3-Alkyl-2-aryl-3*H*-naphth[1,2-*d*]imidazoles, a Novel Class of Nonacidic Antiinflammatory Agents

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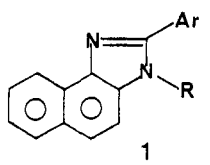
Novel 3-alkyl-2-aryl-3*H*-naphth[1,2-*d*]imidazoles were synthesized and evaluated as antiinflammatory agents in the carrageenin-induced paw edema, cotton pellet induced granuloma, and adjuvant-induced polyarthritis assays in rats. The analgesic, antipyretic, and gastroulcerogenic effects were also tested. Structure–activity relationships are discussed. One of the compounds, 3-(1-methylethyl)-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazole (**35**), was selected for clinical trials as a nonacidic antiinflammatory and analgesic agent.

Nonacidic, nonsteroidal antiinflammatory agents are gaining increasing favor as a result of their better gastrointestinal tolerability in comparison with acidic agents.[1] In a search for such nonacidic agents, Lombardino et al.[2] reported that several 2,4,5-triarylimidazoles exhibited antiinflammatory activity comparable to that of phenylbutazone in the carrageenin rat paw edema test. More recently, a series of 2-aryl- and 2-heteroarylbenzimidazoles have been described as antiinflammatory and analgesic agents:[3a,b] among these, 2-(5-ethylpyridin-2-yl)benzimidazole was claimed to cause less gastrointestinal irritation than either phenylbutazone or tiaramide.[3c] The common structural feature of these classes is the presence of an imidazole ring bearing an aromatic moiety in the 2-position; thus, we reasoned that 2-arylnaphth[1,2-*d*]imidazoles (**1**) might also have the same pharmacological



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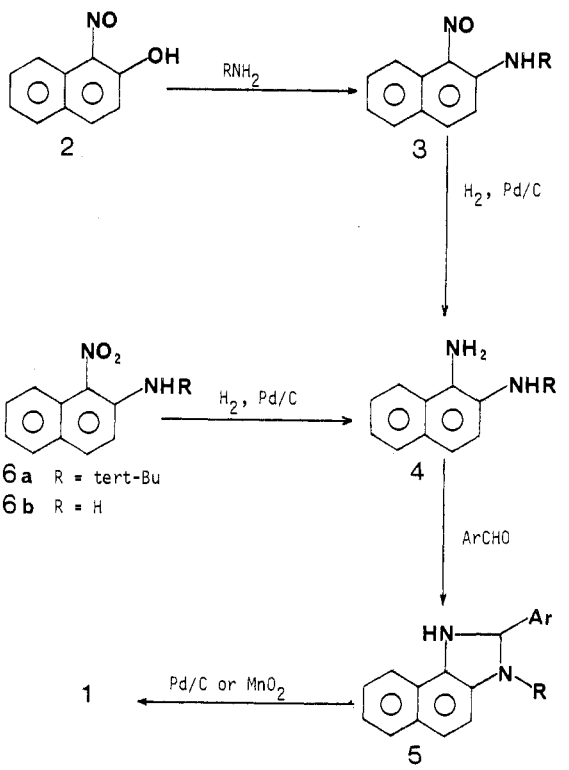
Ar = substituted phenyl or heterocyclic ring
R = H or alkyl, alkenyl

have the same pharmacological profile. Therefore, we decided to synthesize a series of 1-alkyl- and 3-alkyl-2-arylnaphth[1,2-*d*]imidazoles for evaluation with our primary screening tests. Generally, the 1-alkyl derivatives had little antiinflammatory activity, while the isomeric 3-alkyl derivatives (**1**), which we describe in the present paper, had the type of activity that we expected.

Chemistry. The synthetic procedure used for the preparation of compounds **1** is summarized in Scheme I. Treatment of commercially available 1-nitroso-2-naphthol (**2**) with the appropriate primary amines in water gave 2-(alkylamino)-1-nitrosonaphthalenes (**3**) (Table I), according to the method of Fischer et al.[4] After hydrogenation, condensation of the resulting 2-alkyl-1,2-naphthalenediamines (**4**) with substituted benzaldehydes afforded the 1,2-dihydro derivatives (**5**), which were converted to the final compounds (**1**) (Tables II and III) by means of palladium on carbon (method A) or manganese dioxide (method B). Dehydrogenation with palladium gave higher yields and cleaner reaction products (see comparative results with compound **16** in the Experimental Section) and allowed the conversion of **3** to **1** to be done in "one pot". The high yields and the mild reaction conditions of the first step make **2** an ideal starting material for the synthesis of diamines **4**. However, *tert*-butylamine failed to react with **2**; thus, 3-*tert*-butyl-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazole (**39**) was prepared from 2-(*tert*-butylamino)-1-nitronaphthalene (**6a**), which was obtained by treatment of 2-chloro-1-nitronaphthalene[5] with the lithium salt of *tert*-butylamine. Similarly, 2-amino-1-nitronaphthalene (**6b**)[6] was used as starting material for the synthesis of the unsubstituted compound **32**. The 3-alkenyl derivatives **45** and **46** were prepared by reaction of the corresponding 3-(2-hydroxyethyl) derivatives **43** and **44** with thionyl chloride in chloroform and subsequent dehydrohalogenation with sodium hydride in *N*,*N*-dimethylformamide. Finally, compounds **12**, **13**, and **21** were prepared by standard chemical modifications as described in the Experimental Section.

Scheme I



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(1) Shen, T. Y. *J. Med. Chem.* **1981**, *24*, 1.
(2) Lombardino, J. G.; Wiseman, E. H. *J. Med. Chem.* **1974**, *17*, 1182.
(3) (a) Kanebo, Ltd. German Patent 2 754 299, 1978: *Chem. Abstr.* **1978**, *89*, 109485*a*. (b) Tsukamoto, G.; Yoshino, K.; Kohno, T.; Ohtaka, H.; Kagaya, H.; Ito, K. *J. Med. Chem.* **1980**, *23*, 734. (c) Ito, K.: Kagaya, H.; Fukuda, T.; Yoshino, K.; Nose, T. *Arzneim.-Forsch.* **1982**, *32*, 49.
(4) Fischer, O.; Dietrich, C.; Weiss, F. *J. Prakt. Chem.* **1920**, *100*, 167.
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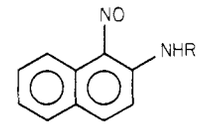
Table I. Intermediate 2-(Alkylamino)-1-nitrosonaphthalenes



no.	R	reaction time, h	reaction temp, °C	yield, %	mp,[a] °C	formula[b]
3a	CH_3	0.5	40	76	144-146 (148-149)	$C_{11}H_{10}N_2O$
3b	CH_2CH_3	4	25	70	108-110 (120-121)	$C_{12}H_{12}N_2O$
3c	$(CH_2)_2CH_3$	4	25	86	113-115 (115 dec)	$C_{13}H_{14}N_2O$
3d	$CH(CH_3)_2$	1	50	69	82-87 dec	$C_{13}H_{14}N_2O$
3e	$(CH_2)_3CH_3$	6	25	82	98-100 (98-99)	$C_{14}H_{16}N_2O$
3f	$CH(CH_3)CH_2CH_3$	1	50	62	oil	$C_{14}H_{16}N_2O$
3g	$CH_2CH(CH_3)_2$	3	25	83	100-102	$C_{14}H_{16}N_2O$
3h	$CH(CH_2CH_3)_2$	3	45	90	oil	$C_{15}H_{18}N_2O$
3i	cyclopropyl	0.5	50	87	123-125	$C_{13}H_{12}N_2O$
3j	cyclohexyl	1	10	83	130-131	$C_{16}H_{18}N_2O$
3k	CH_2CH_2OH	4	25	69	140 dec	$C_{12}H_{12}N_2O_2$
3l	$CH(CH_3)CH_2OH$	4	25	79	119-122	$C_{13}H_{14}N_2O_2$

[a] Literature melting point in parentheses. See ref 4. [b] All compounds were used without recrystallization; thus, the elemental analyses were not carried out. The NMR and IR spectra were in full accord with the proposed structures.

Biological Results and Discussion

The test compounds were screened for antiinflammatory activity by means of the carrageenin-induced rat paw edema test (CE), and the percentages of inhibition relative to the controls are presented in Tables II and III.

The effect of various substituents on the phenyl ring in modifying the potency of the parent compound **7** is shown in Table II. A positive effect is observed with strong electron-donating groups in the para position, such as OCH_3 (**16**), OC_2H_5 (**17**), $NHCH_3$ (**21**), $N(CH_3)_2$ (**22**), and the increase in potency is parallel to the mesomeric contribution of these groups.[7] At the same time, steric parameters are operative, as suggested by the progressive decrease in potency from OCH_3 (**16**) to OC_2H_5 (**17**) to $OCH(CH_3)_2$ (**18**). A mild electron-donating group, such as $NHCOCH_3$ (**20**), does not greatly affect the potency, while a decrease is observed with a CH_3 group (**19**), which has a very weak mesomeric effect. The lack of activity obtained with the OH (**11**) and OCH_2COOH groups (**13**), which does not fit the proposed relationship between the activity and electron-donating ability, can be explained by the metabolic degradation[8] of **13** to **11**, and the poor absorption of the latter. The aqueous solubility of compound **11** is, in fact, negligible at any pH. Electron-withdrawing substituents,[7] such as Cl (**9**) and $OCOCH_3$ (**12**), in the para position have a negative effect, and irrespective of the electron effect of the substituents, a decrease in potency is observed with groups in the ortho (**10** and **14**) or meta position (**8** and **15**). Correspondingly, the combination of meta with para substitution (**23**, **24**, and **26**) leads to a diminished potency, with the exception of compound **25** in which the *m*-CH_3 group seems to produce a moderate positive effect. As for other heterocyclic rings replacing the phenyl ring, only the 4-pyridyl gives a potent compound (**31**), confirming the importance of an electron-rich para position in the aryl moiety. The bioisosterism between phenyl (**7**) and thienyl (**27**) rings explains the same level of activity of the two compounds. The substituents in the 3-position of the imidazole ring generally have a strong effect in increasing the antiinflammatory potency of the unsubstituted compound **32**, as shown in Table III. In this case, the steric parameters seem to predominate because the compounds having small alkyl groups, such as methyl (**16**, Table II), ethyl (**33**), isopropyl (**35**), cyclopropyl (**41**), vinyl (**45**), and isopropenyl (**46**), all display a high and comparable potency in spite of the different inductive and mesomeric effects. In fact, bulky substituents, such as 1-ethylpropyl (**40**) and cyclohexyl (**42**), inactivate the molecule. However, the poor activity obtained with a *n*-propyl group (**34**) and the different potency of the two alcohols (**43** and **44**) cannot be easily rationalized.

Compounds that inhibited the edema by 40% or more at the dose one-fifth of their LD_{50}[9] were further evaluated at the same dose in the cotton pellet induced granuloma (CPG) in normal rats. Their analgesic (Randall–Selitto test), antipyretic, and gastroulcerogenic effects were also determined. Aspirin, phenylbutazone, and indomethacin were used as reference drugs, and the data are collected in Table IV. Nine compounds **16**, **17**, **21**, **25**, **27**, **31**, **33**, **35**, and **45** inhibit the granuloma in the range of 31–45%, and three of them, **25**, **31**, and **35**, have a good analgesic effect compared with aspirin. In addition, the antiyretic effect of **25** is about ten times that of aspirin. A prominent feature of this class of compounds is the lack of ulcerogenic properties, generally accepted to be a prerequisite for the clinical evaluation of novel antiinflammatory agents. In this context, the reference drugs appear far less tolerated. Finally, some compounds were further evaluated in the adjuvant-induced polyarthritis test in rats, and the data are listed in Table V. The most potent compounds are again **25** and **35**, and their potency is about one-half that of phenylbutazone.

Conclusions

About 40% of the test compounds inhibit the carrageenin edema by 30% or more, 22% of them retain this level of activity in the cotton pellet induced granuloma, and 12% of them retain the same level in the adjuvant-induced polyarthritis test. This diffuse antiinflammatory activity is coupled with the lack of gastroulcerogenic effects and low acute toxicity. Moreover, compounds **25**, **31**, and **35** show a good analgesic activity. From the complex of

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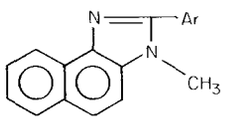
(8) This is a known metabolic step, e.g., in the metabolism of timolol. Tocco, D. J.; Duncan, A. E. W.; DeLuna, F. A.; Smith, J. L.; Walker, R. W.; Vandenheuvel, W. J. A. *Drug Metab. Dispos.* **1980**, *8*(4), 236.

(9) Except for compound **46** because of its close structural similarity with **45**.

Table II. Chemical Data and Carrageenin Edema Inhibition of 2-Aryl-3-methyl-3*H*-naphth[1,2-*d*]imidazoles



no.	Ar	method	reflux,[a] h	yield, %	mp, °C	crystn solvent	formula	anal.[b]	LD_{50} (mice), mg/kg po	CE[c] 200 mg/kg po	CE[c] 100 mg/kg po
7	C_6H_5	B	3	71	129-130	*i*-Pr_2O	$C_{18}H_{14}N_2$	C, H, N	1000	42	37
8	3-ClC_6H_4	B	2	72	142-143	EtOAc	$C_{18}H_{13}ClN_2$	C, H, N, Cl	>1000	7	
9	4-ClC_6H_4	B	3	67	152-153	EtOH	$C_{18}H_{13}ClN_2$	C, H, N, Cl	>1000	21	
10	2-HOC_6H_4	A	1.5	61	143-144	EtOAc	$C_{18}H_{14}N_2O$	C, H, N	500	1	
11	4-HOC_6H_4	A	1.5	65	>300	AcOH	$C_{18}H_{14}N_2O$	H, N; C[d]	>1000	4	
12	4-$AcOC_6H_4$	e		87	175-177	EtOH	$C_{20}H_{16}N_2O_2$	C, H, N	>1000	8	
13	4-$CH_2(COOH)OC_6H_4$	e		24	228-230	EtOH	$C_{20}H_{16}N_2O_3$	C, H, N	>1000	7	
14	2-$CH_3OC_6H_4$	A	1	88	132-133	EtOAc	$C_{19}H_{16}N_2O$	C, H, N	500	0	
15	3-$CH_3OC_6H_4$	B	3	49	149-150	EtOH	$C_{19}H_{16}N_2O$	C, H, N	1000	21	
16	4-$CH_3OC_6H_4$	A	1.5	79	132-134	C_6H_6	$C_{19}H_{16}N_2O$	C, H, N	1000	53	41
		B	3	54							
17	4-$C_2H_5OC_6H_4$	A	2	80	138-139	EtOAc	$C_{20}H_{18}N_2O$	C, H, N	>1000	45	37
18	4-$(CH_3)_2CHOC_6H_4$	A	2	75	144-145	Et_2O	$C_{21}H_{20}N_2O$	C, H, N	500	31	25
19	4-$CH_3C_6H_4$	A	*f*	69	135-136	*i*-Pr_2O	$C_{19}H_{16}N_2$	C, H, N	>1000	21	
20	4-$AcNHC_6H_4$	A	1.5	88	271-272	EtOH	$C_{20}H_{17}N_3O$	C, H, N	500	35	29
21	4-$CH_3NHC_6H_4$	e		79	225-227	C_6H_6	$C_{19}H_{17}N_3$	C, H, N	500	59	47
22	4-$(CH_3)_2NC_6H_4$	A	3	28	136-138	C_6H_6	$C_{20}H_{19}N_3$	C, H, N	500	68	54
23	3-CH_3-4-$CH_3OC_6H_3$	A	2	74	104-105	*i*-Pr_2O	$C_{20}H_{18}N_2O$	C, H, N	>1000	35	24
24	3,4-$OCH_2OC_6H_3$	A	1.5	60	200-201	Me_2CO	$C_{19}H_{14}N_2O_2$	C, H, N	>1000	28	
25	3-CH_3-4-$(CH_3)_2NC_6H_3$	A	2	66	116-118	*i*-Pr_2O	$C_{21}H_{21}N_3$	C, H, N	500	69	64
26	3,5-$(CH_3)_2$-4-$(CH_3)_2NC_6H_3$	A	2	40	136-137	aq EtOH	$C_{22}H_{23}N_3$	C, H, N	>1000	14	
27	2-thienyl	A	3	73	167-169	C_6H_6	$C_{16}H_{12}N_2S$	C, H, N	>1000	40	31
28	2-pyrryl	A	12	57	283-284	dioxane	$C_{16}H_{13}N_3$	C, H, N	>1000	1	
29	2-pyridyl	B	3	64	231 dec	EtOAc	$C_{17}H_{14}ClN_3$[g]	C, H, N, Cl	1000	24	
30	3-pyridyl	B	3	62	245 dec	MeOH	$C_{17}H_{15}Cl_2N_3$[h]	C, H, N; Cl[i]	500	12	
31	4-pyridyl	B	3	76	158-159	EtOH	$C_{17}H_{13}N_3$	C, H, N	1000	63	44

[a] After the addition of MnO_2 (B) or Pd (A) to the reaction mixture. [b] Analyses for C, H, N, and Cl were within ±0.4% of theory for all compounds, except as indicated. [c] Percent inhibition relative to the controls of carrageenin-induced rat paw edema at the two doses shown. CE at 100 mg/kg is reported if the value at 200 mg/kg is >30%. Values in the range 0-16 are statistically not significant; confidence limit, $p < 0.05$. CE of reference drugs: aspirin, 42 at 100 mg/kg po; phenylbutazone, 41 at 50 mg/kg po; indomethacin, 39 at 3 mg/kg po. [d] C: calcd, 78.81; found, 78.04. [e] See Experimental Section. [f] A further addition of Pd is not required. [g] Isolated as the hydrochloride. [h] Isolated as the dihydrochloride. [i] Cl: calcd, 21.34; found, 20.45.

Table III. Chemical Data and Carrageenin Edema Inhibition of 3-Alkyl-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazoles

no.	R	method	reflux,[a] h	yield, %	mp, °C	crystn solvent	formula	anal.[b]	LD_{50} (mice), mg/kg po	CE[c] 200 mg/kg po	CE[c] 100 mg/kg po
32	H	A	3	45	114–115	EtOH	$C_{18}H_{14}N_2O$	H, N; C[d]	>1000	10	
33	C_2H_5	A	5	81	144–146	EtOAc	$C_{20}H_{18}N_2O$	C, H, N	1000	52	49
34	$(CH_2)_2CH_3$	A	2.5	71	142–143	MeOH	$C_{21}H_{20}N_2O$	C, H, N	>1000	20	
35	$CH(CH_3)_2$	A	3.5	64	160–161	EtOAc	$C_{21}H_{20}N_2O$	C, H, N	>1000	48	45
36	$(CH_2)_3CH_3$	A	2	53	100–102	*t*-BuOMe	$C_{22}H_{22}N_2O$	C, H, N	>1000	25	
37	$CH(CH_3)CH_2CH_3$	A	5	54	153–154	*t*-BuOMe	$C_{22}H_{22}N_2O$	C, H, N	>1000	18	
38	$CH_2CH(CH_3)_2$	A	2	68	121–123	cyclohexane	$C_{22}H_{22}N_2O$	C, H, N	>1000	30	
39	$C(CH_3)_3$	A	5	25	213–214	EtOAc	$C_{22}H_{22}N_2O$	C, H, N	>1000	19	
40	$CH(CH_2CH_3)_2$	A	3	39	106–108	cyclohexane	$C_{23}H_{24}N_2O$	C, H, N	>1000	11	
41	cyclopropyl	A	3	46	193–194	MeOH	$C_{21}H_{18}N_2O$	C, H, N	>1000	56	53
42	cyclohexyl	A	2.5	76	248–250 dec	37% HCl	$C_{24}H_{25}ClN_2O$[e]	C, H, N, Cl	500	16	
43	CH_2CH_2OH	A	2	75	187–188	MeOH	$C_{20}H_{18}N_2O_2$	C, H, N	>1000	11	
44	$CH(CH_3)CH_2OH$	A	1	76	180–181	EtOAc	$C_{21}H_{20}N_2O_2$	C, H, N	>1000	35	31
45	$CH{=}CH_2$	*f*		86	84–97[g]	cyclohexane	$C_{20}H_{16}N_2O$	C, H, N	>1000	58	48
46	$C(CH_3){=}CH_2$	*f*		72	116–118	cyclohexane	$C_{21}H_{18}N_2O$	C, H, N	1000	58	54

[a–c] See corresponding footnotes in Table II. [d] C: calcd, 78.81; found, 78.17. [e] Isolated as the hydrochloride. [f] See Experimental Section. [g] Two crystalline forms melting at 85 and 96 °C were shown by DSC.

pharmacological and toxicological data that will be published in future papers, 3-(1-methylethyl)-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazole (**35**) was selected for clinical trials.

Experimental Section

Melting points were determined on a Büchi SMP-510 capillary apparatus and are uncorrected. IR (Perkin-Elmer 157) and ^1H NMR spectra (Bruker WP-60 or WH-270) were obtained for all compounds and were consistent with the assigned structures. The abbreviations s, m, d, br, dd, and dq refer to singlet, multiplet, doublet, broad, doublet of doublets, and doublet of quartets, respectively. The differential scanning calorimetry (DSC) curve of **45** was obtained on a TA 2000 Mettler thermal Analyzer, in a normal pan, with a heating rate of 5 °C/min. The elemental analyses were performed by the Analytical Department of Gruppo Lepetit S.p.A.

2-(Alkylamino)-1-nitrosonaphthalenes (3a–l). General Procedure. To a solution of the appropriate primary amine (0.2 mol) in 40 mL of water was added portionwise 6.92 g (0.04 mol) of finely ground 1-nitroso-2-naphthol (Merck) (**2**), and the mixture was stirred for the time and at the temperature shown in Table I. After standing overnight at room temperature, the green precipitate was filtered, washed with water, vacuum dried, and used in the next step without further purification.

Substituted Benzaldehydes (ArCHO in Scheme I). The following aldehydes were not commercially available: **4-isopropoxybenzaldehyde,** which was prepared by alkylation of 4-hydroxybenzaldehyde with isopropyl iodide in cyclohexanol,[10] and **3-methyl-4-(dimethylamino)benzaldehyde**, which was prepared by formylation of *N,N*-dimethyl-*o*-toluidine[11] with hexamethylenetetramine and paraformaldehyde, according to a patented procedure.[12] The same procedure was used to prepare the unreported **3,5-dimethyl-4-(dimethylamino)benzaldehyde** from *N,N*-dimethyl-2,6-dimethylaniline[13] in 14% yield: bp 64–66 °C (0.09 mmHg); IR (film) ν_{max} 1690, 1600, 1280, 1120, 735 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 6 H, CH_3C), 2.93 (s, 6 H, CH_3N), 7.57 (s, 2 H, aromatic), 9.97 (s, 1 H, CHO).

2-(*tert*-Butylamino)-1-nitronaphthalene (6a). To a solution of 12.8 g (0.061 mol) of 2-chloro-1-nitronaphthalene[5] in 360 mL of anhydrous *tert*-butylamine was added dropwise 63 mL (~0.1 mol of BuLi) of a ~1.6 M solution in hexane of *n*-butyllithium, with the temperature being maintained below 5 °C. Stirring was continued at room temperature for 1 h, the excess amine was evaporated, and the residue was decomposed with 10% aqueous ammonium chloride and extracted with ethyl ether. Chromatography on a silica gel column eluted with 10% ethyl acetate in cyclohexane gave 5.3 g (35%) of a red oil, which crystallized on standing and was recrystallized from petroleum ether: mp 83–85 °C; IR (Nujol) ν_{max} 1630, 1510, 1410, 1220, 1120 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 9 H, *t*-Bu), 7.0–7.8 (m, 5 H, aromatic), 8.57 (d, 1 H, J = 8 Hz, H para to NO_2), 8.73 (br, 1 H, NH). Anal. ($C_{14}H_{16}N_2O_2$) C, H, N.

2-(4-Methoxyphenyl)-3-methyl-3*H*-naphth[1,2-*d*]imidazole (16). Method A. A solution of 11.16 g (0.06 mol) of 2-(methylamino)-1-nitrosonaphthalene (**3a**) in 800 mL of toluene was hydrogenated at room temperature and atmospheric pressure in the presence of 3 g of 5% palladium on carbon. After 1 h, when hydrogen was no longer absorbed, 8.17 g (0.06 mol) of 4-methoxybenzaldehyde was added, and the reaction mixture was stirred at reflux for 3 h under nitrogen atmosphere, removing the water formed with a Dean-Stark trap. Then an additional 1.5 g of 5% palladium on carbon was added, and the reflux continued for 1 h. Filtration of the hot solution and evaporation of toluene under reduced pressure gave a residue, which was recrystallized from benzene to afford 13.7 g (79%) of **16**.

Method B. In a comparative experiment the same amount of reactants was used, but toluene was replaced by benzene. The

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(12) Bayer, A. G. French Patent 1 377 226, 1964; *Chem. Abstr.* **1965**, *62*, 7691*f*.
(13) Giumanini, A. G.; Chiavari, G.; Musiani, M. M.; Rossi, P. *Synthesis* **1980**, 743.

Table IV. Antiinflammatory, Analgesic (Randall-Selitto), and Antipyretic Activity and Ulcerogenic Index of Some Selected Compounds

compd	dose,[a] mg/kg po	CPG[b]	Randall-Selitto (aspirin = 1)	antipyresis (aspirin = 1)	ulcerogenic index[c]
7	200	24	0.9	9.1	0.33
16	200	40	1.2	1.0	0.31
17	200	40	0.3	2.2	0.21
21	100	33	*d*	*d*	0.16
22	100	24	*d*	*d*	1.07
25	100	38	2.8	10.5	0.21
27	200	31	1.0	0.9	0.12
31	200	33	2.4	1.4	0.31
33	200	31	1.1	2.9	0.09
35	200	45	2.2	0.7	0.38
41	200	11[e]	0.7	0.8	0.29
45	200	31	1.1	6.9	0.30
aspirin	100	24	1.0	1.0	1.6
phenylbutazone	50	38	6.5	4.0	1.4
indomethacin	3	41	34.0	15.4	1.5

[a] CPG and ulcerogenic index were obtained at the dose shown, equivalent to one-fifth of the LD_{50}. In the analgesic and antipyretic tests, this was the highest dose administered, as described in the Experimental Section. [b] Percent inhibition relative to the controls of cotton pellet induced granuloma in rats. [c] Treated and control groups are not statistically different when the index is <1. Confidence limit, $p < 0.05$. [d] Test not done. [e] Statistically not significant.

Table V. Adjuvant-Induced Polyarthritis[a]

compd	dose, mg/kg po	mean vol of hind paws	inflammation units	arthritis scores
16	200	33	46	40
17	200	25	60	43
25	100	42	84	69
27	200	23	18	24
31	200	20	3	10
33	200	21	35	21
35	100	43	93	77
45	100	34	61	39
46	100	38	68	70
phenylbutazone	50	45	68	58
indomethacin	1	52	82	65

[a] Numbers are percent variations (−Δ%) relative to the controls. Values <25 are statistically not significant; confidence limit, $p < 0.05$.

reaction mixture was filtered after the hydrogenation step, treated with 4-methoxybenzaldehyde in a flask fitted with a Dean–Stark trap, and heated at reflux for 3 h under nitrogen atmosphere. To this solution cooled at room temperature was added 4 g of manganese dioxide (Carlo Erba), and the mixture stirred at reflux for 3 h. The reaction mixture was filtered while hot, the filtrate was evaporated under reduced pressure, and the residue was chromatographed on a silica gel column eluted with 10% ethyl acetate in benzene. Recrystallization from diisopropyl ether of crude **16** afforded 9.34 g (54%) of a sample that was analytically pure: IR (Nujol) 1610, 1570, 1530 (C=N and C=C), 1250, 1180, 1030 (COC) cm^{-1}; NMR ($CDCl_3$) δ 3.87 (s, 6 H, OCH_3 and NCH_3), 7.07 (d, 2 H, J = 8 Hz, H ortho to OCH_3), 7.2–8.1 (m, 7 H, aromatic), 8.80 (dd, 1 H, J_{ortho} = 8 Hz, J_{meta} = 2.5 Hz, C_9 H).

Following either method A or B, the compounds listed in Tables II and III were prepared. The time of reflux after the addition of either Pd/C or MnO_2 to the reaction mixture is shown in column 4.

4-(3-Methyl-3*H*-naphth[1,2-*d*]imidazol-2-yl)phenol Acetate (12). A solution of 5.48 g (0.02 mol) of **11** in 100 mL of pyridine and 20 mL of acetic anhydride was stirred at 60 °C for 3 h. Evaporation under reduced pressure gave a residue, which was recrystallized from ethanol to yield 5.5 g of **12**: IR (Nujol) ν_{max} 1750, 1200, 1190, 1165 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 3 H, CH_3CO), 4.00 (s, 3 H, CH_3N), 7.37 (d, 2 H, J = 8 Hz, H ortho to OAc), 7.2–8.1 (m, 7 H, aromatic), 8.80 (dd, 1 H, J_{ortho} = 8 Hz, J_{meta} = 2.5 Hz, C_9 H).

[4-(3-Methyl-3*H*-naphth[1,2-*d*]imidazol-2-yl)phenoxy]-acetic Acid (13). To a vigorously stirred solution of 8.22 g (0.03 mol) of **11**, 9.36 g (0.03 mol) of benzyltributylammonium chloride, and 10 mL (0.09 mol) of ethyl bromoacetate in 300 mL of methylene chloride was added 60 mL of 1 N NaOH during 2 h. The reaction mixture was stirred for an additional 2 h: then the same amounts of ethyl bromoacetate and sodium hydroxide were added twice, stirring 4 h after each addition. The unreacted phenol was filtered (4.8 g), and the organic layer was separated, washed with water, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with 20% ethyl acetate in cyclohexane as eluent to give 4.9 g (45%) of the ethyl ester of **13**, mp 103–104 °C (*i*-PrOH). Anal. ($C_{22}H_{20}N_2O_3$) C, H, N. Saponification was effected by heating at reflux for 1.5 h a solution of 4 g of this ethyl ester and 20 mL of 10% NaOH in 40 mL of methanol. The organic solvent was evaporated, and the aqueous solution was cooled to 5 °C and acidified with glacial acetic acid. The resulting precipitate was collected and recrystallized from ethanol to afford 1.95 g of **13**: IR (Nujol) ν_{max} 3500, 1610, 1500, 1265, 1240, 1190, 807 cm^{-1}; NMR (Me_2SO-d_6) δ 4.10 (s, 3 H, CH_3N), 4.93 (s, 2 H, CH_2), 7.27 (d, 2 H, J = 8 Hz, H ortho to OCH_2COOH), 7.5–8.4 (m, 7 H, aromatic), 8.63 (dd, 1 H, J_{ortho} = 8 Hz, J_{meta} = 2.5 Hz, C_9 H).

***N*-Methyl-4-(3-methyl-3*H*-naphth[1,2-*d*]imidazol-2-yl)-benzenamine (21).** To a solution of 5.04 g (0.016 mol) of **20** in 80 mL of dry DMF was gradually added, at a temperature below 5 °C, 0.7 g (0.016 mol of NaH) of a 55% mineral oil dispersion of sodium hydride. When gas was no longer evolved, a solution of 1 mL (0.016 mol) of methyl iodide in 20 mL of DMF was added dropwise while the temperature was maintained at 5 °C. The mixture was allowed to warm to 25 °C, stirred at this temperature for 1.5 h, and poured into 1 L of water. The precipitate was filtered, dissolved in a solution of 200 mL of 10% aqueous NaOH in 300 mL of methanol, and heated at reflux for 6 h. The methanol was distilled off, and the mixture was cooled to 0 °C and diluted with 200 mL of water. The precipitate was filtered and recrystallized from benzene to give 3.6 g of **21**: IR (Nujol) ν_{max} 3350, 1620, 1500, 1330, 1180, 830, 805 cm^{-1}; NMR ($CDCl_3$) δ 2.92 (br, 3 H, CH_3NPh), 3.93 (s, 3 H, CH_3N), 6.73 (d, 2 H, J = 8 Hz, H ortho to CH_3NH), 7.2–8.1 (m, 8 H, aromatic + NH), 8.83 (dd, 1 H, J_{ortho} = 8 Hz, J_{meta} = 2.5 Hz, C_9 H).

3-Ethenyl-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]-imidazole (45). To a boiling solution of 9.14 g (0.028 mol) of **43** in 600 mL of chloroform was added dropwise a solution of 2.32 mL (0.032 mol) of thionyl chloride in 20 mL of chloroform, and the reflux was continued for 20 min. The reaction mixture was cooled, washed successively with saturated aqueous sodium bicarbonate and water, dried over magnesium sulfate, and evaporated to afford 9.3 g of the crude 3-(2-chloroethyl)-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazole, mp 210–212 (EtOH). Anal. ($C_{20}H_{17}ClN_2O$) C, H, N, Cl. Dehydrohalogenation was effected by adding in portions 1.05 g (0.024 mol of NaH) of a 55% mineral oil dispersion of sodium hydride to a solution of 5.3 g (0.016 mol) of this chloroethyl derivative in 100 mL of dry DMF and stirring at 60 °C for 2.5 h. The mixture was poured into 1.5 L of ice–water, the resulting solution was acidified to pH 4 by

the addition of acetic acid, and the precipitate collected and recrystallized from cyclohexane to give 4.2 g of **45**: IR (Nujol) ν_{max} 1640, 1300, 1250, 1170, 840, 800, 740, 705 cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 3 H, CH_3O), 5.20 (dd, 1 H, J_{gem} = 0.5 Hz, J_{vic} = 8 Hz, HC=CN), 5.50 (dd, 1 H, J_{vic} = 15 Hz, HC=CN), 6.90 (d, 2 H, H ortho to OCH_3), 7.03 (dd, 1 H, NCH=C), 7.3–8.1 (m, 7 H, aromatic), 8.67 (dd, 1 H, J_{ortho} = 8 Hz, J_{meta} = 2.5 Hz, C_9 H).

3-(1-Isopropenyl)-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazole (46). The title compound was prepared according to the procedure described for **45**, starting from **44**. The intermediate 3-(2-chloro-1-methylethyl)-2-(4-methoxyphenyl)-3*H*-naphth[1,2-*d*]imidazole had mp 162–164 °C (*i*-PrOH). Anal. ($C_{21}H_{19}ClN_2O$) C, H, N. Spectral data of **46**: IR (Nujol) ν_{max} 1290, 1240; 1180, 915, 840, 805 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (d, 3 H, CH_3C=C), 3.84 (s, 3 H, CH_3O), 5.41 (d, 1 H, J_{gem} = 0.5 Hz, HC=CN), 5.56 (dq, 1 H, J = 1.5 Hz, HC=CN), 7.02 (d, 2 H, J = 8 Hz, H ortho to OCH_3, 7.4–8.1 (m, 7 H, aromatic), 8.76 (dd, 1 H, J_{ortho} = 8 Hz, J_{meta} = 2.5 Hz, C_9 H).

Biological Test Procedure. Sprague–Dawley rats (Charles River strain) were used in the antipyretic assay, and Wistar rats (Charles River strain) were used in the other assays.

Carrageenin-Induced Rat Paw Edema (CE). The procedure of Winter et al.[14] was followed. Female rats weighing 120–150 g were arranged in groups of 10 at each dose. Test compounds and reference drugs were administered orally as aqueous suspensions in 0.5% methocel at a volume of 10 mL/kg of body weight. The control groups were treated with the vehicle at the same volume. The compounds were administered 1 h before the induction of the edema by the injection of 0.05 mL of 1% solution of carrageenin in sterile saline into the aponeurosis of the right hind paw of each rat. The foot volume was measured pletysmographically immediately after the carrageenin injection and then 4 h later. The screening dose was 200 mg/kg, and 100 mg/kg of the compound was administered when the inhibition relative to the controls was >30%. Aspirin, phenylbutazone, and indomethacin were administered orally at 100, 50 and 3 mg/kg, respectively.

Cotton Pellet Induced Granuloma (CPG). According to the method of Meier et al.,[15] two sterile cotton pellets (50 ± 1 mg each) were subcutaneously (sc) inserted under light ether anesthesia into the intrascapular region of male rats weighing 150–180 g. Test compounds and reference drugs were administered orally as aqueous suspensions in 0.5% methocel at a volume of 10 mL/kg of body weight. The control groups were treated with the vehicle at the same volume. The test compounds were administered at a dose one-fifth of their LD_{50} daily for 6 days, to the animals arranged in groups of seven, starting 6 h after surgery. The animals were killed 24 h after the last dosage, and the pellets together with the granulomas were removed and dried for 24 h at 80 °C. Aspirin, phenylbutazone, and indomethacin were administered orally at 100, 50, and 3 mg/kg, respectively.

Adjuvant-Induced Polyarthritis. Adjuvant-induced polyarthritis was produced in female rats weighing 130–150 g by the method of Newbould[16] with the injection of a suspension of killed *Mycobacterium butyricum* (0.6 mg) in mineral oil (0.1 mL) into the plantar aponeurosis of the right hind paw. Groups of eight animals were used at each dose. Test compounds and reference drugs were orally administered as aqueous suspensions in 0.5% methocel at a volume of 10 mL/kg of body weight. The control groups were treated with the vehicle at the same volume. The test compounds were adminstered at a dose one-fifth of their LD_{50}, once a day, following a curative scheme, starting on the 14th day after the injection of the adjuvant until termination of the study on the 27th day. Phenylbutazone and indomethacin were orally administered at 50 and 1 mg/kg, respectively. Evaluation of the arthritic condition was based on the quantitative comparison between the mean value for the volumes of the hind paws of treated and control animals and on a visual scoring system, ranging from 0 to 4, evaluating the secondary lesions of the front paws, tail, and ears according to Newbould's scale:[16] nil, mild, moderate, moderately severe, or severe. The observed values were expressed as "arthritis scores". Plasma inflammation units were determined at the end of the experiment (27th day), as described by Glenn et al.[17] Blood was collected from arthritic and control rats, using heparinized syringes, and the plasma obtained was added to physiological saline solution. Immediately after dilution of 0.2 mL of plasma to a total volume of 10 mL, the samples were read for turbidity in a Nephelometer (Coleman Model 9) against a physiological saline blank. This was the "initial reading". All diluted plasma samples were then placed in a 56 °C water bath for 30 min and cooled to room temperature, and their turbidity was again read. This was the "final reading". The difference between these turbidometric readings was the "corrected inflammation units". The plasma inflammation units which reflect the degree of colloidal lability of plasma proteins are related to extent, progress and regression of inflammatory conditions. Plasma mucoproteins and glycoproteins are elevated in arthritic rats.

Analgesic Activity. The pain threshold was measured on the inflammed paw of male rats weighing 170–200 g arranged in groups of 10 at each dose, according to the procedure of Randall and Selitto.[18] Test compounds and reference drugs were orally administered as aqueous suspensions in 0.5% methocel at a volume of 10 mL/kg of body weight. The control groups were treated with the vehicle at the same volume. The highest dose administered was one-fifth of LD_{50}, scaling down to 100, 50, 20, 10, 5, and 2 mg/kg. Aspirin, phenylbutazone, and indomethacin were administered starting from 100, 50, and 3 mg/kg, respectively. Induction of the edema was obtained by injection of 0.1 mL of a 20% suspension of yeast in saline into the aponeurosis of the right hind paw of each rat. The pain threshold was measured before the administration of the test compounds and every hour for 6 h.

Antipyretic Activity. The method of Buller et al.[19] was followed. Male rats, weighing 120–150 g and arranged in groups of six at each dose, were starved for 18 h before starting the experiment, and on the eve of the experiment they were placed in thermostatically controlled chambers at 24 °C. The body temperature of each animal was measured by means of a rectal thermocouple. Animals with a temperature exceeding 38 °C were excluded from trial. A 1-mL filtered 5% solution of peptone (Witte) incubated at 37 °C for 48 h was injected sc. Rectal temperature was recorded again 4 h after the injection. The measurements were repeated every hour for 4 h, and the increase of body temperature was recorded. The oral doses of test compounds and reference drugs were the same of those described for the analgesic activity.

Gastric Ulcer Assay. The ulcerogenic activity of the test compounds were expressed as the ulcerogenic index, determined according to the procedure of Thuillier et al.[20] Male rats weighing 130–150 g, arranged in groups of seven, were fasted for 2 h before and 2 h after the administration of the test compounds, and the treatment was continued daily for 6 days. Test compounds and reference drugs were orally administered as aqueous suspensions in 0.5% methocel at a volume of 10 mL/kg of body weight. The control groups were treated with the vehicle at the same volume. Test compounds were administered at a dose one-fifth of their LD_{50}. Aspirin, phenylbutazone, and indomethacin were administered at 100, 50, and 3 mg/kg, respectively. Pontamine sky blue 6 Bx (Gurr Ltd. London) (5% aqueous solution, 1 mL/rat) was injected into the caudal vein of each rat 4 h after the last administration. The rats were killed 5 min later, and the stomach was removed, opened, and visually examined. The severity of the lesions observed were scored from 0 to 4 as follows: 0 = absence of any lesion; 1 = ulcerations of limited diffusion, involving not more than one-third of the whole surface of the mucosa; 2 = ulcerations involving not more than two-thirds of the whole

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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.

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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; $3\text{-}ClC_6H_4CHO$, 587-04-2; $4\text{-}ClC_6H_4CHO$, 104-88-1; $2\text{-}HOC_6H_4CHO$, 90-02-8; $4\text{-}HOC_6H_4CHO$, 123-08-0; $2\text{-}CH_3OC_6H_4CHO$, 135-02-4; $3\text{-}CH_3OC_6H_4CHO$, 591-31-1; $4\text{-}CH_3OC_6H_4CHO$, 123-11-5; $4\text{-}C_2H_5OC_6H_4CHO$, 10031-82-0; $4\text{-}(CH_3)_2CHOC_6H_4CHO$, 18962-05-5; $4\text{-}CH_3C_6H_4CHO$, 104-87-0; $4\text{-}AcNHC_6H_4CHO$, 122-85-0; $4\text{-}(CH_3)_2NC_6H_4CHO$, 100-10-7; $3\text{-}CH_3\text{-}4\text{-}CH_3OC_6H_3CHO$, 32723-67-4; $3,4\text{-}OCH_2OC_6H_3CHO$, 120-57-0; $3\text{-}CH_3\text{-}4\text{-}(CH_3)_2NC_6H_3CHO$, 1424-69-7; $3,5\text{-}(CH_3)_2\text{-}4\text{-}(CH_3)_2NC_6H_2CHO$, 76166-10-4; $2\text{-}CH_3C_6H_4N(CH_3)_2$, 609-72-3; $2,6\text{-}(CH_3)_2C_6H_3N(CH_3)_2$, 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.

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

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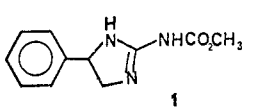
A series of 2-[(alkoxycarbonyl)amino]-4(5)-phenyl-2-imidazolines was prepared and evaluated for central nervous system (CNS) effects (antidepressant, anticonvulsant, muscle relaxant, and depressant) in animal models. Some separation of those CNS activities was achieved through substitutions on the phenyl 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



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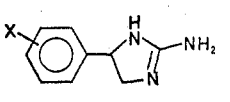
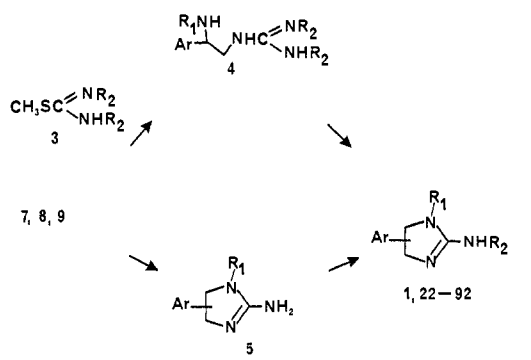


2

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



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