[Chem. Pharm. Bull.]
36(10)4121—4135(1988)

Novel Phenoxyalkylamine Derivatives. V.¹⁾ Synthesis, α -Blocking Activity and Quantitative Structure–Activity Analysis of α -[(Phenoxyethylamino)propyl]- α -phenylacetonitrile Derivatives

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(Received April 20, 1988)

α -[(Phenoxyethylamino)propyl]- α -phenylacetonitrile derivatives possessing various substituents on the benzene ring (A ring) at the phenylacetonitrile moiety, on the quaternary carbon atom and on the benzene ring (B ring) at the phenoxy moiety, and exhibiting various degrees of α -blocking activity, were prepared. The variations in the activity were analyzed qualitatively as well as quantitatively by using physicochemical substituent parameters and a regression technique. The effect of substituents on the A ring was rationalized in terms of a parabolic function of their hydrophobic parameter. As regards substituents on the quaternary carbon atom, alkyl groups were desirable for high activity. The effects of substituents on the B ring were such that an optimum hydrophobic condition exists and that an alkoxy substituent at the *o*-position as well as smaller substituents at the *m*- and *p*-positions are favorable for high activity. The analysis for the combined series of analogs where substituents on the A and B rings are varied showed the existence of an optimum hydrophobicity for the whole molecule for the transport process of the molecule, besides above-mentioned various position-specific structural effects.

Keywords—phenoxyalkylamine; α -[(phenoxyethylamino)propyl]- α -phenylacetonitrile; α -blocking activity; quantitative structure–activity relationship; Hansch–Fujita analysis

As a part of our studies of cardiovascular agents, we designed and synthesized novel phenoxyalkylamine derivatives (I) which are considered as analogs of verapamil.²⁾ We examined them for two types of pharmacological activities, namely, Ca^{2+} -antagonistic and α -blocking activities. The effects of the carbon chain length, *m* and *n*, of the alkylene parts and the substituent at the amino nitrogen on these activities were examined and it was shown that structural conditions of *m* = *n* = 3 and $\text{R}_1 = \text{Me}$ were desirable for Ca^{2+} -antagonistic activity, while those of *m* = 3, *n* = 2 and $\text{R}_1 = \text{H}$ (I') were favorable for α -blocking activity.³⁾

The aim of the present study was to investigate the effect of structural modifications of I on the α -blocking activity, under conditions of *m* = 3, *n* = 2 and $\text{R}_1 = \text{H}$. We attempted to examine compounds in which various substituents, R_2 , were introduced into the A ring (II-1—22), alkyl and alkoxyalkyl substituents, R_3 , were placed on the quaternary carbon atom (II-23—30) and various substituents, R_4 , were attached to the B ring (II-31—68). We report here the synthesis of these compounds and the relationships of their structure with the α -blocking activity.

Synthesis

α -[(Phenoxyethylamino)propyl]- α -phenylacetonitrile derivatives (II) were synthesized by the method shown in Chart 2.

Chart 1

The desired compounds (II) were obtained by the reductive condensation of α -(2-formylethyl)- α -phenylacetonitriles (III) with phenoxyethylamines using sodium borohydride (method A) or by the reaction of α -(3-chloropropyl)- α -isopropyl- α -phenylacetonitriles (IV) with phenoxyethylamines (method B). The NO₂ derivatives (II-18, 38, 50, 60) were hydrogenated to give the corresponding NH₂ analogs (II-19, 39, 51, 61). The R₄=*o*-OCH₂Ph derivative (II-43) was debenzylated reductively to yield the R₄=*o*-OH derivative (II-44). The preparation of all starting materials (III, IV) was described previously.³⁻⁵⁾

The physicochemical properties of II are summarized in Tables I—III.

Results and Discussion

The α -blocking activity is shown as the pA₂ value in Tables I—III.

The Effect of Substituent R₂ (Table I)

First, we examined the effect of the substituent R₂ on the A ring while the substituents R₃ and R₄ were fixed as iso-Pr and *o*-OMe, respectively. Among compounds (II-1—21) monosubstituted at the *o*-, *m*- or *p*-position on the A ring, the *p*-OMe (II-14) and *p*-NO₂ (II-18) derivatives showed activities close to pA₂=8. The 3,4-(OMe)₂ derivative (II-22) with the *p*-OMe group exhibited an activity higher than pA₂=8, but its activity was lower than that of the 3,4,5-(OMe)₃ derivative (I') reported previously.³⁾

To understand the physicochemical background of the effect of substituent R₂ on the α -blocking activity, we have performed quantitative structure-activity analyses using physicochemical substituent parameters and a regression technique.⁷⁾ We analyzed the pA₂ value of unsubstituted (II-1) and monosubstituted derivatives (II-2—21) using single parameters. The result indicated that the activity was correlated best with a parabolic function of the hydrophobic parameter π as shown in Eq. 2 in Table IV with a satisfied quality of the correlation. The π value used here is that for monosubstituted benzenes.⁸⁾ In Fig. 1, the

Chart 2

TABLE I. Physicochemical and Pharmacological Data for R₂-Substituted α-Isopropyl-α-[(phenoxyethylamino)propyl]-α-phenylacetonitriles (II-1—22)

Compd. No.	R ₂	Yield ^{a)} (%) (Method)	Salt ^{b)}	mp (°C)	Recrystn. solvent	Formula	Analysis (%)			pA ₂
							Calcd (Found)			
							C	H	N	
II-1	H	87 (A)	Free	Oil	—	C ₂₃ H ₃₀ N ₂ O ₂	366.2307 ^{c)} (366.2318)			7.75
II-2	<i>o</i> -Me	70 (A)	f	141.5— 143	EtOH— Et ₂ O	C ₂₄ H ₃₂ N ₂ O ₂ ·C ₄ H ₄ O ₄	67.72 7.31 5.64 (67.45 7.49 5.53)			7.54
II-3	<i>o</i> -OMe	54 (A)	o	139— 140	EtOH— iso-Pr ₂ O	C ₂₄ H ₃₂ N ₂ O ₃ ·C ₂ H ₂ O ₄	64.18 7.04 5.76 (63.93 7.40 5.61)			7.65
II-4	<i>o</i> -F	63 (A)	HCl	89— 90	EtOH— Et ₂ O	C ₂₃ H ₂₉ FN ₂ O ₂ ·HCl · 1/2 H ₂ O	64.25 7.27 6.52 (64.64 7.51 6.48)			7.42
II-5	<i>o</i> -Cl	58 (A)	HCl	96— 97	EtOH— Et ₂ O	C ₂₃ H ₂₉ ClN ₂ O ₂ ·HCl · H ₂ O	60.66 7.08 6.15 (60.79 7.36 5.90)			7.11
II-6	<i>o</i> -Br	51 (A)	f	141— 143	EtOH— Et ₂ O	C ₂₃ H ₂₉ BrN ₂ O ₂ ·C ₄ H ₄ O ₄	57.76 5.92 4.99 (57.48 5.98 4.89)			7.24
II-7	<i>m</i> -Me	48 (A)	f	126— 127.5	EtOH— Et ₂ O	C ₂₄ H ₃₂ N ₂ O ₂ ·C ₄ H ₄ O ₄	67.72 7.31 5.64 (67.78 7.35 5.54)			7.47
II-8	<i>m</i> -OMe	86 (A)	HCl	128— 129	EtOH— Et ₂ O	C ₂₄ H ₃₂ N ₂ O ₃ ·HCl	66.58 7.68 6.47 (66.49 7.64 6.24)			7.87
II-9	<i>m</i> -F	68 (A)	f	157.5— 159.5	EtOH	C ₂₃ H ₂₉ FN ₂ O ₂ ·C ₄ H ₄ O ₄	64.79 6.64 5.60 (64.70 6.49 5.42)			7.90
II-10	<i>m</i> -Cl	70 (A)	f	153— 154.5	EtOH— Et ₂ O	C ₂₃ H ₂₉ ClN ₂ O ₂ ·C ₄ H ₄ O ₄	62.72 6.43 5.42 (62.37 6.50 5.09)			7.66
II-11	<i>m</i> -CONMe ₂	51 (B)	Free	Oil	—	C ₂₆ H ₃₅ N ₃ O ₃	437.2678 ^{c)} (437.2690)			7.60
II-12	<i>p</i> -Me	34 (A)	m	127.5— 130	EtOH	C ₂₄ H ₃₂ N ₂ O ₂ ·C ₄ H ₄ O ₄	67.72 7.31 5.64 (67.65 7.28 5.57)			7.32
II-13	<i>p</i> -iso-Pr	30 (A)	HCl	153— 154.5	EtOH— Et ₂ O	C ₂₆ H ₃₆ N ₂ O ₂ ·HCl	70.17 8.38 6.29 (69.95 8.06 6.06)			6.87
II-14	<i>p</i> -OMe	72 (A)	Free	Oil	—	C ₂₄ H ₃₂ N ₂ O ₃	396.2413 ^{c)} (396.2410)			8.02
II-15	<i>p</i> -F	72 (A)	m	148— 149	EtOH	C ₂₃ H ₂₉ FN ₂ O ₂ ·C ₄ H ₄ O ₄	64.79 6.64 5.60 (64.51 6.88 5.49)			7.57
II-16	<i>p</i> -Cl	57 (A)	m	161.5— 163.5	EtOH	C ₂₃ H ₂₉ ClN ₂ O ₂ ·C ₄ H ₄ O ₄	62.72 6.43 5.42 (62.61 6.25 5.08)			7.35
II-17	<i>p</i> -Br	60 (A)	f	85— 90	EtOH— Et ₂ O	C ₂₃ H ₂₉ BrN ₂ O ₂ · 1/2 C ₄ H ₄ O ₄ · H ₂ O	57.58 6.38 5.37 (57.31 6.47 5.04)			7.28
II-18	<i>p</i> -NO ₂	73 (B)	m	184— 186	MeOH	C ₂₃ H ₂₉ N ₃ O ₄ ·C ₄ H ₄ O ₄	61.47 6.30 7.96 (61.43 6.30 7.81)			8.04
II-19	<i>p</i> -NH ₂	93 (B)	o	155— 158	H ₂ O— EtOH	C ₂₃ H ₃₁ N ₃ O ₂ ·2C ₂ H ₂ O ₄	57.75 6.28 7.48 (57.68 6.35 7.41)			7.85
II-20	<i>p</i> -NHAc	74 (B)	Free	Oil	—	C ₂₅ H ₃₃ N ₃ O ₃	423.2522 ^{c)} (423.2518)			7.68
II-21	<i>p</i> -CONMe ₂	65 (B)	Free	Oil	—	C ₂₆ H ₃₅ N ₃ O ₃	437.2678 ^{c)} (437.2685)			7.88
II-22	3,4-(OMe) ₂	88 (A)	m	130— 132	EtOH— iso-Pr ₂ O	C ₂₅ H ₃₄ N ₂ O ₄ ·C ₄ H ₄ O ₄	64.19 7.06 5.16 (63.80 7.19 5.12)			8.25
I' ^{d)}	3,4,5-(OMe) ₃									8.42

a) Yield of the free base. b) f, fumarate; o, oxalate; m, maleate. c) MW determined by high-resolution mass spectrography. d) Ref. 3.

TABLE II. Physicochemical and Pharmacological Data for R_3 -Substituted α -[(Phenoxyethylamino)propyl]- α -phenylacetonitriles (II-23—30)

Compd. No.	R_3	Yield ^{a)} (%) (Method)	Salt ^{b)}	mp (°C)	Recrystn. solvent	Formula	Analysis (%)			pA_2
							Calcd	(Found)		
							C	H	N	
II-23	H	60 (A)	HCl	112— 114	EtOH— Et ₂ O	C ₂₃ H ₃₀ N ₂ O ₅ HCl · H ₂ O	58.91 (58.50)	7.09 (7.16)	5.97 (5.87)	7.83
II-24	Me	70 (A)	f	118— 119	EtOH	C ₂₄ H ₃₂ N ₂ O ₅ · C ₄ H ₄ O ₄	61.75 (61.54)	6.66 (6.83)	5.14 (5.06)	8.40
II-25	Et	74 (A)	f	143.5— 144	EtOH	C ₂₅ H ₃₄ N ₂ O ₅ · C ₄ H ₄ O ₄	62.35 (62.17)	6.86 (6.92)	5.01 (4.83)	8.79
II-26	<i>n</i> -Pr	60 (A)	f	151— 152	EtOH	C ₂₆ H ₃₆ N ₂ O ₅ · C ₄ H ₄ O ₄	62.92 (62.63)	7.04 (7.38)	4.89 (4.75)	8.46
II-27	<i>n</i> -Bu	46 (A)	Free	Oil	—	C ₂₇ H ₃₈ N ₂ O ₅	470.2781 ^{c)} (470.2787)			8.57
II-28	iso-Bu	87 (A)	f	150— 153	EtOH	C ₂₇ H ₃₈ N ₂ O ₅ · C ₄ H ₄ O ₄	63.47 (63.42)	7.22 (7.26)	4.77 (4.68)	8.67
II-29	(CH ₂) ₂ OMe	41. (A)	o	175— 176	MeOH— Et ₂ O	C ₂₆ H ₃₆ N ₂ O ₆ · C ₂ H ₂ O ₄	59.78 (59.65)	6.81 (6.97)	4.98 (4.89)	7.76
II-30	(CH ₂) ₂ OEt	41 (A)	o	160— 161	MeOH	C ₂₇ H ₃₈ N ₂ O ₆ · C ₂ H ₂ O ₄	60.40 (60.17)	6.99 (7.14)	4.86 (4.82)	7.46
I' ^{d)}	iso-Pr									8.42

a) Yield of the free base. b) f, fumarate; o, oxalate. c) MW determined by high-resolution mass spectrography. d) Ref. 3.

situation of the correlation is illustrated. The π values used in this analysis are listed in Table V.

In Eq. 2, the 3,4-(OMe)₂ (II-22) and 3,4,5-(OMe)₃ (I') derivatives were not included. The activity of these compounds was higher than expected from the parabola, as shown in Fig. 1. The higher activity of the 3,4-(OMe)₂ and 3,4,5-(OMe)₃ derivatives is consistent with the fact that the activity of *m*-OMe and *p*-OMe analogs also deviated upward to some extent, although the reason for this is not clear.

Equation 2 shows that π values between -0.3 and -0.4 are favorable for the activity. The fact that the *p*-NO₂ derivative (II-18) was the most effective among the monosubstituted compounds could be rationalized in terms of Eq. 2.

The Effect of Substituent R_3 (Table II)

Compounds where the substituent R_3 is alkyl (II-24—28) exhibited a potency higher than $pA_2 = 8$. The unsubstituted (II-23) and alkoxyalkyl (II-29, 30) analogs showed lower activity. Since the activity is highest in the Et derivative, an optimum hydrophobicity seems to exist also for R_3 . Unfortunately, quantitative analyses of the effect of R_3 gave no significant correlation, since the number of compounds in the set used is too small.

The Effect of Substituent R_4 (Table III)

Among derivatives monosubstituted on the B ring, *o*-substituted derivatives such as the *o*-OMe (I') and *o*-OEt (II-35) analogs exhibited higher potency. Bulkier alkoxy groups decreased the activity. Since the *o*-OMe group was thought to be favorable for potent activity among various substituents, disubstituted analogs with the *o*-OMe group were synthesized.

TABLE III. Physicochemical and Pharmacological Data for R₄-Substituted α -Isopropyl- α -[(phenoxyethyl-amino)propyl]- α -phenylacetonitriles (II-31—68)

Compd. No.	R ₄	Yield ^{a)} (%) (Method)	Salt ^{b)}	mp (°C)	Recrystn. solvent	Formula	Analysis (%)			pA ₂
							Calcd	Found	N	
II-31	H	61 (A)	HCl	175— 176	EtOH— iso-Pr ₂ O	C ₂₅ H ₃₄ N ₂ O ₄ ·HCl	64.85 (64.47)	7.62 7.67	6.05 (5.86)	7.37
II-32	<i>o</i> -Me	39 (A)	HCl	165— 168	EtOH— iso-Pr ₂ O	C ₂₆ H ₃₆ N ₂ O ₄ ·HCl	65.47 (65.07)	7.82 8.15	5.87 (5.88)	6.57
II-33	<i>o</i> - <i>n</i> -Pr	65 (A)	f	157— 158	EtOH— iso-Pr ₂ O	C ₂₈ H ₄₀ N ₂ O ₄ ·C ₄ H ₄ O ₄	65.73 (65.68)	7.58 7.58	4.79 (4.65)	6.30
II-34	<i>o</i> - <i>tert</i> -Bu	60 (A)	f	146— 148	MeOH— iso-Pr ₂ O	C ₂₉ H ₄₂ N ₂ O ₄ ·C ₄ H ₄ O ₄	66.20 (65.99)	7.74 7.77	4.68 (4.53)	5.57
II-35	<i>o</i> -OEt	60 (A)	HCl	167.5— 170	EtOH	C ₂₇ H ₃₈ N ₂ O ₅ ·HCl	63.96 (63.62)	7.75 7.78	5.52 (5.10)	8.48
II-36	<i>o</i> -F	53 (A)	f	139— 141	EtOH— iso-Pr ₂ O	C ₂₅ H ₃₃ FN ₂ O ₄ ·C ₄ H ₄ O ₄	62.13 (61.82)	6.65 6.99	5.00 (4.73)	7.45
II-37	<i>o</i> -Cl	69 (A)	f	147— 148	EtOH	C ₂₅ H ₃₃ ClN ₂ O ₄ ·C ₄ H ₄ O ₄	60.36 (60.38)	6.46 6.67	4.85 (4.64)	6.91
II-38	<i>o</i> -NO ₂	51 (A)	f	171— 172	EtOH— iso-Pr ₂ O	C ₂₅ H ₃₃ N ₃ O ₆ ·C ₄ H ₄ O ₄	59.28 (59.07)	6.35 6.48	7.15 (6.95)	7.01
II-39	<i>o</i> -NH ₂	97	Free	Oil	—	C ₂₅ H ₃₅ N ₃ O ₄	441.2628 ^{c)} (441.2617)			6.53
II-40	<i>o</i> -CN	36 (A)	f	165— 166	EtOH	C ₂₆ H ₃₃ N ₃ O ₄ ·C ₄ H ₄ O ₄	63.48 (63.27)	6.57 6.96	7.40 (7.32)	7.44
II-41	<i>o</i> -OPr	76 (A)	f	162.5— 164	EtOH— Et ₂ O	C ₂₈ H ₄₀ N ₂ O ₅ ·C ₄ H ₄ O ₄	63.98 (63.99)	7.38 7.69	4.66 (4.56)	7.57
II-42	<i>o</i> -OBu	65 (A)	o	128.5— 130	EtOH— iso-Pr ₂ O	C ₂₉ H ₄₂ N ₂ O ₅ ·1/2 C ₂ H ₂ O ₄ ·1/2 H ₂ O	65.20 (64.94)	8.02 7.90	5.07 (4.88)	7.37
II-43	<i>o</i> -OCH ₂ Ph	52 (A)	o	164— 165	MeOH	C ₃₂ H ₄₀ N ₂ O ₅ ·1/2 C ₂ H ₂ O ₄ ·1/2 H ₂ O	67.56 (67.76)	7.22 7.34	4.77 (4.78)	6.90
II-44	<i>o</i> -OH	60	f	190.5— 192.5	MeOH	C ₂₅ H ₃₄ N ₂ O ₅ ·C ₄ H ₄ O ₄	62.35 (62.18)	6.86 6.70	5.01 (4.95)	7.55
II-45	<i>m</i> -Me	46 (A)	HCl	153— 156	EtOH— iso-Pr ₂ O	C ₂₆ H ₃₆ N ₂ O ₄ ·HCl·1/2 H ₂ O	64.25 (64.34)	7.88 7.74	5.76 (5.57)	6.30
II-46	<i>m</i> - <i>tert</i> -Bu	92 (A)	f	159— 160	EtOH— iso-Pr ₂ O	C ₂₉ H ₄₂ N ₂ O ₄ ·C ₄ H ₄ O ₄	66.20 (65.96)	7.74 8.03	4.68 (4.52)	5.37
II-47	<i>m</i> -OMe	33 (A)	HCl	103— 105	EtOH— iso-Pr ₂ O	C ₂₆ H ₃₆ N ₂ O ₅ ·HCl	63.34 (62.98)	7.56 7.85	5.68 (5.71)	6.34
II-48	<i>m</i> -F	77 (A)	f	180— 181	EtOH	C ₂₅ H ₃₃ FN ₂ O ₄ ·C ₄ H ₄ O ₄	62.13 (62.32)	6.65 6.90	5.00 (4.99)	7.35
II-49	<i>m</i> -Cl	50 (A)	f	163— 165	MeOH— Et ₂ O	C ₂₅ H ₃₃ ClN ₂ O ₄ ·C ₄ H ₄ O ₄	60.36 (60.73)	6.46 6.52	4.85 (4.51)	6.63
II-50	<i>m</i> -NO ₂	87 (A)	f	162— 163	EtOH— iso-Pr ₂ O	C ₂₅ H ₃₃ N ₃ O ₆ ·C ₄ H ₄ O ₄	59.28 (59.03)	6.35 6.52	7.15 (7.12)	6.30
II-51	<i>m</i> -NH ₂	98	f	162— 164	EtOH— iso-Pr ₂ O	C ₂₅ H ₃₅ N ₃ O ₄ ·1/2 C ₄ H ₄ O ₄ ·3/2 H ₂ O	61.58 (61.69)	7.66 7.31	7.98 (7.72)	5.94
II-52	<i>m</i> -CN	52 (A)	o	162— 163	EtOH	C ₂₆ H ₃₃ N ₃ O ₄ ·C ₂ H ₂ O ₄ ·H ₂ O	60.10 (60.48)	6.66 7.04	7.51 (7.18)	6.11
II-53	<i>m</i> -CF ₃	81 (A)	f	110— 111	EtOH— iso-Pr ₂ O	C ₂₆ H ₃₃ F ₃ N ₂ O ₄ ·C ₄ H ₄ O ₄ ·H ₂ O	57.32 (57.48)	6.25 6.14	4.46 (4.20)	5.48

TABLE III.(continued)

Compd. No.	R ₄	Yield ^{a)} (%) (Method)	Salt ^{b)}	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found)			pA ₂
							C	H	N	
II-54	<i>p</i> -Me	73 (A)	f	167— 168	EtOH— iso-Pr ₂ O	C ₂₆ H ₃₆ N ₂ O ₄ · C ₄ H ₄ O ₄	64.73 (64.64)	7.24 (7.25)	5.03 (4.82)	6.31
II-55	<i>p-n</i> -Pr	63 (A)	f	145— 147	EtOH— iso-Pr ₂ O	C ₂₈ H ₄₀ N ₂ O ₄ · C ₄ H ₄ O ₄	65.73 (65.59)	7.58 (7.80)	4.79 (4.56)	5.23
II-56	<i>p-tert</i> -Bu	69 (A)	f	151— 152	MeOH— iso-Pr ₂ O	C ₂₉ H ₄₂ N ₂ O ₄ · C ₄ H ₄ O ₄	66.20 (65.99)	7.74 (8.05)	4.68 (4.53)	5.24
II-57	<i>p</i> -OMe	67 (A)	f	160.5— 162	EtOH— iso-Pr ₂ O	C ₂₆ H ₃₆ N ₂ O ₅ · C ₄ H ₄ O ₄	62.92 (63.01)	7.04 (6.98)	4.89 (4.68)	5.86
II-58	<i>p</i> -F	56 (A)	Free	Oil	—	C ₂₅ H ₃₃ FN ₂ O ₄	444.2424 ^{c)} (444.2437)			6.36
II-59	<i>p</i> -Cl	70 (A)	Free	Oil	—	C ₂₅ H ₃₃ ClN ₂ O ₄	460.2129 ^{c)} (460.2151) 462.2099 ^{c)} (462.2100)			5.84
II-60	<i>p</i> -NO ₂	64 (A)	f	191— 193	MeOH	C ₂₅ H ₃₃ N ₃ O ₆ · C ₄ H ₄ O ₄	59.28 (59.17)	6.35 (6.35)	7.15 (7.11)	5.42
II-61	<i>p</i> -NH ₂	59	f	152— 154	EtOH— iso-Pr ₂ O	C ₂₅ H ₃₅ N ₃ O ₄ C ₄ H ₄ O ₄ · 1/4 H ₂ O	61.96 (61.86)	7.08 (7.12)	7.47 (7.35)	6.26
II-62	<i>p</i> -CN	65 (A)	o	190.5— 192.5	MeOH— EtOH	C ₂₆ H ₃₃ N ₃ O ₄ · C ₂ H ₂ O ₄	62.10 (61.93)	6.51 (6.67)	7.76 (7.67)	5.64
II-63	2,3-(OMe) ₂	79 (A)	HCl	151— 153	EtOH— Et ₂ O	C ₂₇ H ₃₈ N ₂ O ₆ · HCl	62.00 (61.79)	7.52 (7.60)	5.36 (5.29)	5.71
II-64	2,4-(OMe) ₂	76 (A)	f	133— 134	EtOH— Et ₂ O	C ₂₇ H ₃₈ N ₂ O ₆ · C ₄ H ₄ O ₄	61.78 (61.39)	7.02 (7.08)	4.65 (4.43)	6.04
II-65	2,5-(OMe) ₂	77 (A)	f	142— 145	EtOH	C ₂₇ H ₃₈ N ₂ O ₆ · C ₄ H ₄ O ₄	61.78 (61.75)	7.02 (7.14)	4.65 (4.60)	6.81
II-66	2,6-(OMe) ₂	64 (A)	HCl	186— 189	EtOH	C ₂₇ H ₃₈ N ₂ O ₆ · HCl	62.00 (61.91)	7.52 (7.66)	5.36 (5.20)	6.09
II-67	2-OMe,5-Me	98 (A)	Free	Oil	—	C ₂₇ H ₃₈ N ₂ O ₅	470.2781 ^{c)} (470.2776)			7.34
II-68	2-OMe,5-F	86 (A)	f	141— 142	iso-PrOH	C ₂₆ H ₃₅ FN ₂ O ₅ · C ₄ H ₄ O ₄	61.01 (60.88)	6.66 (6.71)	4.74 (4.69)	8.69
I ^{d)} Prazosin ^{e)}	<i>o</i> -OMe									8.42 8.63

a) Yield of the free base. b) f, fumarate; o, oxalate. c) MW determined by high-resolution mass spectrography. d) Ref. 3. e) Reference α -blocker.⁶⁾

TABLE IV. Development of the Correlation Equations for the α -Blocking Activity of R₂-Substituted Derivatives (II-1—21)

Eq. No.	π	π^2	Const.	$n^a)$	$r^b)$	$s^c)$	$F_{l,n-m-1}^d)$
1	-0.30 (0.14) ^{e)}		7.62 (0.10)	21	0.71	0.22	18.96
2	-0.23 (0.14)	-0.30 (0.11)	7.73 (0.11)	21	0.84	0.18	12.00

a) Number of compounds used for correlations. b) Correlation coefficient. c) Standard deviation. d) Observed F value: l , the number of additional parameter terms; m , the number of total parameter terms. Theoretical F values are $F_{1,19; \alpha=0.05}=4.38$ for Eq. 1 and $F_{1,18; \alpha=0.05}=4.41$ for Eq. 2. e) Figures in parentheses are 95% confidence intervals.

TABLE V. α -Blocking Activity and Physicochemical Parameters of R_2 -Substituted Derivatives (II-1—22, I')

Compd. No.	R_2	π^a	pA_2	
			Obsd.	Eq. 2
				Calcd. (Δ) ^b
II-1	H	0.00	7.75	7.73 (0.02)
II-2	<i>o</i> -Me	0.56	7.54	7.50 (0.04)
II-3	<i>o</i> -OMe	-0.02	7.65	7.74 (-0.09)
II-4	<i>o</i> -F	0.14	7.42	7.69 (-0.27)
II-5	<i>o</i> -Cl	0.71	7.11	7.41 (-0.30)
II-6	<i>o</i> -Br	0.86	7.24	7.31 (-0.07)
II-7	<i>m</i> -Me	0.56	7.47	7.50 (-0.03)
II-8	<i>m</i> -OMe	-0.02	7.87	7.74 (0.13)
II-9	<i>m</i> -F	0.14	7.90	7.69 (0.21)
II-10	<i>m</i> -Cl	0.71	7.66	7.41 (0.25)
II-11	<i>m</i> -CONMe ₂	-1.05 ^c	7.60	7.80 (-0.20)
II-12	<i>p</i> -Me	0.56	7.32	7.50 (-0.18)
II-13	<i>p</i> -iso-Pr	1.53	6.87	6.75 (0.12)
II-14	<i>p</i> -OMe	-0.02	8.02	7.74 (0.28)
II-15	<i>p</i> -F	0.14	7.57	7.69 (-0.12)
II-16	<i>p</i> -Cl	0.71	7.35	7.41 (-0.06)
II-17	<i>p</i> -Br	0.86	7.28	7.31 (-0.03)
II-18	<i>p</i> -NO ₂	-0.28	8.04	7.80 (0.24)
II-19	<i>p</i> -NH ₂	-1.23	7.85	7.76 (0.09)
II-20	<i>p</i> -NHAc	-0.97	7.68	7.81 (-0.13)
II-21	<i>p</i> -CONMe ₂	-1.05 ^c	7.88	7.80 (0.08)
II-22 ^d	3,4-(OMe) ₂	-0.04 ^e	8.25	7.74
I' ^d	3,4,5-(OMe) ₃	-0.06 ^e	8.42	7.74

a) π value for monosubstituted benzene series. b) Δ , the difference between observed and calculated values. c) Estimated from the equation $\pi(\text{CONMe}_2) = \pi(\text{CONHMe}) + [\pi(\text{CONHMe}) - \pi(\text{CONH}_2)]$. d) Omitted from the calculation. e) Values are the sum of the values for the substituents at each position.

Fig. 1. Plots of pA_2 versus Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative; ●, disubstituted derivative.

Fig. 2. Plots of pA_2 versus Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative.

Fig. 3. Plots of $pA_2 - 0.95I_{ortho}$ versus Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative.

Contrary to our expectation, the activities of all dimethoxy derivatives including the 2,6-(OMe)₂ analog (II-66), which possesses two *o*-OMe groups, were low, but the 2-OMe-5-F derivative (II-68) exhibited an activity higher than that of the *o*-OMe derivative itself (I'). The activity of II-68 was close to that of prazosin, a typical α -blocker.⁶⁾

The quantitative analysis for unsubstituted (II-31) and monosubstituted derivatives (II-32–62, I') using single parameters showed that the activity was correlated best by a quadratic equation of the hydrophobic parameter π , as shown by Eq. 3 in Table VI, although the quality of correlation was not satisfactory. The π value used here is that for substituted

TABLE VI. Development of the Correlation Equations for the α -Blocking Activity of R_4 -Substituted Derivatives (II-31—65, 67, 68, I')

Eq. No.	π^2	I_{ortho}	ΔL_{para}	ΔB_5^{meta}	Const.	$n^{a)}$	$r^{b)}$	$s^{c)}$	$F_{l,n-m-1}^{d)}$
3	-0.35 (0.27) ^{e)}				6.83 (0.37)	33	0.43	0.80	6.92
4	-0.37 (0.20)	1.50 (0.58)			6.63 (0.28)	33	0.76	0.59	27.35
5	-0.33 (0.16)	1.28 (0.50)	-0.43 (0.23)		6.81 (0.25)	33	0.85	0.49	15.16
6	-0.30 (0.14)	1.02 (0.43)	-0.57 (0.20)	-0.47 (0.25)	7.03 (0.24)	33	0.90	0.40	14.59
7	-0.28 (0.14)	0.95 (0.34)	-0.66 (0.19)	-0.54 (0.21)	7.08 (0.25)	38	0.90	0.43	34.01

a) Number of compounds used for correlations. b) Correlation coefficient. c) Standard deviation. d) Observed F value; l , the number of additional parameter terms; m , the number of total parameter terms. Theoretical F values are $F_{1,31; \alpha=0.05} = 4.16$ for Eq. 3, $F_{1,30; \alpha=0.05} = 4.17$ for Eq. 4, $F_{1,29; \alpha=0.05} = 4.18$ for Eq. 5, $F_{1,28; \alpha=0.05} = 4.20$ for Eq. 6 and $F_{4,33; \alpha=0.05} = 2.66$ for Eq. 7. e) Figures in parentheses are 95% confidence intervals.

anisoles estimated according to the equation given in the experimental section. In Fig. 2, the correlation is illustrated. In trying to improve the correlation, we noticed that the activity of *o*-alkoxy derivatives deviated markedly upward from the parabola. By introducing an indicator variable I_{ortho} which takes the value of one for *o*-alkoxy derivatives, Fig. 3 was drawn. The coefficient, -0.95 , of the I_{ortho} term added to pA_2 on the ordinate was selected so that at least the plot for the *ortho* derivatives was aligned as well as possible, as shown by the solid line. We further noticed in Fig. 3 that most of the *m*- and *p*-substituted derivatives deviated downward from the parabola regardless of the electronic properties of the substituent, the deviations for the *p*-substituted derivatives being mostly larger. These facts suggest that position-specific steric effects may participate at the *m*- and *p*-positions.

By considering the position-specific steric parameters, ΔB_5 for the *m*-substituents and ΔL for the *p*-substituents, in addition to π^2 and the indicator variable I_{ortho} , Eq. 6 was derived, where the linear term of π is insignificant; L^9 represents the length of substituents along an axis connecting the α -atom of the substituent and the rest of the molecule, and $B_5^{10)}$ is the maximum width of the substituent from the L axis. For the sake of simplicity, the values relative to that of H were used: $\Delta L = L(X) - L(H)$ and $\Delta B_5 = B_5(X) - B_5(H)$. The stepwise development of Eq. 6 justified statistically for thirty-three derivatives is shown in Table VI. The physicochemical parameters of each substituent used in this analysis are listed in Table VII.

The I_{ortho} parameter probably accounts for a stereospecific hydrogen-bond accepting effect of the *o*-alkoxy groups. This type of hydrogen-bonding effect was shown to be expressible by an indicator variable.¹¹⁾ The hydrogen-bond formation may be either with an acidic group on the receptor or with the NH hydrogen in the *o*-alkoxy derivatives. In Eq. 7 and Fig. 4, five disubstituted compounds where one of the substituents is *o*-OMe were included, but not the 2,6-(OMe)₂ derivative (II-66). The I_{ortho} was not assigned to the *o*-alkoxy substituent, which may not work as a hydrogen-bond acceptor. Thus, $I_{ortho} = 1$ was applied to the 2,4-(OMe)₂ (II-64), 2,5-(OMe)₂ (II-65), 2-OMe-5-Me (II-67) and 2-OMe-5-F (II-68) derivatives, but not to the 2,3-(OMe)₂ analog (II-63). Being sandwiched by the oxyalkylene bridge and the 3-OMe, the *o*-OMe group in II-63 could not take such a conformation for intra- or intermolecular hydrogen-bond formation as that in II-64—68. The activity of the 2,6-(OMe)₂ compound (II-66) was much lower than that expected for $I_{ortho} = 0$. The reason is not clear, but a buttressing effect of vicinally located 6-OMe and oxyalkylene groups may be

TABLE VII. α -Blocking Activity and Physicochemical Parameters of R_4 -Substituted Derivatives (II-31—68, I')

No.	R_4	$\pi^a)$	$I_{ortho}^b)$	$\Delta L_{para}^c)$	$\Delta B_5^{*meta\ c)}$	pA_2		
						Eq. 7		
						Obsd.	Calcd. (Δ) ^{d)}	
II-31	H	0.00	0.00	0.00	0.00	7.37	7.08	(0.29)
II-32	<i>o</i> -Me	0.52	0.00	0.00	0.00	6.57	7.01	(-0.44)
II-33	<i>o</i> - <i>n</i> -Pr	1.43	0.00	0.00	0.00	6.30	6.51	(-0.21)
II-34	<i>o</i> - <i>tert</i> -Bu	1.82	0.00	0.00	0.00	5.57	6.15	(-0.58)
I'	<i>o</i> -OMe	-0.08	1.00	0.00	0.00	8.42	8.03	(0.39)
II-35	<i>o</i> -OEt	0.30	1.00	0.00	0.00	8.48	8.00	(0.48)
II-36	<i>o</i> -F	0.21	0.00	0.00	0.00	7.45	7.07	(0.38)
II-37	<i>o</i> -Cl	0.77	0.00	0.00	0.00	6.91	6.92	(-0.01)
II-38	<i>o</i> -NO ₂	0.03	0.00	0.00	0.00	7.01	7.08	(-0.07)
II-39	<i>o</i> -NH ₂	-1.35	0.00	0.00	0.00	6.53	6.57	(-0.04)
II-40	<i>o</i> -CN	-0.30	0.00	0.00	0.00	7.44	7.06	(0.38)
II-41	<i>o</i> -OPr	0.92	1.00	0.00	0.00	7.57	7.79	(-0.22)
II-42	<i>o</i> -OBu	1.38	1.00	0.00	0.00	7.37	7.49	(-0.12)
II-43	<i>o</i> -OCH ₂ Ph	1.48	1.00	0.00	0.00	6.90	7.41	(-0.51)
II-44	<i>o</i> -OH	-0.80	0.00	0.00	0.00	7.55	6.90	(0.65)
II-45	<i>m</i> -Me	0.54	0.00	0.00	1.04	6.30	6.44	(-0.14)
II-46	<i>m</i> - <i>tert</i> -Bu	1.85	0.00	0.00	2.17	5.37	4.95	(0.42)
II-47	<i>m</i> -OMe	0.03	0.00	0.00	2.07	6.34	5.96	(0.38)
II-48	<i>m</i> -F	0.26	0.00	0.00	0.35	7.35	6.87	(0.48)
II-49	<i>m</i> -Cl	0.79	0.00	0.00	0.80	6.63	6.47	(0.16)
II-50	<i>m</i> -NO ₂	-0.03	0.00	0.00	1.44	6.30	6.30	(0.00)
II-51	<i>m</i> -NH ₂	-1.14	0.00	0.00	0.97	5.94	6.19	(-0.25)
II-52	<i>m</i> -CN	-0.32	0.00	0.00	0.60	6.11	6.73	(-0.62)
II-53	<i>m</i> -CF ₃	0.98	0.00	0.00	1.61	5.48	5.94	(-0.46)
II-54	<i>p</i> -Me	0.52	0.00	0.81	0.00	6.31	6.47	(-0.16)
II-55	<i>p</i> - <i>n</i> -Pr	1.43	0.00	2.86	0.00	5.23	4.62	(0.61)
II-56	<i>p</i> - <i>tert</i> -Bu	1.82	0.00	2.05	0.00	5.24	4.80	(0.44)
II-57	<i>p</i> -OMe	-0.08	0.00	1.92	0.00	5.86	5.81	(0.05)
II-58	<i>p</i> -F	0.21	0.00	0.59	0.00	6.36	6.68	(-0.32)
II-59	<i>p</i> -Cl	0.77	0.00	1.46	0.00	5.84	5.95	(-0.11)
II-60	<i>p</i> -NO ₂	0.03	0.00	1.38	0.00	5.42	6.17	(-0.75)
II-61	<i>p</i> -NH ₂	-1.35	0.00	0.72	0.00	6.26	6.10	(0.16)
II-62	<i>p</i> -CN	-0.30	0.00	2.17	0.00	5.64	5.62	(0.02)
II-63	2,3-(OMe) ₂	-0.05 ^{e)}	0.00	0.00	2.07	5.71	5.96	(-0.25)
II-64	2,4-(OMe) ₂	-0.16 ^{e)}	1.00	1.92	0.00	6.04	6.75	(-0.71)
II-65	2,5-(OMe) ₂	-0.05 ^{e)}	1.00	0.00	2.07	6.81	6.91	(-0.10)
II-66 ^{f)}	2,6-(OMe) ₂	-0.16 ^{e)}	0.00	0.00	0.00	6.09	7.07	
II-67	2-OMe,5-Me	0.46 ^{e)}	1.00	0.00	1.04	7.34	7.41	(-0.07)
II-68	2-OMe,5-F	0.18 ^{e)}	1.00	0.00	0.35	8.69	7.83	(0.86)

a) π value for monosubstituted anisoles. b) Indicator variable which takes the value of one for *o*-alkoxy groups and zero for others. c) Taken from a brochure distributed by Dr. A. Verloop. d) Δ , the difference between observed and calculated values. e) Value summed up for component substituents. f) Omitted from the calculation.

TABLE IX. Calculated pA_2 values from Eq. 8

Compd. No.	Obsd.	Calcd. (Δ) ^{a)}	Compd. No.	Obsd.	Calcd. (Δ) ^{a)}
II-1	7.75	7.71 (0.04)	II-39	6.53	6.86 (−0.33)
II-2	7.54	7.56 (−0.02)	II-40	7.44	7.08 (0.36)
II-3	7.65	7.71 (−0.06)	II-41	7.57	7.74 (−0.17)
II-4	7.42	7.68 (−0.26)	II-42	7.37	7.44 (−0.07)
II-5	7.11	7.50 (−0.39)	II-43	6.90	7.36 (−0.46)
II-6	7.24	7.43 (−0.19)	II-44	7.55	7.04 (0.51)
II-7	7.47	7.56 (−0.09)	II-45	6.30	6.37 (−0.07)
II-8	7.87	7.71 (0.16)	II-46	5.37	4.90 (0.47)
II-9	7.90	7.68 (0.22)	II-47	6.34	5.96 (0.38)
II-10	7.66	7.50 (0.16)	II-48	7.35	6.82 (0.53)
II-11	7.60	7.61 (−0.01)	II-49	6.63	6.39 (0.24)
II-12	7.32	7.56 (−0.24)	II-50	6.30	6.30 (0.00)
II-13	6.87	6.99 (−0.12)	II-51	5.94	6.43 (−0.49)
II-14	8.02	7.71 (0.31)	II-52	6.11	6.77 (−0.66)
II-15	7.57	7.68 (−0.11)	II-53	5.48	5.86 (−0.38)
II-16	7.35	7.50 (−0.15)	II-54	6.31	6.40 (−0.09)
II-17	7.28	7.43 (−0.15)	II-55	5.23	4.56 (0.67)
II-18	8.04	7.73 (0.31)	II-56	5.24	4.75 (0.49)
II-19	7.85	7.55 (0.30)	II-57	5.86	5.83 (0.03)
II-20	7.68	7.64 (0.04)	II-58	6.36	6.64 (−0.28)
II-21	7.88	7.61 (0.27)	II-59	5.84	5.87 (−0.03)
I'	8.42	8.06 (0.36)	II-60	5.42	6.16 (−0.74)
II-31	7.37	7.06 (0.31)	II-61	6.26	6.40 (−0.14)
II-32	6.57	6.92 (−0.35)	II-62	5.64	5.68 (−0.04)
II-33	6.30	6.41 (−0.11)	II-63	5.71	5.97 (−0.26)
II-34	5.57	6.08 (−0.51)	II-64	6.04	6.83 (−0.79)
II-35	8.48	7.99 (0.49)	II-65	6.81	6.97 (−0.16)
II-36	7.45	7.02 (0.43)	II-67	7.34	7.39 (−0.05)
II-37	6.91	6.82 (0.09)	II-68	8.69	7.84 (0.85)
II-38	7.01	7.05 (−0.04)			

a) Δ , the difference between observed and calculated values.

rings. An indicator variable $I(A)$ which takes the value of one for the derivatives with $R_2 = 3,4,5\text{-(OMe)}_3$ was newly introduced, since the upward deviation in the activity of the 3,4,5-(OMe)₃ derivative (I') was not accounted for by Eq. 2. As the hydrophobic parameter, $\Sigma\pi$ was used since the coefficient of the π^2 term in Eq. 2 is close to that in Eq. 7. Equation 8 shows that actually a single optimum value, $\Sigma\pi = -0.39$, exists for the total hydrophobicity of the entire molecule, which presumably reflects the requirements of the transport process. Compounds having various R_3 substituents (II-23—30) were not included in Eq. 8, since relevant physicochemical parameters were not found. The pattern of the activity variations, suggesting an optimum hydrophobicity, in these compound series, however, seems to conform with Eq. 8 as described above.

In summary, the above quantitative analyses of the effects of substituents on the A and B rings are considered to have revealed the most effective structural conditions for α -blocking activity.

Experimental

α -Blocking Activity—Pharmacological procedures using rabbit thoracic aorta were described previously.³⁾

Hydrophobic Parameter—As the hydrophobic parameter for substituents R_2 , the π value⁸⁾ estimated from the

monosubstituted benzene system was adopted. For substituents R_4 , the π value for substituted anisoles estimated according to the following equation¹²⁾ was used, as described previously.⁵⁾

$$\pi(X/\text{subst. anisoles}) = 0.924\pi_X + 0.272\sigma_X^0 - 0.193\rho_X(\text{para}) + 0.037$$

In this equation, π_X is the π value of the substituents X in monosubstituted benzenes, σ_X^0 is a " σ " value representing the electron-withdrawing effect of substituents X applicable to cases in which the reaction center is insulated from direct conjugation with X.¹³⁾ ρ_X is the susceptibility constant of substituent X to the electronic effect of the OMe group on the partitioning in the 1-octanol/water system.¹²⁾

Compounds

Melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded using a JASCO A-202 or Hitachi 270-30 spectrophotometer. Proton nuclear magnetic resonance (¹H-NMR) spectra were measured with a JEOL FX-90Q spectrometer using tetramethylsilane as an internal standard. High-resolution mass spectra (High MS) were measured using a JEOL DX-300 mass spectrometer.

Preparation of α -[(Phenoxyethylamino)propyl]- α -phenylacetonitriles (II) : (Method A): α -Isopropyl- α -[3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]- α -phenylacetonitrile (II-1)—A solution of α -(2-formylethyl)- α -isopropyl- α -phenylacetonitrile (III-1, 3.00 g) and 2-(2-methoxyphenoxy)ethylamine (2.00 g) in EtOH (70 ml) was refluxed for 1.5 h, then cooled with ice water, and NaBH₄ (0.53 g) was added. The mixture was stirred at room temperature for 2.5 h, and then concentrated. The residue was acidified with aqueous HCl and washed with Et₂O. The aqueous layer and the insoluble oily layer were combined, made alkaline with K₂CO₃ and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified on a column of silica gel using CHCl₃ and CHCl₃-MeOH (95:5) as eluents to give II-1 (3.80 g, 87%) as a colorless oil. IR $\nu_{\text{max}}^{\text{liq}}$, cm⁻¹: 2240 (CN). ¹H-NMR (CDCl₃) δ : 0.78 and 1.20 (each 3H, d, J = 6.5 Hz, CH(CH₃)₂), 1.72 (1H, s, NH), 2.91 (2H, t, J = 5.5 Hz, NCH₂CH₂O), 3.83 (3H, s, OCH₃), 4.07 (2H, t, J = 5.5 Hz, NCH₂CH₂O), 6.89 (4H, s, aromatic protons). High MS m/z : 366.2318 (M⁺) (Calcd for C₂₃H₃₀N₂O₂ 366.2307).

Compounds II-2—10, 12—17, 22—38, 40—43, 45—50, 52—60, 62—68 were also prepared in a manner similar to that described above. The yields and characteristics of the products are listed in Tables I—III.

(Method B): 3-[1-(Cyano-1-isopropyl-4-[[2-(2-methoxyphenoxy)ethyl]amino]butyl)-*N,N*-dimethylbenzamide (II-11)—A mixture of 3-(4-chloro-1-cyano-1-isopropylbutyl)-*N,N*-dimethylbenzamide (IV-1, 0.64 g) and 2-(2-methoxyphenoxy)ethylamine (0.70 g) was stirred at 95 °C for 10 h. After cooling, the mixture was acidified with aqueous HCl and washed with Et₂O. The aqueous layer was extracted with CHCl₃ and the CHCl₃ layer was washed with aqueous K₂CO₃. The CHCl₃ layer was washed with water, dried over Na₂SO₄ and evaporated under reduced pressure. The residue was purified on a column of silica gel using CHCl₃ and CHCl₃-MeOH (95:5) as eluents to give II-11 (0.47 g, 51%) as a yellowish brown oil. IR $\nu_{\text{max}}^{\text{liq}}$, cm⁻¹: 2236 (CN), 1638 (CO). ¹H-NMR (CDCl₃) δ : 0.78, 1.20 (each 3H, d, J = 6.5 Hz, CH(CH₃)₂), 2.18 (1H, s, NH), 2.64 (2H, t, J = 6.5 Hz, CH₂CH₂CH₂N), 2.92 (2H, t, J = 5.0 Hz, NCH₂CH₂O), 2.95, 3.07 (each 3H, br s, CON(CH₃)₂), 3.83 (3H, s, OCH₃), 4.07 (2H, t, J = 5.0 Hz, NCH₂CH₂O), 6.89 (4H, s, aromatic protons), 7.42 (4H, s, aromatic protons). High MS m/z : 437.2690 (M⁺) (Calcd for C₂₆H₃₅N₃O₃ 437.2678).

Compounds II-18, 20 and 21 were also prepared in a manner similar to that described above. The yields and characteristics of the products are listed in Table I.

α -(4-Aminophenyl)- α -isopropyl- α -[3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]acetonitrile (II-19)—A solution of α -isopropyl- α -[3-[[2-(2-methoxyphenoxy)ethyl]amino]propyl]- α -(4-nitrophenoxy)acetonitrile (II-18, 2.20 g) in MeOH (20 ml) was hydrogenated over PtO₂ (22 mg) under atmospheric pressure at room temperature. After H₂ absorption had ceased, the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified on a column of silica gel using CHCl₃ and CHCl₃-MeOH (98:2) as eluents to give II-19 (1.90 g, 93%) as a pale yellow oil. The obtained free base was converted into the oxalate in a usual manner and the resulting salt was recrystallized from H₂O-EtOH to give pale yellow crystals, mp 155—158 °C. IR $\nu_{\text{max}}^{\text{KBr}}$, cm⁻¹: 2235 (CN). ¹H-NMR (DMSO-*d*₆) δ : 0.72, 1.07 (each 3H, d, J = 6.5 Hz, CH(CH₃)₂), 3.23 (2H, t, J = 5.5 Hz, NCH₂CH₂O), 3.77 (3H, s, OCH₃), 4.18 (2H, t, J = 5.5 Hz, NCH₂CH₂O). Anal. Calcd for C₂₃H₃₁N₃O₂·2C₂H₂O₄: C, 57.75; H, 6.28; N, 7.48. Found: C, 57.68; H, 6.35; N, 7.41.

Compounds II-39, 51 and 61 were also prepared in a manner similar to that described above. The yields and characteristics of the products are listed in Tables I and III.

α -[3-[[2-(2-Hydroxyphenoxy)ethyl]amino]propyl]- α -isopropyl- α -(3,4,5-trimethoxyphenyl)acetonitrile (II-44)—A solution of α -[3-[[2-(2-benzyloxyphenoxy)ethyl]amino]propyl]- α -isopropyl- α -(3,4,5-trimethoxyphenyl)acetonitrile (II-43, 0.50 g) in MeOH (20 ml) was hydrogenated over PtO₂ (50 mg) under atmospheric pressure at room temperature. After usual operations including purification by silica gel chromatography, II-44 (0.25 g, 60%) was obtained as the free base (a colorless oil). It was converted into the fumarate in a usual manner and the resulting salt was recrystallized from MeOH to give colorless plates, mp 190.5—192.5 °C. IR $\nu_{\text{max}}^{\text{KBr}}$, cm⁻¹: 2250 (CN). ¹H-NMR (CD₃OD) δ : 0.79 and 1.22 (each 3H, d, J = 6.5 Hz, CH(CH₃)₂), 3.75 (3H, s, OCH₃), 3.85 (6H, s, 2 × OCH₃), 4.21 (2H, t, J = 5.0 Hz, NCH₂CH₂O), 6.68 (2H, s, olefinic protons), 6.72 (2H, s, aromatic protons). Anal. Calcd for C₂₅H₃₄N₂O₅·C₄H₄O₄: C, 62.35; H, 6.86; N, 5.01. Found: C, 62.18; H, 6.70; N, 4.95.

Acknowledgement We thank Miss Y. Shoken for her technical assistance.

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