 afforded an 88% yield of 4-(4-methoxyphenyl)-2-imidazolidone (106), mp 161–162°. Hydrolysis of 106 with concentrated HCl gave **β-amino-4-methoxyphenethylamine dihydrochloride (60)** in 65% yield.

Method 9 (Route C in Scheme I). 4-Chlorostyrene was con-

#Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected except as indicated. The structures of all compounds are supported by their ir and nmr spectra. Spectra were recorded on a Beckman IR-9 and a Varian A-60 spectrometer. Microanalytical and spectral data were supplied by the Physical Analytical Department of Mead Johnson and Co. Where analyses are indicated only by symbols of the elements, the analytical results obtained for C, H, and N are within ±0.4% of the theoretical value unless stated otherwise.

verted to ethyl *N*-[2-chloro-2-(4-chlorophenyl)ethyl]carbamate by the method of Foglia and Swern.[17] This compound (8.0 g, 0.03 mol) was then added to a slurry of K phthalimide (18.5 g, 0.1 mol) in dry DMF (50 ml). The mixture was stirred and heated at 95–100° under N_2 for 16 hr and then cooled. After removal of insoluble material, the filtrate was diluted with H_2O (200 ml) and extracted several times with $CHCl_3$ (75 ml). The extracts were washed with 0.2 *N* NaOH, dried (K_2CO_3), and concentrated to an oil (10 g) under reduced pressure. The Et_2O soluble portion of this oil was washed with 0.2 *N* NaOH and dried (K_2CO_3). Concentration of the Et_2O solution afforded 8.0 g of viscous oil, which was refluxed and stirred with concentrated HCl (150 ml) for 72 hr. The mixture was cooled and extracted with $CHCl_3$. The aqueous phase was made basic with 50% NaOH, extracted with $CHCl_3$, dried (K_2CO_3), and concentrated under reduced pressure to afford an oil (2.0 g). A solution of this oil in absolute EtOH was treated with EtOH–HCl and then *i*-Pr_2O to afford 2.8 g (41%) of **β-amino-4-chlorophenethylamine dihydrochloride (71).**

Resolution of β-Amino-2-chlorophenethylamine (74). *d*-Camphorsulfonic acid (2 equiv) was added to a solution of **β-amino-2-chlorophenethylamine** (1 equiv) in absolute EtOH, and solution was concentrated under reduced pressure. Several recrystallizations of the residue from 95% EtOH afforded ***l*-β-amino-2-chlorophenethylamine di-*d*-camphorsulfonate**, $\alpha^{25}D$ +6.5° (*c* 1, H_2O). This salt was converted to the di-HCl salt, $\alpha^{25}D$ −26.0° (*c* 1, H_2O). The *d*-camphorsulfonate filtrates were converted to free diamine with 10% NaOH and then to the *l*-tartrate salt with *l*-tartaric acid (1 equiv). Successive crystallizations from aqueous EtOH afforded ***d*-β-amino-2-chlorophenethylamine *l*-tartrate**, $\alpha^{25}D$ −5.0° (*c* 1, H_2O), which was then converted to the di-HCl salt, $\alpha^{25}D$ +26.0° (*c* 1, H_2O). See Table II for additional data.

4-Aryl-2-imidazolines. See Table I for additional data and other compounds prepared by these methods.

Method 10. β-Amino-2-chlorophenethylamine dihydrochloride (8.8 g, 0.04 mol) (74) was converted to the free base in H_2O with 50% NaOH and extracted into $CHCl_3$. To a solution of the diamine in PhH (100 ml), a solution of BrCN (4.2 g, 0.04 mol) in PhH (50 ml) was added in one lot, and the mixture was stirred for 4 hr at 25°. Precipitated solid was filtered and washed with PhH to give 9.1 g (92%) of **2-amino-4-(2-chlorophenyl)-2-imidazoline hydrobromide** (18), mp 190–200°. One crystallization from absolute EtOH–*i*-Pr_2O gave 7.0 g of analytical product.

Method 11. A solution of 2-amino-4-(3,4-dibenzyloxyphenyl)-2-imidazoline hydrobromide (11) (18.2 g, 0.04 mol) in MeOH (250 ml) at 25° was hydrogenated over a 10% Pd/C catalyst at 50 psi overnight. After removal of catalyst and evaporation of solvent, 10.9 g (99%) of crude **2-amino-4-(3,4-dihydroxyphenyl)-2-imidazoline hydrobromide** (14) was isolated.

Method 12. β-Aminophenethylamine dihydrochloride (51) (65 g, 0.31 mol) was converted to its free base in H_2O with 50% NaOH and extracted into $CHCl_3$. To the base in 80% aqueous EtOH (400 ml) was added 18.6 ml (23.6 g, 0.31 mol) of CS_2 in one lot, and the solution was refluxed for 1 hr. At this time, concentrated HCl (0.5 ml) was added and the mixture was stirred at reflux for 7 hr and then at room temperature for another 15 hr. Insoluble product was filtered, washed with H_2O, and dried to yield 38.5 g (70%) of **4-phenyl-2-thio-2-imidazoline** (30).

A solution of 4-phenyl-2-thio-2-imidazoline (38.5 g, 0.22 mol) and 14.8 ml (33.8 g, 0.24 mol) of MeI in *i*-PrOH (200 ml) was refluxed for 2 hr and then concentrated to half-volume under reduced pressure. The remaining solution was poured into Et_2O (800 ml) to precipitate 69 g (99%) of **2-methylthio-4-phenyl-2-imidazoline hydriodide** (31).

To 20 g (0.06 mol) of this compound in MeOH (75 ml) was added a solution of Na (1.43 g, 0.06 g-atom) in MeOH (25 ml). The solvent was removed and the residue was stirred with Et_2O. Filtration removed undissolved solids and the filtrate was concentrated under reduced pressure to 10.5 g (88%) of **2-methylthio-4-phenyl-2-imidazoline** (31) free base, mp 110–116°.

Method 13. To 8.0 g (0.025 mol) of 2-methylthio-4-phenyl-2-imidazoline hydriodide (31) in *i*-PrOH (100 ml) was added benzylamine (2.7 g, 0.025 mol), and the solution was refluxed for 48 hr. Removal of *i*-PrOH under reduced pressure gave an oil which was dissolved in H_2O and washed several times with Et_2O. Basification of the aqueous fraction with 10% NaOH precipitated an oil which was extracted into $CHCl_3$. Evaporation of the $CHCl_3$ extract gave an oil which was dissolved in absolute EtOH (15 ml) and treated with fumaric acid (1.5 g, 0.5 equiv); *i*-Pr_2O was added to this solution at its boiling point until it became almost turbid. On cooling, 7.0 g (91%) of **2-benzylamino-4-phenyl-2-imidazoline fumarate** (23) separated.

Method 14. A solution of 4-(2-chlorophenyl)-2-hydrazino-2-imidazoline hydriodide (36) (5.1 g, 0.015 mol), 2,6-dichlorobenzaldehyde (2.63 g, 0.015 mol), and a few drops of AcOH in absolute EtOH (50 ml) was refluxed 18 hr. Solvent was removed under reduced pressure to yield a solid. Trituration of this solid with absolute EtOH (10 ml) and filtration afforded 4.4 g (60%) of **2-(2,6-dichlorobenzylidenehydrazino)-4-(2-chlorophenyl)-2-imidazoline hydriodide** (40).

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