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New 2-Aryliminoimidazolidines. I. Synthesis and Antihypertensive Properties of 2-(2-Phenoxyphenylimino)imidazolidines and Related Compounds[1)]

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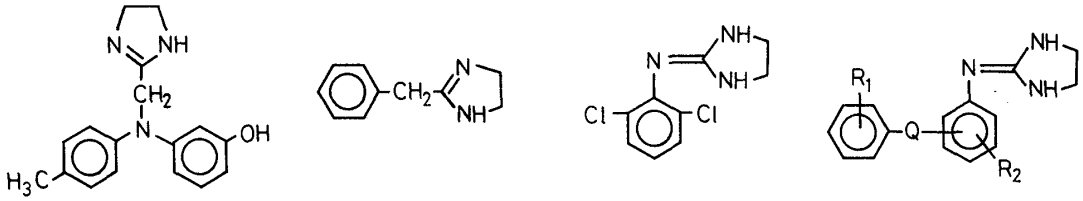
2-(2-Phenoxyphenylimino)imidazolidine and related compounds (IV and XII) were synthesized and evaluated for hypotensive activity in rats. Most of the 2-aryliminoimidazolidines (IV) were synthesized *via* the aniline derivatives (VI) by two different methods. Some imidazolidines (IV) were found to be significantly active, with 2-(5-chloro-2-phenoxyphenylimino)imidazolidine (IV-19) being more active than prazosin, the reference compound. The mechanism of action of IV-19 may involve the blockade of peripheral α-adrenergic receptors.

This paper describes the synthesis, pharmacology, and structure–activity relationships of the 2-(2-phenoxyphenylimino)imidazolidines.

Keywords——hypotensive activity; 2-imidazoline; 2-aryliminoimidazolidine; 2-(2-phenoxyphenylimino)imidazolidine; phenoxyaniline; prazosin; structure–activity relationship

Many drugs having an imidazoline or imidazolidine moiety are known to interact with α-adrenergic receptors in living systems.[2–4)] Of a number of imidazolines, phentolamine (I) and tolazoline (II) have found clinical uses as antagonists to peripheral α-adrenergic receptors.[2,5)] Clonidine (III), among other imidazolidines, shows a centrally mediated hypotensive effect through its agonistic activity on the α-adrenergic receptors in the medullary vasomotor center.[2,3,6)] A study of the quantitative structure–activity relationship for clonidine (III) and related compounds indicates that substitution, especially *ortho* substitution, on the phenyl ring plays a substantial part in determining the biological activities.[7)]

We have found during the last decade that in some biologically active compounds replacement of a halogen or lower alkyl group with a phenoxy group enhances the efficacy and changes the pharmacological profile. This led us to investigate some molecular alterations of clonidine (III). One of the compounds obtained was 2-(2-phenoxy-5-chlorophenylimino)imidazolidine (IV-19), which was found to have a potent hypotensive activity, with affinity for peripheral α-adrenergic receptors. This article describes the chemistry and pharmacology of a number of imidazolidine derivatives (IV) illustrated in Chart 1.



phentolamine (I) tolazoline (II) clonidine (III) IV

Chart 1

Most of the 2-phenyliminoimidazolidines (IV) were prepared by two different methods as shown in Chart 2: one *via* thiourea derivatives (VIII) prepared from the aniline derivatives (VI) (method A),[7a,8] and the other *via* a one-step reaction of VI with 2-chloro-2-imidazoline (method B).[9]

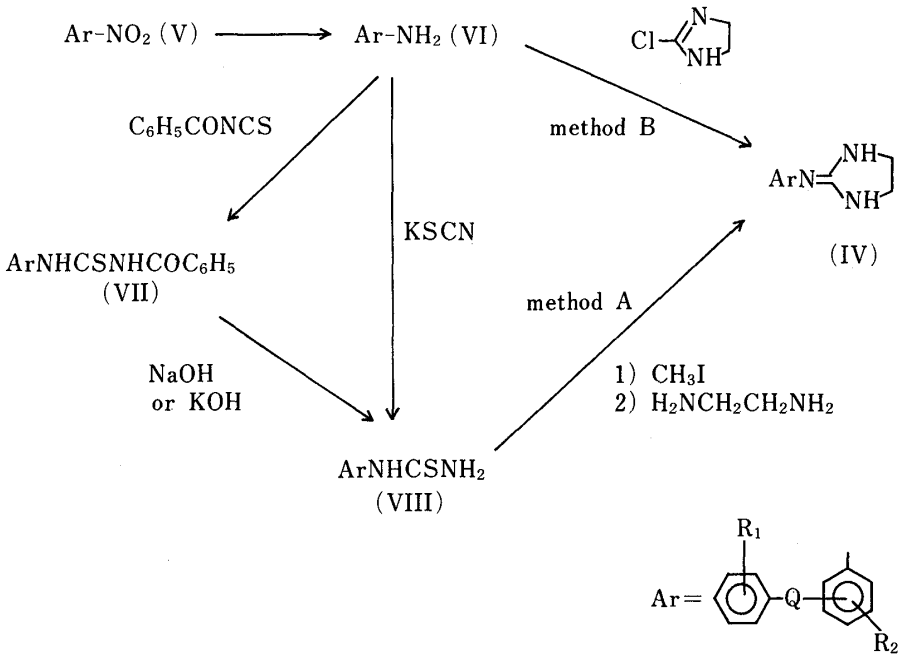


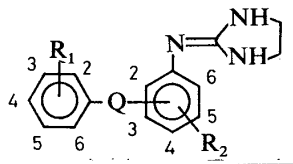
Chart 2

The starting materials (V) were prepared by the reaction of substituted nitrobenzenes, which have a halogen or nitro group as a leaving group, with phenols or thiophenol under typical conditions of the Ullman reaction (method C). Those compounds (V) having an amino group such as dimethylamino-, pyrrolidino-, morpholino-, and methanesulfonylamino- were prepared as follows. 2-(4-Dimethylaminophenoxy)- and 5-dimethylamino-2-phenoxy-1-nitrobenzenes (Vd and Vk) were prepared by methylation of the corresponding amino derivatives with dimethyl sulfate. 5-(1-Pyrrolidino)-, 5-(4-morpholino)-, and 5-methanesulfonylamino-2-phenoxy-1-nitrobenzenes (Vl, Vm, and Vn) were prepared also by the reaction of the corresponding amino derivative with 1,4-ditosyloxybutane, 2,2′-ditosyloxydiethyl ether, and methanesulfonyl chloride under the conditions described in the literature.[10] 5-Aminosulfonyl- and 5-dimethylaminosulfonyl-1-nitro-2-phenoxybenzenes (Vh and Vi) were synthesized *via* the corresponding sulfonyl chloride (IX), obtained by chlorination of potassium 3-nitro-4-phenoxybenzenesulfonate with phosphorus pentachloride at 120 °C. The reaction of IX with 2.4 eq of 25% aqueous dimethylamine in benzene produced Vi in 74.1% yield. Meanwhile, treatment of IX with excess 50% aqueous dimethylamine in ether afforded *N*,*N*-dimethyl-4-dimethylamino-3-nitrobenzenesulfonamide (X) in 82.2% yield.

Aniline derivatives (VI), one of the important key intermediates, were prepared by reduction of the corresponding nitro derivatives (V) with iron powder in the presence of ammonium chloride in aqueous ethanol (method D). 5-Hydroxy-2-phenoxyaniline (VIj) was synthesized by demethylation and simultaneous reduction of 5-methoxy-1-nitro-2-phenoxybenzene using hydroiodic acid.[11]

Preparation of the thiourea function was performed by the two procedures shown in Chart 2. The aniline derivatives (VI) were allowed to react with *N*-benzoylisothiocyanate to give *N*-benzoylthiourea derivatives (VII),[12] which were converted to the corresponding thioureas (VIII) by treatment with a base, such as sodium hydroxide or potassium hydroxide.

TABLE I. Physical Properties of 2-Phenyliminoimidazolidines (IV)



IV

Compound No.	Q	R_1	R_2	Salt[a]	Method	Yield (%)	mp (°C) (Solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{Nujol} cm^{-1}
IV-1	2-O	H	H	F	A	50.4	167—171 (EA–IPA)	$C_{15}H_{15}N_3O$	71.12 (71.25	5.97 5.96	16.59 16.44)	3470 3180 1655 1225
IV-2	2-O	2-Cl	H	F	A	58.2	158—161 (IPE–IPA)	$C_{15}H_{14}ClN_3O$	62.61 (62.74	4.90 4.89	14.60 14.45)	3450 3200 1660 1645 1235
IV-3	2-O	3-Cl	H	F	A	36.1	77—78 (H–EA)	$C_{15}H_{14}ClN_3O$	62.61 (62.45	4.90 4.83	14.60 14.58)	3430 3150 1665 1220
IV-4	2-O	4-Cl	H	F	A	45.7	118—119.5 (EA)	$C_{15}H_{14}ClN_3O$	62.61 (62.72	4.90 4.98	14.60 14.57)	3420 3150 1650 1220
IV-5	2-O	2,6-Cl_2	H	F	A	37.8	182—185 (EA–Alc)	$C_{15}H_{13}Cl_2N_3O$	55.92 (56.32	4.07 3.94	13.04 12.83)	3450 3170 1670 1240
IV-6	2-O	3,4-Cl_2	H	FA	A	41.8	166—169 (Alc)	$C_{15}H_{13}Cl_2N_3O$ $C_4H_4O_4$	52.07 (52.22	3.91 3.80	9.59 9.61)	3320 3140 1700 1680 1660 1230
IV-7	2-O	3,5-Cl_2	H	F	A	57.0	168—170 (EA)	$C_{15}H_{13}Cl_2N_3O$	55.92 (55.88	4.07 4.01	13.04 12.92)	3500 3170 1660 1240
IV-8	2-O	2-CH_3	H	F	A	31.2	116—117 (EA)	$C_{16}H_{17}N_3O$	71.89 (71.63	6.41 6.22	15.72 15.71)	3430 3200 1670 1650 1225
IV-9	2-O	3-CH_3	H	F	A	30.7	85—86 (H–EA)	$C_{16}H_{17}N_3O$	71.89 (71.81	6.41 6.32	15.72 15.78)	3440 3170 1665 1200
IV-10	2-O	4-CH_3	H	F	A	35.3	126—129 (EA)	$C_{16}H_{17}N_3O$	71.89 (71.81	6.41 6.34	15.72 15.59)	3430 3150 1670 1220
IV-11	2-O	4-F	H	F	A	36.6	118—121 (H–EA)	$C_{15}H_{14}FN_3O$	66.41 (65.93	5.20 5.16	15.49 15.41)	3450 3150 1665 1625 1205
IV-12	2-O	4-Br	H	F	A	12.1	68—70 (H–EA)	$C_{15}H_{14}BrN_3O$	54.23 (54.51	4.25 4.32	12.65 12.30)	3480 1645 1215
IV-13	2-O	4-CN	H	F	A	21.0	161—163 (EA)	$C_{16}H_{14}N_4O$	69.05 (69.40	5.07 4.93	20.13 20.12)	3450 2260 1660 1245
IV-14	2-O	4-$N(CH_3)_2$	H	F	A	41.9	143—148 (H–EA)	$C_{17}H_{20}N_4O$	68.89 (68.72	6.80 6.77	18.91 18.92)	3390 3300 1655 1220

TABLE I. (continued)

Compound No.	Q	R_1	R_2	Salt[a]	Method	Yield (%)	mp (°C) (Solvent)[b]	Formula	Analysis (%) Calcd (Found) C	H	N	IR ν_{max}^{Nujol} cm^{-1}
IV-15	2-O	3,4,5-$(OCH_3)_3$	H	F	A	63.4	156—159	$C_{18}H_{21}N_3O_4$	62.96	6.16	12.24	3450 3160 1680
					B	48.7	(EA–Alc)		(62.68	6.07	12.15)	1225 1125
IV-16	2-O	2,3-Benzo	H	F	A	28.1	130.5—131.5	$C_{19}H_{17}N_3O$	75.22	5.65	13.85	3410 3140 1695
							(H–EA)		(75.45	5.60	13.91)	1670 1250
IV-17	2-O	H	3-Cl	F	A	60.2	150—150.5	$C_{15}H_{14}ClN_3O$	62.61	4.90	14.60	3420 3240 1670
							(EA)		(62.61	4.90	14.51)	1245
IV-18	2-O	H	4-Cl	F	A	54.9	164—165.5	$C_{15}H_{14}ClN_3O$	62.61	4.90	14.60	3400 3140 1660
							(EA)		(62.51	4.83	14.54)	1225
IV-19	2-O	H	5-Cl	F	A	52.8	179—180	$C_{15}H_{14}ClN_3O$	62.61	4.90	14.60	3430 3100 1660
							(EA–Alc)		(62.44	4.79	14.73)	1210
IV-20	2-O	H	6-Cl	F	A	46.5	167—170	$C_{15}H_{14}ClN_3O$	62.61	4.90	14.60	3480 3200 1660
							(EA–Alc)		(62.58	4.82	14.57)	1215
IV-21	2-O	H	3-CH_3	F	A	42.8	133—134	$C_{16}H_{17}N_3O$	71.89	6.41	15.72	3460 3390 3150
							(EA)		(71.50	6.38	15.54)	1675 1660 1215
IV-22	2-O	H	4-CH_3	F	A	62.8	131—135	$C_{16}H_{17}N_3O$	71.89	6.41	15.72	3470 3180 1670
							(EA)		(72.06	6.41	15.55)	1220
IV-23	2-O	H	5-CH_3	F	A	50.2	172—174	$C_{16}H_{17}N_3O$	71.89	6.41	15.72	3420 3120 1675
							(EA)		(71.74	6.30	15.74)	1645 1220
IV-24	2-O	H	6-CH_3	F	A	40.5	129—133	$C_{16}H_{17}N_3O$	71.89	6.41	15.72	3490 3200 1670
							(H–Alc)		(72.02	6.36	15.72)	1215
IV-25	2-O	H	5-NO_2	F	A	33.7	164—166	$C_{15}H_{14}N_4O_3$	60.40	4.73	18.78	3440 3370 3150
							(EA)		(60.31	4.64	18.60)	1640 1560 1340
IV-26	2-O	H	5-CN	F	A	43.8	168—170	$C_{16}H_{14}N_4O$	69.05	5.07	20.13	3425 2250 1640
							(EA)		(68.98	4.70	19.81)	1220
IV-27	2-O	H	5-$CONH_2$	F	A	29.2	236—238	$C_{16}H_{16}N_4O_2$	64.12	5.64	18.92	3365 1680 1625
							(DMF)	1/5 DMF	(64.18	5.53	18.88)	1225
IV-28	2-O	H	5-SO_2NH_2	F	A	43.6	174—178	$C_{15}H_{16}N_4O_3S$	54.20	4.85	16.86	3380 1635 1325
							(E)		(53.94	4.77	16.27)	1210 1145
IV-29	2-O	H	5-$SO_2N(CH_3)_2$	F	A	54.1	149	$C_{17}H_{20}N_4O_3S$	56.65	5.59	15.55	3150 1650 1330
							(EA)		(56.91	5.60	15.52)	1220 1150

IV-30	2-O	H	5-CF_3	F	A	57.6	165—168 (H–EA)	$C_{16}H_{14}F_3N_3O$	59.81 (59.83	4.39 4.20	13.08 13.11)	3450 3200 1645 1215
IV-31	2-O	H	5-OH	F	A	17.7	210—211 (M)	$C_{15}H_{15}N_3O_2$	66.90 (67.00	5.61 5.47	15.60 15.71)	3470 2650 1645 1210
IV-32	2-O	H	5-OCH_3	F	A	47.7	210—217 (C–THF–M)	$C_{16}H_{17}N_3O_2$	67.83 (68.05	6.05 6.05	14.83 14.75)	3430 3170 1670 1220
IV-33	2-O	H	5-NH_2	F	c)	63.0	153—157 (H–EA–Alc)	$C_{15}H_{16}N_4O$	67.14 (67.15	6.01 5.89	20.88 20.55)	3460 3370 3240 1660 1225
IV-34	2-O	H	5-$N(CH_3)_2$	F	A	40.6	164—168 (EA–Alc)	$C_{17}H_{20}N_4O$	68.89 (68.81	6.80 6.74	18.91 18.72)	3490 3210 3130 1670 1235
IV-35	2-O	H	5- 	F	A	48.6	203—208 (THF–Alc)	$C_{19}H_{22}N_4O$	70.78 (70.61	6.88 6.83	17.38 17.23)	3460 1665 1235
IV-36	2-O	H	5- 	F	A	38.9	167—168 (EA–Alc)	$C_{19}H_{22}N_4O_2$	67.43 (67.11	6.55 6.24	16.56 16.32)	3380 3140 1655 1225
IV-37	2-O	H	5-$NHSO_2CH_3$	F	A	24.4	199—202 (A–M)	$C_{16}H_{18}N_4O_3S$	55.48 (55.57	5.24 4.99	16.17 16.12)	3270 2410 1670 1325 1220 1100
IV-38	2-O	4-Cl	5-Cl	F	A	57.7	155—156 (EA)	$C_{15}H_{13}Cl_2N_3O$	55.92 (56.09	4.07 4.00	13.04 12.98)	3440 3170 1660 1220
IV-39	2-O	4-Cl	5-CH_3	F	A	68.4	132—135 (EA)	$C_{16}H_{16}ClN_3O$	63.68 (63.51	5.34 5.30	13.93 13.89)	3480 3200 3130 1660 1225
IV-40	3-O	H	H	HCl	A	22.7	155—157 (A–Alc)	$C_{15}H_{15}N_3O \cdot HCl$	62.17 (62.41	5.57 5.52	14.50 14.45)	3280 3140 1660 1215
IV-41	4-O	H	H	HCl	A	26.1	154—157 (A–Alc)	$C_{15}H_{15}N_3O \cdot HCl$	62.17 (61.98	5.57 5.48	14.50 14.44)	3290 1660 1225
IV-42	2-S	H	H	F	A	58.6	150—155 (IPA–Alc)	$C_{15}H_{15}N_3S$	66.88 (66.85	5.61 5.61	15.60 15.38)	3480 3210 1670
IV-43	2-NH	H	H	F	B	33.8	147—150 (IPA)	$C_{15}H_{16}N_4$	71.40 (71.76	6.39 6.43	22.21 22.17)	3430 3180 1650
IV-44	2-CH_2	H	H	F	A	54.0	112—113 (EA)	$C_{16}H_{17}N_3$	76.46 (76.46	6.82 6.84	16.72 16.58)	3410 3180 1670

a) F, free base. FA, fumarate. *b*) H, *n*-hexane; IPE, diisopropyl ether; E, diethyl ether; C, chloroform; A, acetone; EA, ethyl acetate; IPA, isopropanol; Alc, ethanol; M, methanol; THF, tetrahydrofuran; DMF, *N*, *N*-dimethylformamide. *c*) See Experimental.

in methanol.[12] The 5-aminosulfonylthiourea derivative (VIII-28) was prepared in a moderate yield by the one-step reaction of the corresponding aniline (VIh) with potassium thiocyanate.[13]

The desired imidazolidines (IV) were synthesized by cyclization of the *S*-methylisothiouronium salts, which are the reaction products of the thioureas (VIII) and methyl iodide, using ethylenediamine (method A). The imidazolidines (IV) were also prepared by the one-step reaction of the anilines (VI) with 2-chloro-2-imidazoline (method B). For example, 2-[2-(3,4,5-trimethoxyphenoxy)phenylimino]imidazolidine (IV-15) was obtained in yields of 63.4% (method A) and 48.7% (method B). A 5-aminoimidazolidine derivative (IV-33) was prepared in 63.0% yield by catalytic reduction of the corresponding nitro derivative (IV-25) on palladium–carbon in methanol. The other imidazolidines (IV) synthesized in this study are listed in Table I.

In order to synthesize 2-(2-phenoxyphenylamino)imidazole (XII), *S*-methyl-*N*-(2-phenoxyphenyl)isothiourea hydroiodide (XI) was allowed to react with 2-aminoacetaldehyde diethylacetal, and then acid-catalized cyclization was carried out according to the method described in the literature[8] (Chart 3). The product obtained was shown to consist of two different components, which were separated and purified by silica gel column chromatography. The structures of XII and XIII were identified on the basis of the elemental analysis and spectral data.

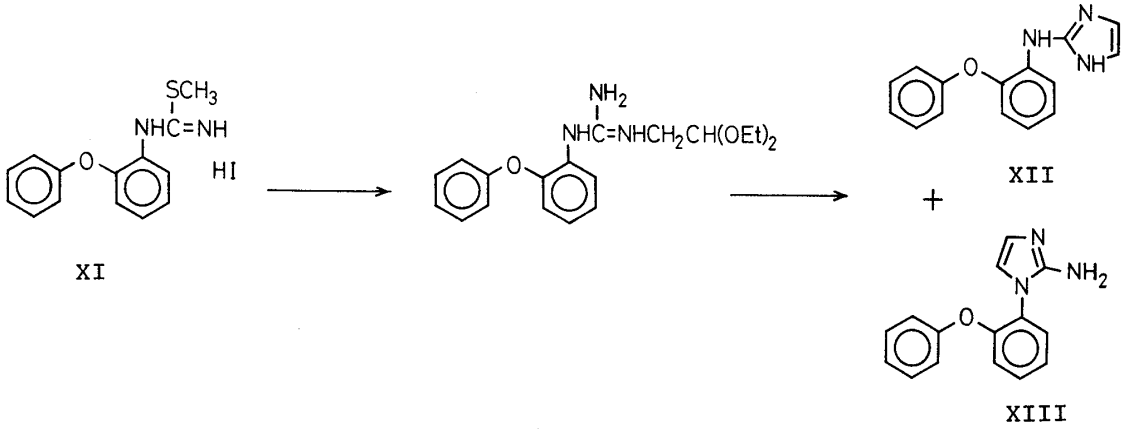


Chart 3

Pharmacological Results

Compounds prepared were tested for hypotensive activity. Each compound was given orally to conscious normotensive rats of the Wistar strain at a dose of 10 mg/kg. Mean arterial blood pressure was measured with a pressure transducer through a polyethylene cannula inserted into a femoral artery, and recorded on a polygraph. The experiments were conducted on groups of five animals. The test results are summarized in Table II.

Compound (IV-1), which has no substituent on the benzene ring, nearly equaled prazosin in hypotensive activity. However, IV-40 and IV-41, which are isomers of IV-1 as regards the position of the phenoxy group, had no activity. Replacement of the phenoxy group of IV-1 with a phenylthio (IV-42), phenylamino (IV-43), or benzyl (IV-44) group reduced the potency. In a series of congeners substituted with a chloro or methyl on the phenoxy group of IV-1, the potency tended to decrease in the order of *ortho* (IV-2 and IV-8), *para* (IV-4 and IV-10), and *meta* (IV-3 and IV-9). Dichloro-substituted compounds (IV-5 and IV-6, and IV-7) and a naphthoxy derivative (IV-16) showed relatively weak activity. 4-Fluoro (IV-11), 4-bromo (IV-12), 4-cyano (IV-13), 4-dimethylamino (IV-14), and 3,4,5-trimethoxy (IV-15) derivatives were

TABLE II. Antihypertensive Activities of 2-Phenyliminoimidazolidines (IV) and Related Compounds in Normotensive Rats

Compound No.	Maximum decrease in blood pressure (% of initial value) 10 mg/kg *p.o.*	Compound No.	Maximum decrease in blood pressure (% of initial value) 10 mg/kg *p.o.*
IV-1	41.3	IV-26	20.1
IV-2	29.0	IV-27	IA[c]
IV-3	18.7	IV-28	IA
IV-4	22.7	IV-29	IA
IV-5	5.6	IV-30	35.7
IV-6	IA[a]	IV-31	IA
IV-7	9.0	IV-32	IA[b]
IV-8	26.9	IV-33	IA[c]
IV-9	5.6	IV-34	40.3
IV-10	IA[b]	IV-35	12.7
IV-11	IA[b]	IV-36	10.3
IV-12	IA	IV-37	IA
IV-13	IA[b]	IV-38	34.3
IV-14	IA	IV-39	35.4
IV-15	IA	IV-40	IA
IV-16	29.6	IV-41	IA
IV-17	26.4	IV-42	22.1
IV-18	28.8	IV-43	35.7
IV-19	57.4	IV-44	28.0
IV-20	33.0	XII	8.6
IV-21	39.6	VII-19	IA[b]
IV-22	44.3	VIII-19	IA[b]
IV-23	53.3	Prazosin	41.2
IV-24	34.9	Clonidine	23.5
IV-25	35.0		

a) IA, inactive. *b*) 1 mg/kg *p.o.* *c*) Increase in blood pressure was observed. Maximum increases were 22.4% for IV-27 and 22.8% for IV-33.

inactive. These results indicate that any substitution on the phenoxy group of IV-1 tended to decrease the potency. On the other hand, introduction of a chloro or methyl on the benzene ring of the phenylimino moiety of IV-1 enhanced the potency in some compounds. The potency was highest in IV-19 and IV-23, which have a chloro or methyl at the 5-position, and less high in compounds having the group at other positions. Unlike clonidine (III), substitution at the 6-position did not necessarily maximize the potency. Compounds having nitro (IV-25), trifluoromethyl (IV-30), and dimethylamino (IV-34) at the 5-position retained the potency of the parent compound (IV-1). Other substituents, such as cyano (IV-26), carbamoyl (IV-27), aminosulfonyl (IV-28), dimethylaminosulfonyl (IV-29), hydroxy (IV-31), methoxy (IV-32), amino (IV-33), pyrrolidino (IV-35), morpholino (IV-36), and methanesulfonylamino (IV-37), reduced the potency markedly. No clear relationship was apparent between the electronic or steric effect of the substituents and the biological potency. As expected, introduction of a chloro on the phenoxy group of IV-19 or IV-23 resulted in reduction of the potency (IV-38 and IV-39). Replacement of the imidazolidine moiety with imidazole also reduced the activity markedly (XII).

Of the compounds tested, IV-19 was found to be the most active. It appears to differ from centrally acting antihypertensive agents such as clonidine (III) in pharmacological profile. The mechanism of action of IV-19 is supposed to involve the blockade of peripheral α receptors.

Compound IV-19 is now under clinical study, and details of the pharmacology will be published elsewhere.

Experimental

The melting points were determined on a capillary melting point apparatus (Electrothermal) and are uncorrected. The infrared (IR) spectra were taken with Hitachi 215 and Hitachi 260-10 spectrometers. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded with Varian EM-60 and JEOL MH-60 spectrometers using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, br s = broad singlet, d = doublet, dd = double doublet, m = multiplet.

1-Nitro-2-(3,4,5-trimethoxyphenoxy)benzene (Ve). Method C——A mixture of 2-chloro-1-nitrobenzene (126.0 g), 3,4,5-trimethoxyphenol (162.1 g), and K_2CO_3 (132.7 g) in dimethylformamide (DMF, 600 ml) was stirred under reflux for 6 h, and concentrated *in vacuo*. The residue was partitioned between Et_2O and 5% NaOH. The ether layer was washed with brine, dried, and evaporated *in vacuo*. The residue was recrystallized from MeOH to give Ve (154.1 g, 63.1%). ^{1}H-NMR ($CDCl_3$) δ: 3.84 (6H, s, CH_3), 3.86 (3H, s, CH_3), 6.35 (2H, s, aromatic H), 6.95—8.05 (4H, m, aromatic H).

Compounds (V) prepared by method C are listed in Table III.

2-(4-Dimethylaminophenoxy)-1-nitrobenzene (Vd)——The reaction of 2-(4-aminophenoxy)-1-nitrobenzene[14] with dimethylsulfate, in the presence of K_2CO_3 in DMF, at 100 °C for 4 h gave Vd in 33.6% yield. ^{1}H-NMR ($CDCl_3$) δ: 2.87 (6H, s, CH_3), 6.6—7.55 (7H, m, aromatic H), 7.86 (1H, dd, J=8 and 2 Hz, aromatic H).

5-Dimethylamino-1-nitro-2-phenoxybenzene (Vk)——The reaction of 5-amino-2-phenoxy-1-nitrobenzene (Vo)[15] with dimethylsulfate in refluxing 25% NaOH for 6 h gave Vk in 31.2% yield. ^{1}H-NMR ($CDCl_3$) δ: 3.02 (6H, s, CH_3), 6.75—7.5 (8H, m, aromatic H).

5-Aminosulfonyl-1-nitro-2-phenoxybenzene (Vh)——3-Nitro-4-phenoxybenzenesulfonyl chloride (IX) was prepared as follows. Potassium 3-nitro-4-phenoxybenzenesulfonate[16] (10.0 g) was allowed to react with PCl_5 (6.0 g) at 120 °C for 5.5 h. The resulting mixture was cooled and partitioned between benzene and cold water. The organic layer was washed with chilled water, dried, and concentrated *in vacuo* to give an oil (IX, 9.35 g, 99.4%). This oil was used without purification for the following experiment. IR ν_{max}^{film} cm^{-1}: 1530, 1380, 1360, 1260, 1180. ^{1}H-NMR ($CDCl_3$) δ: 7.0—7.8 (6H, m, aromatic H), 8.12 (1H, dd, J=9 and 2 Hz, aromatic H), 8.64 (1H, d, J=2 Hz, aromatic H).

The reaction of IX with excess 14% NH_4OH in benzene at room temperature gave Vh in 57.7% yield. ^{1}H-NMR (DMSO-d_6) δ: 6.9—7.8 (8H, m, aromatic H and SO_2NH_2), 8.03 (1H, dd, J=9 and 2 Hz, aromatic H), 8.42 (1H, d, J=2 Hz, aromatic H).

5-Dimethylaminosulfonyl-1-nitro-2-phenoxybenzene (Vi)——The treatment of IX with 2.4 eq of 25% aqueous dimethylamine in benzene at room temperature for 30 min gave Vi in 74.1% yield. mp 104—105 °C (lit.[17] 105 °C).

***N,N*-Dimethyl-4-dimethylamino-3-nitrobenzenesulfonamide (X)**——The treatment of IX with excess 50% aqueous dimethylamine in ice-cooled Et_2O for 30 min gave X in 82.2% yield. mp 102.5—104.5 °C (from *n*-hexane and EtOH, lit.[18] 102—104.5 °C).

5-(1-Pyrrolidino)-, 5-(4-Morpholino)-, and 5-Methanesulfonylamino-1-nitro-2-phenoxybenzenes (Vl, Vm, and Vn)——Vo was treated with 1,4-ditosyloxybutane, 2,2′-ditosyloxydiethylether, or methanesulfonyl chloride according to the methods described in the literature[10] to give Vl, Vm, or Vn in 62.4, 67.5, or 61.5% yield, respectively. Vl; ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.2 (4H, m, CH_2), 3.15—3.6 (4H, m, CH_2), 6.55—7.9 (8H, m, aromatic H). Vm; ^{1}H-NMR (DMSO-d_6) δ: 3.05—3.9 (8H, m, CH_2), 6.8—7.85 (8H, m, aromatic H). Vn; ^{1}H-NMR (DMSO-d_6) δ: 3.07 (3H, s, CH_3), 6.95—7.9 (8H, m, aromatic H), 10.12 (1H, br s, NH).

The other derivatives (V) were synthesized according to the literature.

2-(3,4,5-Trimethoxyphenoxy)aniline (VIe). Method D——Ve (29.0 g) was slowly added to a stirred mixture of iron powder (29.0 g) and NH_4Cl (3.5 g) in refluxing EtOH (493 ml) and water (87 ml), and the mixture was stirred under reflux for 45 min. After removal of the solvent, the residue was diluted with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. This extract was dried and evaporated *in vacuo*. The residue was recrystallized from EtOH to give VIe (24.1 g, 92.2%). ^{1}H-NMR ($CDCl_3$) δ: 3.77 and 3.82 (11H, each s, CH_3 and NH_2), 6.26 (2H, s, aromatic H), 6.55—7.14 (4H, m, aromatic H).

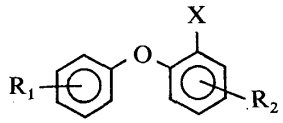
Compounds (VI) prepared according to method D are listed in Table III.

5-Hydroxy-2-phenoxyaniline (VIj)——The treatment of 5-methoxy-1-nitro-2-phenoxybenzene[19] with 57% aqueous HI in Ac_2O and AcOH under reflux for 3 h gave VIj in 98.1% yield. ^{1}H-NMR (DMSO-d_6) δ: 4.71 (2H, br s, NH_2), 5.9—7.45 (8H, m, aromatic H), 8.90 (1H, s, OH).

The other derivatives (VI) used in this report were prepared according to the literature.

1-Benzoyl-3-(5-chloro-2-phenoxyphenyl)thiourea (VII-19)——Benzoyl chloride (8.86 g) was added dropwise to a hot solution of NH_4SCN (5.26 g) in dry acetone (60 ml). The mixture was refluxed for 1 h, and then 5-chloro-2-phenoxyaniline[20] (13.2 g) in dry acetone (130 ml) was added dropwise. The resulting mixture was stirred under reflux for 1 h, concentrated *in vacuo*, and diluted with water. The precipitate obtained was collected, washed with water, and

TABLE III. Physical Properties of Aniline and Nitrobenzene Derivatives (V and VI)

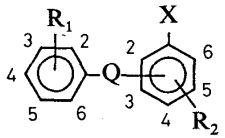


V: X=NO_2
VI: X=NH_2

Compound No.	R_1	R_2	V				VI			
			Method	Yield (%)	mp (°C)	IR ν_{max}^{Nujol} cm^{-1}	Method	Yield (%)	mp (°C)	IR ν_{max}^{Nujol} cm^{-1}
a	2,6-Cl_2	H					D	80.1	79—81	3430 3380 1240
b	3,4-Cl_2	H					D	100	Oil	3480 3390 1220[b]
c	3,5-Cl_2	H	C	64.0	77—79	1525 1355 1255	D	100	Oil	3480 3390 1245[b]
d	4-$N(CH_3)_2$	H	a)	33.6	96—100	1510 1350 1250	D	61.3	71—76	3460 3370 1220
e	3,4,5-$(OCH_3)_3$	H	C	63.1	70—74	1520 1365 1220 1130	D	92.2	127—132	3480 3380 1225 1120
f	H	6-Cl	C	71.8	Oil[c]	1530 1370 1265[b] 1190	D	88.6	Oil[d]	3460 3370 1200[b]
g	H	5-$CONH_2$	C	48.4	173—174	3450 3300 3200 1650 1530 1350	D	58.7	144—146	3430 3350 3310 3200 1660 1215
h	H	5-SO_2NH_2	a)	57.7	123—125	3310 3230 1520[e] 1335 1250 1170	D	97.1	153—157	3440 3350 3320 1330 1220 1155
i	H	5-$SO_2N(CH_3)_2$	a)	74.1	104—105		D	100	Oil	3480 3380 1350[b] 1230 1155
j	H	5-OH					a)	98.1	154—156	3390 3320 3130 1225
k	H	5-$N(CH_3)_2$	a)	31.2	74.5—76	1530 1350 1240	D	99.6	59—65	3460 3370 1220
l	H	5-N⟨ ⟩	a)	62.4	102—105	1525 1365 1240	D	51.5	76—80	3460 3370 1210
m	H	5-N⟨ ⟩O	a)	67.5	95—100	1525 1360 1255	D	47.8	120—124	3450 3370 1220[e]
n	H	5-$NHSO_2CH_3$	a)	61.5	124—126	3270 1520 1345 1320 1255 1150	D	98.3	140—145	3430 3340 1335 1220 1150

a) See Experimental. *b*) Measured by the film method. *c*) bp 135—148 °C (1.0 mmHg). *d*) bp 128—135 °C (0.5 mmHg). *e*) Measured by the KBr method.

TABLE IV. Physical Properties of Benzoylthiourea and Thiourea Derivatives (VII and VIII)



VII: X=NHCSNHCOC$_6$H$_5$
VIII: X=NHCSNH$_2$

Compound No.	Q	R_1	R_2	VII			VIII		
				Yield (%)	mp (°C)	IR ν_{max}^{Nujol} cm^{-1}	Yield (%)	mp (°C)	IR ν_{max}^{Nujol} cm^{-1}
1	2-O	H	H	91.4	171—173	3260 1675 1225	81.6	124—127	3410 3310 3190 1220
2	2-O	2-Cl	H	a)			89.8[b]	125—128	3440 3260 3170 1230
3	2-O	3-Cl	H	76.5	119—121	3320 1680 1230	88.5	102—107	3370 3340 3280 3160 1220
4	2-O	4-Cl	H	83.1	155—156.5	3310 1680 1235	90.6	142—142.5	3380 3330 3270 3160 1230
5	2-O	2,6-Cl$_2$	H	94.4	200—205	3290 1670 1240	58.9	186—190	3430 3300 3180 3130 1240
6	2-O	3,4-Cl$_2$	H	58.1	141—142	3440 1675 1260	97.7	147—150	3420 3270 3180 1220
7	2-O	3,5-Cl$_2$	H	76.3	134—135	3330 1670 1250 1200	83.4	148—150	3430 3270 3180 1270
8	2-O	2-CH$_3$	H	68.9	165—166	3245 1680 1210	81.0	135—136	3440 3270 3170 1225
9	2-O	3-CH$_3$	H	70.4	144—146	3425 3325 1675 1255 1205	100	104—106	3440 3405 3260 3160 1265
10	2-O	4-CH$_3$	H	68.2	187—188	3340 1675 1245 1225	87.7	154—155	3405 3245 3140 1220
11	2-O	4-F	H	60.4	137—140	3425 1675 1205	82.6	139—141	3325 3275 3150 1205
12	2-O	4-Br	H	77.0	170—172	3375 1670 1225	89.9	155—157	3375 3325 3275 3150 1220
13	2-O	4-CN	H	74.6	146—148	3305 2240 1660 1250	71.6	159—161	3400 3370 3260 3150 2200 1210
14	2-O	4-N(CH$_3$)$_2$	H	88.0	203—208	3340 1670 1250	95.6	191—194	3420 3260 3160 1230
15	2-O	3,4,5-(OCH$_3$)$_3$	H	63.8	149—151	3420 1670 1230 1130	90.3	154—156	3380 3300 3170 1220 1125
16	2-O	2,3-Benzo	H	96.6	159—161.5	3420 3320 1680 1245 1210	68.9	172—179	3410 3250 3170 1230
17	2-O	H	3-Cl	74.2	137—141	3340 1675 1240	82.3	142—143	3400 3350 3280 3180 1240
18	2-O	H	4-Cl	53.4	164—166	3290 1670 1245 1220	99.3	137—138	3400 3360 3290 3180 1220

19	2-O	H	5-Cl	51.4	163—166	3470 1685 1225	89.3	140—145	3460 3340 3250 3150 1225
20	2-O	H	6-Cl	90.9	151—158	3410 3170 1675 1210	92.5	107—120	3440 3410 3270 3150 1210
21	2-O	H	3-CH_3	68.1	146—148	3400 1670 1215	94.4	141—145	3400 3350 3290 3170 1210
22	2-O	H	4-CH_3	a)			60.1[b]	131—133	3420 3290 3180 1220
23	2-O	H	5-CH_3	61.2	175—180	3400 1670 1230	90.4	161—163	3400 3270 3220 3180 1230
24	2-O	H	6-CH_3	84.1	141—145	3240 3140 1670 1230	97.2	137—142	3420 3270 3160 1210
25	2-O	H	5-NO_2	83.9	210—212	3330 1670 1540 1340 1220	85.6	164—166.5	3420 3280 3180 1550 1345 1225
26	2-O	H	5-CN	69.5	206—208	3330 2230 1670 1255 1240	91.4	187—189	3310 3290 3180 2225 1230
27	2-O	H	5-$CONH_2$	60.0	213—215	3370 3180 1670 1640 1225	76.7	195—196	3375 3175 3125 1660 1625 1225
29	2-O	H	5-$SO_2N(CH_3)_2$	98.0	140—145	3410 3150 1660 1340 1220 1150	79.4	153—157	3400 3280 3180 1345 1220 1160
30	2-O	H	5-CF_3	64.5	170—172	3330 1670 1210	95.9	159—160	3430 3290 3170 3130 1220
31	2-O	H	5-OH	98.0	183—186	3370 3100 1675 1225	72.6	174—176	3450 3320 3150 1215
32	2-O	H	5-OCH_3	93.4	163—165	3180 1675 1220	67.5	169—170.5	3400 3300 3140 1230
34	2-O	H	5-$N(CH_3)_2$	77.0	154.5—158	3420 1680 1255	83.2	163—164	3380 3350 3270 3170 1260 1220
35	2-O	H	5- 	73.3	174.5—176	3250 1680 1255	74.7	192—196	3360 3330 3270 3160 1250
36	2-O	H	5- 	84.9	195—197	3270 1675 1245	78.4	189—193	3450 3320 3130 1240
37	2-O	H	5-$NHSO_2CH_3$	73.7	231—232	3370 3230 1670 1320 1235 1155	88.1	191—195	3360 3320 3280 3190 1325 1210 1145
38	2-O	4-Cl	5-Cl	81.8	183—189	3260 1670 1230	91.2	163—165	3430 3260 3160 3100 1225
39	2-O	4-Cl	5-CH_3	75.5	196—197	3330 1670 1240	80.7	108—113	3430 3240 3170 1230
40	3-O	H	H	83.5	97—98.5	3240 3150 1680 1225	83.4	123.5—126	3390 3270 3180 1210
41	4-O	H	H	84.9	123—126	3250 1670 1245	95.6	181—184	3440 3270 3190 1240
42	2-S	H	H	97.1	65—75	3430 3240 1675	46.1	99—103	3420 3260 3210 3160
44	2-CH_2	H	H	78.7	132—133	3280 1670	83.3	125—126	3395 3360 3280 3190

a) The crude product was used for the next step without further purification. *b*) Yield based on the aniline derivative (VI) used.

recrystallized from acetone to give VII-19 (11.8 g, 51.4%). ^{1}H-NMR ($CDCl_3$) δ: 6.75—7.95 (12H, m, aromatic H), 8.93 (1H, d, J=2 Hz, aromatic H), 9.11 (1H, br s, NH), 13.11 (1H, br s, NH).

The other compounds (VII) were prepared in a manner similar to that used for VII-19 (Table IV).

5-Chloro-2-phenoxyphenylthiourea (VIII-19)——A mixture of VII-19 (8.0 g) and KOH (1.17 g) in MeOH (80 ml) was stirred at 50 °C for 10 min, concentrated *in vacuo*, and diluted with water. The precipitate obtained was collected, washed with water, and recrystallized from aqueous MeOH to give VIII-19 (5.2 g, 89.3%). ^{1}H-NMR (DMSO-d_6) δ: 6.8—7.6 (7H, m, aromatic H), 7.78 (2H, br s, NH_2), 8.36 (1H, d, J=2 Hz, aromatic H), 9.42 (1H, br s, NH).

The other compounds (VIII) were prepared in a manner similar to that used for VIII-19 (Table IV).

5-Aminosulfonyl-2-phenoxyphenylthiourea (VIII-28)——VIh was treated with KSCN according to the literature.[13] The crude powder obtained was purified by silica gel column chromatography using $CHCl_3$–AcOEt (7 : 3) to give VIII-28 in 58.9% yield. mp 117—120 °C (dec.) (from diisopropylether and iso-PrOH). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3150, 1320, 1260, 1150. ^{1}H-NMR (DMSO-d_6) δ: 6.85—7.85 (11H, m, aromatic H, SO_2NH_2, and $CSNH_2$), 8.60 (1H, d, J= 2 Hz, aromatic H), 9.48 (1H, s, NH).

Preparation of 2-(Phenylimino)imidazolidines (IV). Method A: 2-(5-Chloro-2-phenoxyphenylimino)imidazolidine (IV-19)——A mixture of VIII-19 (2.2 g) and CH_3I (1.34 g) in MeOH (26 ml) was stirred under reflux for 1 h, and then concentrated *in vacuo* to give *N*-(5-chloro-2-phenoxyphenyl)-*S*-methylisothiourea hydroiodide (3.3 g), which was used without purification for the following reaction. A mixture of *S*-methylisothiourea hydroiodide (3.3 g) and ethylenediamine (1.48 g) in EtOH (27 ml) was stirred under reflux for 4 h, cooled, and concentrated *in vacuo*. The resulting residue was partitioned between CH_2Cl_2 and 5% NaOH, and the CH_2Cl_2 layer was washed with brine, dried, and evaporated *in vacuo*. The residue was recrystallized from AcOEt–EtOH to give IV-19 (1.2 g, 52.8%). ^{1}H-NMR (DMSO-d_6) δ: 3.27 (4H, s, CH_2), 6.25 (2H, br s, NH), 6.8—7.5 (8H, m, aromatic H).

Method B: 2-[2-(3,4,5-Trimethoxyphenoxy)phenylimino]imidazolidine (IV-15)——2-Chloro-2-imidazoline sulfate[9] (1.0 g) was added to 5% NaOH (10 ml), and the solution was extracted with four 5-ml portions of CH_2Cl_2. These extracts were combined, and dried over $MgSO_4$. $MgSO_4$ was removed, and VIe (0.906 g) was added to the solution. The mixture was allowed to stand at room temperature for 42 h, then filtered. This filtrate was evaporated *in vacuo*, and the residue was partitioned between AcOEt and dil. HCl. The aqueous layer was separated, washed with AcOEt, made alkaline with aqueous Na_2CO_3, and extracted with CH_2Cl_2. This extract was washed with brine, dried, and evaporated *in vacuo*. The residue was recrystallized from AcOEt–EtOH to give IV-15 (0.55 g, 48.7%). ^{1}H-NMR (DMSO-d_6) δ: 3.28 (4H, s, CH_2), 3.62 (3H, s, CH_3), 3.68 (6H, s, CH_3), 6.10 (2H, br s, NH), 6.22 (2H, s, aromatic H), 6.8—7.25 (4H, m, aromatic H).

Compounds (IV) prepared by methods A and B are listed in Table I.

2-(5-Amino-2-phenoxyphenylimino)imidazolidine (IV-33)——IV-25 (3.0 g) was catalytically hydrogenated in MeOH (240 ml) at room temperature using 10% Pd on carbon. After removal of the catalyst, the solution was concentrated *in vacuo* to give a powder, which was purified by alumina column chromatography using $CHCl_3$–MeOH (9 : 1) to give IV-33 (1.7 g, 63.0%). ^{1}H-NMR (DMSO-d_6) δ: 3.20 (4H, s, CH_2), 4.67 (2H, br s, NH), 5.90 (2H, br s, NH), 6.0—7.25 (8H, m, aromatic H).

2-(2-Phenoxyphenylamino)imidazole (XII) and 2-Amino-1-(2-phenoxyphenyl)imidazole (XIII)——A mixture of *S*-methyl-*N*-(2-phenoxyphenyl)isothiourea hydroiodide (XI, 27.2 g) and 2-aminoacetaldehyde diethylacetal (11.2 g) was stirred at 110 °C for 5.5 h, then cooled. The reaction mixture was basified with aqueous NaOH, and extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated *in vacuo* to give a red oil (25.3 g), which was treated with conc. HCl (21.1 ml) and heated at 90 °C for 45 min. The solution was cooled, basified with aqueous NaOH, and extracted with CH_2Cl_2. The extract was washed with water, dried (treated with activated carbon), and concentrated *in vacuo*. The residue was recrystallized from *n*-hexane–AcOEt to give crystals, which were purified by silica gel column chromatography using $CHCl_3$–EtOH (1 : 1). The first eluate gave XII (0.60 g, 3.4%) as needles; mp 173—176 °C (from AcOEt–EtOH). *Anal.* Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.59; H, 5.08; N, 16.50. IR ν_{max}^{Nujol} cm^{-1}: 3390, 1600, 1580, 1245, 1210. ^{1}H-NMR (DMSO-d_6) δ: 6.7—7.6 (10H, m, aromatic H and imidazole H), 8.18 (1H, s, NH), 8.51 (1H, d, J=8 Hz, aromatic H), 10.58 (1H, br s, NH). The subsequent eluate gave XIII (1.2 g, 6.8%) as prisms; mp 132—135 °C (from AcOEt). *Anal.* Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.51; H, 5.07; N, 16.68. IR ν_{max}^{Nujol} cm^{-1}: 3430, 3400, 3270, 1635, 1230. ^{1}H-NMR (DMSO-d_6) δ: 5.22 (2H, br s, NH_2), 6.43 (1H, d, J=2 Hz, imidazole H), 6.63 (1H, d, J=2 Hz, imidazole H), 6.95—7.5 (9H, m, aromatic H).

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References

1) I. Ueda, M. Matsuo, K. Taniguchi, and Y. Katsura, European Patent 17484 (1980) [*Chem. Abstr.*, **94**, 139807*c* (1981)].
2) M. Wilhelm and G. deStevens, *Progress in Drug Research*, **20**, 197 (1976).

3) O. Schier and A. Marxer, *Progress in Drug Research*, **25**, 9 (1981).
4) R. R. Ruffolo, Jr., E. L. Rosing, and J. E. Waddell, *J. Pharmacol. Exp. Ther.*, **209**, 429 (1979).
5) N. Weiner, "The Pharmacological Basis of Therapeutics," 6th ed., ed. by A. G. Gilman, L. S. Goodman, and A. Gilman, The Macmillan Publishing Company, New York, 1980, pp. 183—184.
6) L. Isaac, *J. Cardiovasc. Pharmacol.*, **2**, Suppl. 5 (1980); W. A. Pettinger, *ibid.*, **2**, Suppl. 21 (1980).
7) *a*) B. Rouot, G. Leclerc, and C. Wermuth, *J. Med. Chem.*, **19**, 1049 (1976); *b*) P. B. M. W. M. Timmermans and P. A. van Zwieten, *ibid.*, **20**, 1636 (1977).
8) T. Jen, H. Hoeven, W. Groves, R. A. Mclean, and B. Loev, *J. Med. Chem.*, **18**, 90 (1975).
9) A. Trani and E. Bellasio, *J. Heterocycl. Chem.*, **11**, 257 (1974).
10) D. D. Reynolds and W. O. Kenyon, *J. Am. Chem. Soc.*, **72**, 1597 (1950); R. G. Shepherd, *J. Org. Chem.*, **12**, 275 (1947).
11) N. M. Cullinane, H. G. Davey, and H. J. Padfield, *J. Chem. Soc.*, **1934**, 716.
12) Y. Kinoshita, N. Matsuda, S. Sakai, Y. Oshima, T. Harada, and T. Nishihara, *Agric. Biol. Chem.*, **30**, 447 (1966).
13) K. V. Viswanathan, M. Raghavan, and P. C. Guha, *J. Indian Inst. Sci.*, **35A**, 251 (1953) [*Chem. Abstr.*, **48**, 11380*e* (1954)].
14) Farbenfabriken Bayer A.-G., Fr. Patent 1560940 (1969) [*Chem. Abstr.*, **72**, 66617*z* (1970)].
15) P. E. Verkade and C. P. van Dijk, *An. R. Soc. Esp. Fis. Quim., Ser. B*, **62**, 451 (1966) [*Chem. Abstr.*, **65**, 18449*h* (1966)].
16) H. Zahn and K. H. Lebkücher, *Biochem. Z.*, **334**, 133 (1961); C. Haeussermann and E. Bauer, *Chem. Ber.*, **30**, 738 (1897).
17) V. Petrow, O. Stephenson, and A. M. Wild, *J. Pharm. Pharmacol.*, **12**, 705 (1960).
18) V. L. Plakidin and V. N. Vostrova, *Zh. Obshch. Khim.*, **18**, 342 (1982) [*J. Org. Chem. USSR*, **18**, 295 (1982)].
19) J. Forrest, *J. Chem. Soc.*, **1960**, 581.
20) Y. Hamada, M. Sugiura, T. Nishida, K. Araki, K. Horigome, and Z. Henmi, *Yakugaku Zasshi*, **98**, 1597 (1978).