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Novel Phenoxyalkylamine Derivatives. IV.[1] Synthesis, Ca^{2+}-Antagonistic Activity and Quantitative Structure–Activity Analysis of α-Isopropyl-α-[3-[3-(3-methoxyphenoxy)propylamino]propyl]-α-phenylacetonitrile Derivatives

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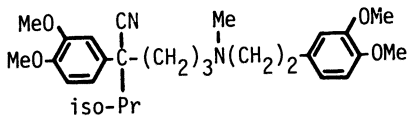
α-Isopropyl-α-[3-[3-(3-methoxyphenoxy)propylamino]propyl]-α-phenylacetonitrile derivatives containing various substituents on the benzene ring (A ring) at the phenylacetonitrile moiety were prepared, and their Ca^{2+}-antagonistic activity was evaluated. Among these compounds, the *N*-Me derivatives with *m*-OMe, *p*-F, *p*-Cl, 3,4-$(OMe)_2$ and 3,5-$(OMe)_2$ substituents on the A ring were found to show higher Ca^{2+}-antagonistic activity than verapamil. The effect of substituents on the A ring was examined quantitatively using physicochemical substituent parameters and regression analysis. The analysis showed that substituents with a π value close to zero are favorable to the activity and that optimum steric conditions exist for *m*- and *p*-substituents, corresponding to those of *m*-OMe and *p*-F or *p*-Cl. The analysis for the whole series of analogs where substituents on the A ring, the benzene ring (B ring) at the phenoxy moiety and the quaternary carbon atom are simultaneously varied suggested that there is an optimum molecular hydrophobicity, perhaps participating in the transport process to the site of action, besides position-specific steric and hydrophobic effects.

Keywords——phenoxyalkylamine; α-isopropyl-α-[3-[3-(3-methoxyphenoxy)propylamino]-propyl]-α-phenylacetonitrile; calcium-antagonistic activity; quantitative structure–activity relationship; Hansch–Fujita analysis

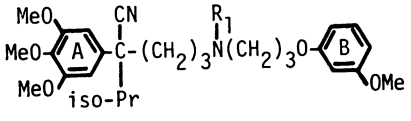
Recently, we synthesized a series of novel phenoxyalkylamine derivatives (I) in which the phenethylamino moiety of verapamil[2] was transformed to phenoxyalkylamino structures. We observed that these compounds exhibited various degrees of Ca^{2+}-antagonistic and α-blocking activities depending upon the structural modifications, and that compounds in which $m=n=3$ and $R_1=Me$ in I were Ca^{2+}-antagonists, while those in which $m=3$, $n=2$ and $R_1=H$ were α-blockers.[3] Further structural modifications of substituents R_2, R_3 and R_4 showed that such *N*-Me derivatives as $m=n=3$, $R_2=3,4,5\text{-}(OMe)_3$, $R_3=$iso-Pr and $R_4=m$-OMe (I′-2) are potent Ca^{2+}-antagonists.[4]

In the preceding part of this series, the effects of substituents R_3 and R_4 in compounds I′-2—44 were analyzed quantitatively. The analysis revealed an optimum steric dimension for the substituent R_3. For the substituent R_4, an electron-releasing substituent with the hydrophobic parameter π close to zero was observed to be most favorable for the Ca^{2+}-antagonistic activity. The correlations with position-specific steric and hydrophobic parameters indicated that *m*-OMe is the optimum R_4 substituent.[1]

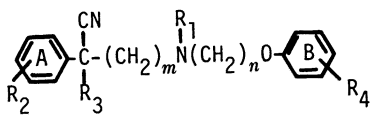
In order to examine the effect of substituent R_2 on the Ca^{2+}-antagonism, we have synthesized a number of R_2-substituted derivatives (II-1—26, III-1—26) with $m=n=3$, $R_3=$ iso-Pr and $R_4=m$-OMe. This paper reports the results of analyses of the quantitative



verapamil



I'-1: R_1=H
I'-2: R_1=Me



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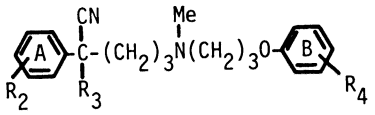
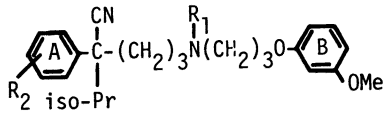


I'-3-33 : R_2=3,4,5-$(OMe)_3$, R_3=iso-Pr
I'-33-44: R_2=3,4,5-$(OMe)_3$, R_4=*o*-OMe
I'-45-50: R_3=iso-Pr, R_4=*o*-OMe



II-1-26 : R_1=H
III-1-26: R_1=Me

Chart 1

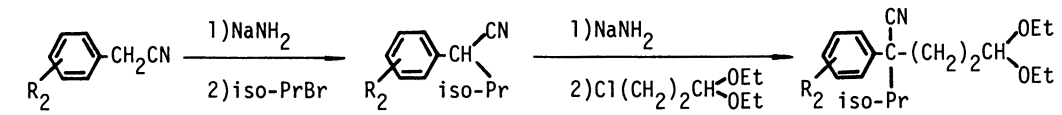
structure–activity relationships for these compounds and also the whole series of *N*-Me analogs (III-1—26, I'-2—50[1,4]) where the R_2-, R_3- and R_4-substituents are simultaneously varied, by means of the Hansch–Fujita method.[5]

The quantitative structure–activity relationships of verapamil analogs have been studied by Mannhold *et al.*[6] However, their studies still leave much to be elucidated, because they used a rather small number of compounds and limited kinds of substituents. Since the structural environment of the benzene ring (A ring) in the phenylacetonitrile moiety of our compounds is similar to that of the benzene ring in the corresponding moiety of verapamil, our analysis of the effect of substituents on the A ring is expected to be helpful in further understanding the structure–activity relationships of verapamil analogs.

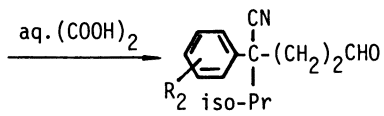
Synthesis

α-Isopropyl-α-[3-[3-(3-methoxyphenoxy)propylamino]propyl]-α-phenylacetonitrile derivatives (II, III) were synthesized by means of the procedures shown in Charts 2—4.

α-Isopropyl-α-phenylacetonitriles (V) obtained from benzeneacetonitriles (IV) were alkylated with 3-chloropropionaldehyde diethylacetal to give α-(3,3-diethoxypropyl)-α-isopropyl-α-phenylacetonitriles (VI), which were subsequently hydrolyzed with aqueous oxalic acid to yield the key intermediates α-(2-formylethyl)-α-isopropyl-α-phenylacetonitriles (VII) (Chart 2). Other key intermediates, α-(3-chloropropyl)-α-isopropyl-α-phenylacetonitriles (VIII), were obtained by alkylating V with 3-bromo-1-chloropropane. The unsubstituted derivative (VIII-1: R_2=H) was nitrated to give the *p*-NO_2 derivative (VIII-21), which was hydrogenated and then acylated using acetic anhydride to yield the *p*-NHAc derivative (VIII-23) (Chart 3).



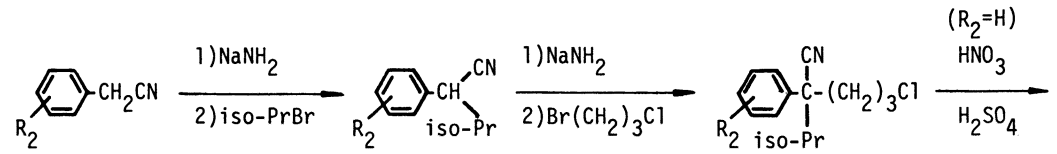
IV-1-12,14-20,25 V-1-12,14-20,25 VI-1-12,14-20,25



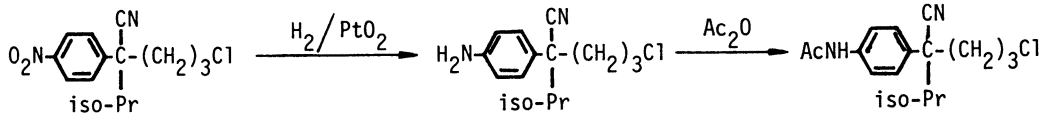
VII-1-12,14-20,25

1: R_2=H
2: R_2=*o*-Me
3: R_2=*o*-OMe
4: R_2=*o*-OEt
5: R_2=*o*-F
6: R_2=*o*-Cl
7: R_2=*o*-Br
8: R_2=*m*-Me
9: R_2=*m*-OMe
10: R_2=*m*-OEt
11: R_2=*m*-F
12: R_2=*m*-Cl
14: R_2=*p*-Me
15: R_2=*p*-iso-Pr
16: R_2=*p*-OMe
17: R_2=*p*-OEt
18: R_2=*p*-F
19: R_2=*p*-Cl
20: R_2=*p*-Br
25: R_2=3,4-$(OMe)_2$

Chart 2



IV-1,13,24,26 V-1,13,24,26 VIII-1,13,24,26

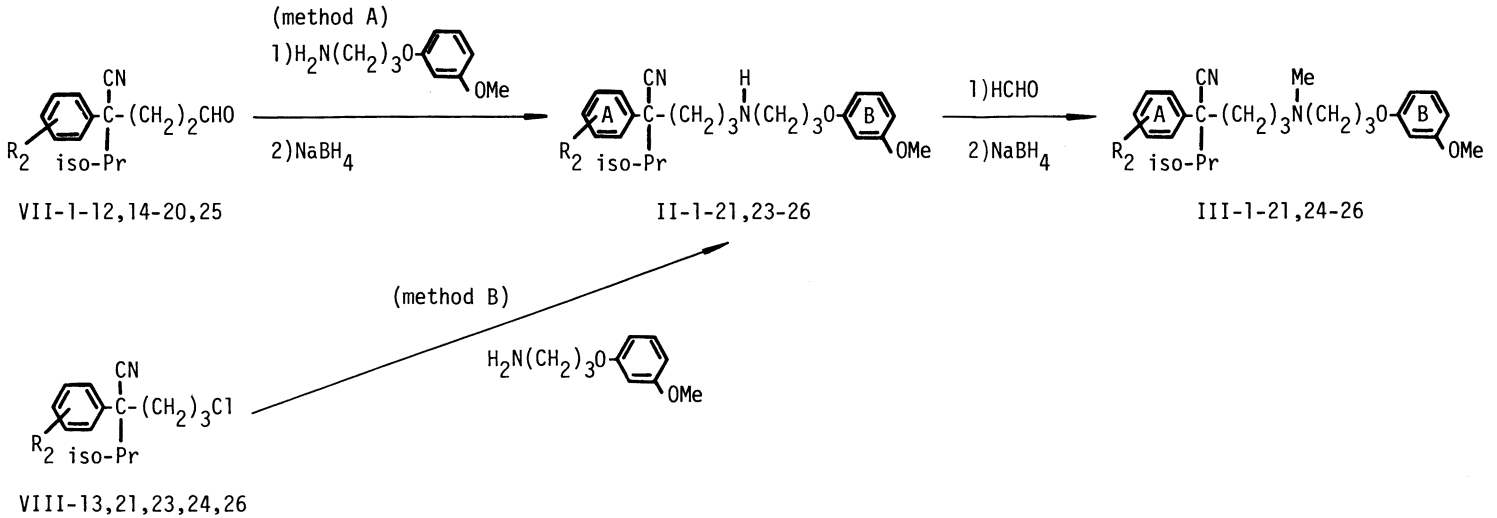


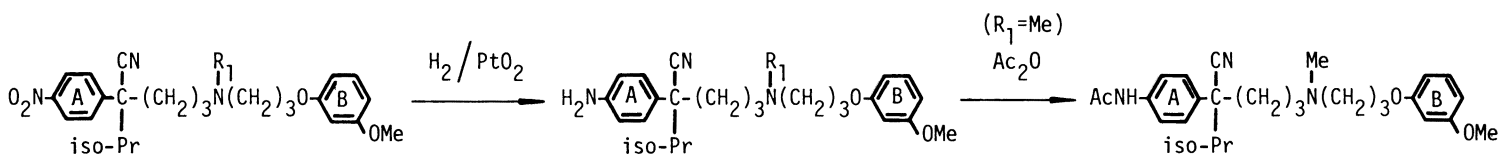
VIII-21 VIII-22 VIII-23

1: R_2=H
13: R_2=*m*-$CONMe_2$
21: R_2=*p*-NO_2
22: R_2=*p*-NH_2
23: R_2=*p*-NHAc
24: R_2=*p*-$CONMe_2$
26: R_2=3,5-$(OMe)_2$

Chart 3

The desired *N*-H derivatives (II) were obtained by the reductive condensation of VII with 3-(3-methoxyphenoxy)propylamine using sodium borohydride (method A) or by the reaction of VIII with 3-(3-methoxyphenoxy)propylamine (method B). The *N*-H derivatives (II) were reacted with formalin and sodium borohydride to give *N*-Me derivatives (III). Both the *N*-H (II-21) and *N*-Me (III-21) derivatives with R_2=*p*-NO_2 were hydrogenated to yield the corresponding derivatives (II-22, III-22) with R_2=*p*-NH_2, of which III-22 was acylated with





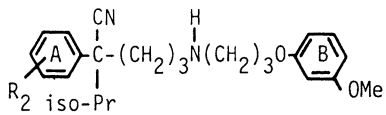
II-21: R_1=H
III-21: R_1=Me

II-22: R_1=H
III-22: R_1=Me

III-23

Chart 4

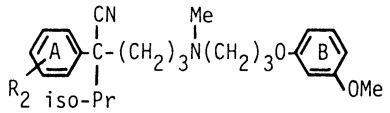
TABLE I. Physicochemical and Pharmacological Data for *N*-Unsubstituted α-Isopropyl-α-[3-[3-(3-methoxyphenoxy)propylamino]propyl]-α-phenylacetonitrile Derivatives (II)



Compd. No.	R_2	Yield[a] (%) (Method)	Salt[b]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	pA_2[c]
II-1	H	51 (A)	f	129—131	EtOH–Et_2O	$C_{24}H_{32}N_2O_2 \cdot 1/2C_4H_4O_4$	71.21 (70.81)	7.81 (7.89)	6.39 (6.28)	6.44
II-2	*o*-Me	70 (A)	HCl	109—111	EtOH–Et_2O	$C_{25}H_{34}N_2O_2 \cdot HCl$	69.67 (69.46)	8.18 (8.02)	6.50 (6.28)	6.05
II-3	*o*-OMe	64 (A)	f	97.5—99	EtOH–Et_2O	$C_{25}H_{34}N_2O_3 \cdot C_4H_4O_4$	66.14 (66.01)	7.27 (7.43)	5.32 (5.04)	6.30
II-4-	*o*-OEt	34 (A)	f	99.5—101.5	EtOH–Et_2O	$C_{26}H_{36}N_2O_3 \cdot C_4H_4O_4$	66.65 (66.52)	7.46 (7.52)	5.18 (5.15)	5.92
II-5	*o*-F	75 (A)	f	138—140	EtOH–Et_2O	$C_{24}H_{31}FN_2O_2 \cdot C_4H_4O_4$	65.35 (65.21)	6.86 (6.72)	5.44 (5.36)	6.50
II-6	*o*-Cl	88 (A)	f	118—120	EtOH–Et_2O	$C_{24}H_{31}ClN_2O_2 \cdot C_4H_4O_4$	63.33 (63.34)	6.64 (6.62)	5.28 (5.25)	6.30
II-7	*o*-Br	72 (A)	f	117—118	EtOH–Et_2O	$C_{24}H_{31}BrN_2O_2 \cdot C_4H_4O_4$	58.44 (58.41)	6.13 (6.33)	4.87 (4.86)	5.80
II-8	*m*-Me	49 (A)	HCl	121—123	EtOH–Et_2O	$C_{25}H_{34}N_2O_2 \cdot HCl$	69.67 (69.65)	8.18 (7.93)	6.50 (6.25)	5.90
II-9	*m*-OMe	62 (A)	o	159.5—160.5	EtOH	$C_{25}H_{34}N_2O_3 \cdot C_2H_2O_4$	64.78 (64.69)	7.25 (7.25)	5.60 (5.54)	6.70
II-10	*m*-OEt	54 (A)	f	108.5—110.5	EtOH–Et_2O	$C_{26}H_{36}N_2O_3 \cdot C_4H_4O_4$	66.65 (66.72)	7.46 (7.32)	5.18 (5.10)	6.51
II-11	*m*-F	70 (A)	HCl	132—135	EtOH–Et_2O	$C_{24}H_{31}FN_2O_2 \cdot HCl$	66.27 (66.27)	7.42 (7.37)	6.44 (6.44)	6.30
II-12	*m*-Cl	60 (A)	HCl	133—134.5	EtOH–Et_2O	$C_{24}H_{31}ClN_2O_2 \cdot HCl$	63.85 (63.81)	7.14 (7.16)	6.21 (6.14)	6.05
II-13	*m*-$CONMe_2$	68 (B)	Free	Oil	—	$C_{27}H_{37}N_3O_3$	451.2835[d] (451.2840)			5.68
II-14	*p*-Me	73 (A)	o	165—168.5	EtOH	$C_{25}H_{34}N_2O_2 \cdot C_2H_2O_4$	66.92 (66.69)	7.49 (7.64)	5.78 (5.70)	6.58
II-15	*p*-iso-Pr	79 (A)	f	127—128	EtOH–Et_2O	$C_{27}H_{38}N_2O_2 \cdot C_4H_4O_4$	69.12 (69.22)	7.86 (7.64)	5.20 (5.14)	5.53
II-16	*p*-OMe	66 (A)	f	124—126	EtOH–Et_2O	$C_{25}H_{34}N_2O_3 \cdot C_4H_4O_4$	66.14 (66.06)	7.27 (7.46)	5.32 (5.58)	6.40
II-17	*p*-OEt	78 (A)	Free	Oil	—	$C_{26}H_{36}N_2O_3$	424.2726[d] (424.2723)			6.12
II-18	*p*-F	59 (A)	f	140—142	EtOH–Et_2O	$C_{24}H_{31}FN_2O_2 \cdot C_4H_4O_4$	65.35 (65.32)	6.86 (7.03)	5.44 (5.32)	6.78
II-19	*p*-Cl	46 (A)	Free	Oil	—	$C_{24}H_{31}ClN_2O_2$	414.2074[d] (414.2092) 416.2044[d] (416.2051)			6.04
II-20	*p*-Br	42 (A)	o	157—158	EtOH	$C_{24}H_{31}BrN_2O_2 \cdot C_2H_2O_4$	56.83 (57.08)	6.05 (6.03)	5.10 (5.11)	5.70
II-21	*p*-NO_2	83 (B)	m	151—153	EtOH	$C_{24}H_{31}N_3O_4 \cdot C_4H_4O_4$	62.10 (61.97)	6.51 (6.52)	7.76 (7.62)	6.69
II-22	*p*-NH_2	87	o	104.5—106	EtOH	$C_{24}H_{33}N_3O_2 \cdot 3/2C_2H_2O_4$	61.12 (61.01)	6.84 (6.76)	7.92 (7.87)	5.63
II-23	*p*-NHAc	67 (B)	Free	Oil	—	$C_{26}H_{35}N_3O_3$	437.2678[d] (437.2670)			5.65
II-24	*p*-$CONMe_2$	64 (B)	Free	Oil	—	$C_{27}H_{37}N_3O_3$	451.2835[d] (451.2841)			5.82
II-25	3,4-$(OMe)_2$	69 (A)	o	145—147.5	EtOH	$C_{26}H_{36}N_2O_4 \cdot C_2H_2O_4$	63.38 (63.10)	7.22 (7.10)	5.28 (5.29)	6.01
II-26	3,5-$(OMe)_2$	49 (B)	f	137—138	EtOH–Et_2O	$C_{26}H_{36}N_2O_4 \cdot C_4H_4O_4$	64.73 (64.68)	7.24 (6.86)	5.03 (5.03)	6.98
I′-1[e]	3,4,5-$(OMe)_3$									6.83

a) Yield of free base. *b*) f, fumarate; o, oxalate; m, maleate. *c*) pA_2 values in KCl-depolarized guinea-pig taenia coli. *d*) High mass data. The upper values are calculated and the lower ones are those found. *e*) Ref. 4.

TABLE II. Physicochemical and Pharmacological Data for *N*-Methylated α-Isopropyl-α-[3-[3-(3-methoxyphenoxy)propylamino]propyl]-α-phenylacetonitrile Derivatives (III)



Compd. No.	R_2	Yield[a] (%)	Salt[b]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	pA_2[c]
III-1	H	71	f	105—106	EtOH–Et_2O	$C_{25}H_{34}N_2O_2 \cdot C_4H_4O_4$	68.21 (68.02)	7.50 (7.31)	5.49 (5.24)	7.59
III-2	*o*-Me	87	o	128—129.5	EtOH	$C_{26}H_{36}N_2O_2 \cdot C_2H_2O_4$	67.45 (67.63)	7.68 (7.69)	5.62 (5.67)	7.25
III-3	*o*-OMe	85	o	118.5—120	EtOH	$C_{26}H_{36}N_2O_3 \cdot C_2H_2O_4$	65.35 (65.32)	7.44 (7.61)	5.44 (5.32)	7.60
III-4	*o*-OEt	86	Free	Oil	—	$C_{27}H_{38}N_2O_3$	438.2882[d] (438.2857)			7.53
III-5	*o*-F	88	f	115—116	EtOH	$C_{25}H_{33}FN_2O_2 \cdot C_4H_4O_4$	65.89 (65.85)	7.05 (7.18)	5.30 (5.30)	7.00
III-6	*o*-Cl	83	f	105—106.5	EtOH–iso-Pr_2O	$C_{25}H_{33}ClN_2O_2 \cdot C_4H_4O_4$	63.90 (63.70)	6.84 (6.60)	5.14 (5.17)	7.40
III-7	*o*-Br	83	o	149—150	EtOH	$C_{25}H_{33}BrN_2O_2 \cdot C_2H_2O_4$	57.55 (57.38)	6.26 (6.20)	4.97 (4.91)	7.60
III-8	*m*-Me	82	o	135—136.5	EtOH	$C_{26}H_{36}N_2O_2 \cdot C_2H_2O_4$	67.45 (67.32)	7.68 (7.56)	5.62 (5.27)	7.80
III-9	*m*-OMe	86	o	121.5—122	EtOH	$C_{26}H_{36}N_2O_3 \cdot C_2H_2O_4$	65.35 (65.22)	7.44 (7.26)	5.44 (5.46)	8.20
III-10	*m*-OEt	74	f	90.5—91.5	EtOH–Et_2O	$C_{27}H_{38}N_2O_3 \cdot C_4H_4O_4$	67.13 (66.91)	7.63 (7.73)	5.05 (5.00)	7.84
III-11	*m*-F	90	f	116—117	EtOH	$C_{25}H_{33}FN_2O_2 \cdot C_4H_4O_4$	65.89 (65.82)	7.05 (7.11)	5.30 (5.19)	7.35
III-12	*m*-Cl	84	o	148.5—149.5	EtOH	$C_{25}H_{33}ClN_2O_2 \cdot C_2H_2O_4$	62.48 (62.44)	6.80 (6.62)	5.40 (5.22)	7.50
III-13	*m*-$CONMe_2$	86	Free	Oil	—	$C_{28}H_{39}N_3O_3$	465.2991[d] (465.2968)			6.64
III-14	*p*-Me	83	Free	Oil	—	$C_{26}H_{36}N_2O_2$	408.2777[d] (408.2774)			7.71
III-15	*p*-iso-Pr	86	o	120.5—121.5	EtOH–Et_2O	$C_{28}H_{40}N_2O_2 \cdot C_2H_2O_4$	68.42 (68.30)	8.04 (8.00)	5.32 (5.25)	7.26
III-16	*p*-OMe	79	o	151.5—152.5	EtOH	$C_{26}H_{36}N_2O_3 \cdot C_2H_2O_4$	65.35 (65.34)	7.44 (7.38)	5.44 (5.38)	7.64
III-17	*p*-OEt	89	f	100—101.5	EtOH–Et_2O	$C_{27}H_{38}N_2O_3 \cdot C_4H_4O_4$	67.13 (66.99)	7.63 (7.38)	5.05 (4.94)	7.32
III-18	*p*-F	86	f	98—101.5	EtOH–Et_2O	$C_{25}H_{33}FN_2O_2 \cdot C_4H_4O_4$	65.89 (65.89)	7.05 (7.21)	5.30 (5.15)	8.25
III-19	*p*-Cl	85	f	117—118	EtOH	$C_{25}H_{33}ClN_2O_2 \cdot C_4H_4O_4$	63.90 (63.88)	6.84 (6.96)	5.14 (5.02)	8.04
III-20	*p*-Br	64	f	125—126	EtOH	$C_{25}H_{33}BrN_2O_2 \cdot C_4H_4O_4$	59.08 (59.08)	6.33 (6.41)	4.75 (4.76)	7.80
III-21	*p*-NO_2	75	Free	Oil	—	$C_{25}H_{33}N_3O_4$	439.2471[d] (439.2466)			7.87
III-22	*p*-NH_2	86	Free	Oil	—	$C_{25}H_{35}N_3O_2$	409.2729[d] (409.2727)			7.15
III-23	*p*-NHAc	80	Free	Oil	—	$C_{27}H_{37}N_3O_3$	451.2835[d] (451.2812)			6.76
III-24	*p*-$CONMe_2$	81	Free	Oil	—	$C_{28}H_{39}N_3O_3$	465.2991[d] (465.2979)			6.93
III-25	3,4-$(OMe)_2$	60	o	113—115	EtOH–Et_2O	$C_{27}H_{38}N_2O_4 \cdot C_2H_2O_4$	63.95 (63.67)	7.40 (7.28)	5.14 (5.19)	7.99
III-26	3,5-$(OMe)_2$	90	Free	Oil	—	$C_{27}H_{38}N_2O_4$	454.2832[d] (454.2840)			8.88
I′-2[e] Varapamil	3,4,5-$(OMe)_3$									9.00 7.88

a) Yield of free base. *b*) f, fumarate; o, oxalate. *c*) pA_2 values in the KCl-depolarized guinea-pig taenia coli. *d*) High mass data. The upper values are calculated and the lower ones are those found. *e*) Ref. 4.

acetic anhydride to give the *p*-NHAc derivative (III-23) (Chart 4).

The physicochemical properties of II and III are summarized in Tables I and II, and those of V, VII and VIII are listed in Tables VII—IX in the experimental section.

Results and Discussion

Pharmacological data on Ca^{2+}-antagonistic activity for the *N*-H (II) and *N*-Me (III) derivatives obtained here are given in Tables I and II, respectively. Ca^{2+}-antagonistic activity was tested in KCl-depolarized guinea-pig taenia coli and is shown as the pA_2 value.

The Effect of Substituent R_2 in Analogs (III)

The *N*-H derivatives (II) exhibited activities lower than $pA_2=7$, but *N*-methylation increased the potency remarkably. Among the *N*-Me derivatives (III) with monosubstitution at the *o*-, *m*- or *p*-position on the A ring, *o*-substituted derivatives (III-2—7) were less potent, while some of the *m*- and *p*-substituted analogs (III-8—10, 14, 16, 18—21) were more potent than the unsubstituted compound (III-1). In particular, the *m*-OMe (III-9), *p*-F (III-18) and *p*-Cl (III-19) derivatives showed activity higher than that of verapamil. The 3,5-$(OMe)_2$ derivative (III-26) exhibited a very high activity almost equal to that of the 3,4,5-$(OMe)_3$ derivative (I′-2) reported previously.[4]

To understand the physicochemical background of the effect of substituent R_2 on the Ca^{2+}-antagonistic activity, we have performed quantitative structure–activity analyses for the *N*-Me derivatives (III) using physicochemical substituent parameters by a regression technique.[5]

First, we analyzed the pA_2 values of unsubstituted (III-1) and monosubstituted derivatives (III-2—24) using single parameters. The results indicated that the activity was correlated best by a quadratic function of the hydrophobic parameter π, as shown in Eq. 1 in Table III, although the quality of correlation was not satisfactory. In this case, the linear term of π was insignificant. The situation is illustrated in Fig. 1. The π value used here is that for monosubstituted benzenes. In trying to improve the correlation, we observed that the activity of *m*-substituted derivatives such as F or $CONMe_2$ deviated downward from the parabola, while that of the *m*-OMe derivative deviated upward. Since F is the smallest and $CONMe_2$ is much bulkier than OMe, this suggests the possible existence of an optimum bulk for *m*-substituents. We also observed that longer substituents such as OEt, $CONMe_2$ and NHAc at the *para* position were unfavorable for the activity. Compared with *m*- and *p*-substituted

TABLE III. Development of the Correlation Equations for the Ca^{2+}-Antagonistic Activity of the *N*-Methylated Derivatives (III)

Eq. No.	π^2	ΔL^2_{para}	ΔL_{para}	ΔMR^2_{meta}	ΔMR_{meta}	Const.	$n^{a)}$	$r^{b)}$	$s^{c)}$	$F_{l,n-m-1}{}^{d)}$
1	−0.35					7.67	24	0.48	0.37	6.76
	(0.28)[e)]					(0.21)				
2	−0.37	−0.30	0.74			7.59	24	0.74	0.30	6.89
	(0.25)	(0.17)	(0.45)			(0.19)				
3	−0.29	−0.32	0.82	−0.88	1.34	7.48	24	0.87	0.23	8.34
	(0.20)	(0.13)	(0.37)	(0.45)	(0.74)	(0.17)				
4	−0.27	−0.30	0.73	−0.77	1.12	7.50	25	0.87	0.23	11.81
	(0.19)	(0.13)	(0.34)	(0.42)	(0.66)	(0.17)				

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 $F_{1,22;\alpha=0.05}=4.30$ for Eq. 1, $F_{2,20;\alpha=0.05}=3.49$ for Eq. 2, $F_{2,18;\alpha=0.05}=3.56$ for Eq. 3 and $F_{5,19;\alpha=0.05}=2.74$ for Eq. 4. *e*) Figures in parentheses are 95% confidence intervals.

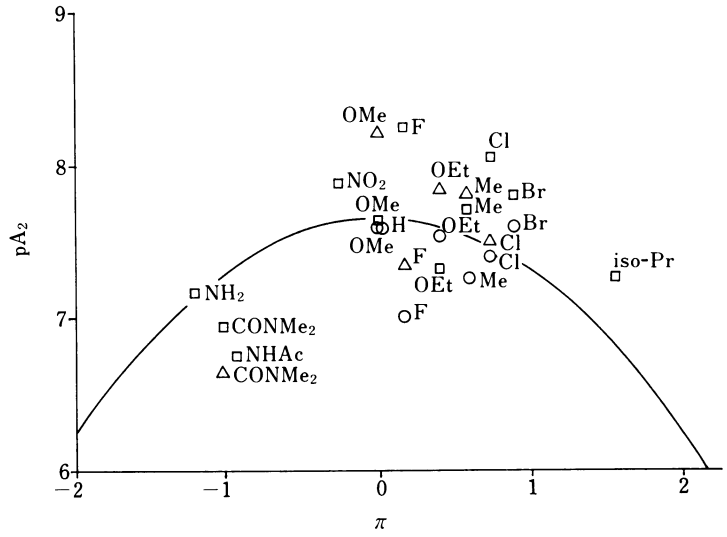


Fig. 1. Plots of pA_2 *versus* Hydrophobic Parameter π

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

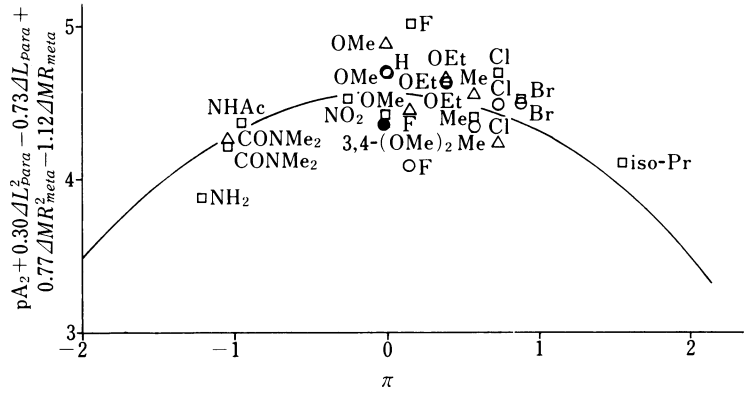


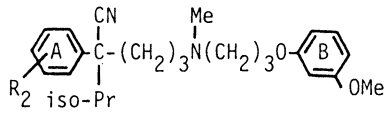
Fig. 2. Plots of the Value of $(pA_2+0.30\Delta L^2_{para}-0.73\Delta L_{para}+0.77\Delta MR^2_{meta}-1.12\Delta MR_{meta})$ *versus* Hydrophobic Parameter π

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

derivatives, the range of the activity variation of *o*-substituted compounds was narrower, suggesting that proximity effects of *o*-substituents are not important in determining the activity. On the basis of these observations, we examined various combinations of physicochemical substituent parameters at each substituent position.

For *m*- and *p*-substituents, the effect was better rationalized by considering position-specific steric parameter terms. Among the steric parameters examined, MR[7] (molecular refractivity) was best for *m*-substituents, while L[8] (the STERIMOL length parameter) was most suitable for *p*-substituents in illustrating the position-specific effects: MR is a parameter nearly collinear with the molecular volume, representing the overall bulk of substituents, and L is the length of substituents along an axis connecting the α-atom of the substituent and the rest of the molecule. For the sake of simplicity, these steric parameters were used as values

TABLE IV. Ca^{2+}-Antagonistic Activity and Physicochemical Parameters of the *N*-Methylated Derivatives (III)



No.	R_2	π[a]	ΔMR_{meta}[a]	ΔL_{para}[b]	pA_2 Obsd.	pA_2 Eq. 4 Calcd. (Δ)[c]
III-1	H	0.00	0	0	7.59	7.50 (0.09)
III-2	*o*-Me	0.56	0	0	7.25	7.42 (−0.17)
III-3	*o*-OMe	−0.02	0	0	7.60	7.50 (0.10)
III-4	*o*-OEt	0.38	0	0	7.53	7.46 (0.07)
III-5	*o*-F	0.14	0	0	7.00	7.50 (−0.50)
III-6	*o*-Cl	0.71	0	0	7.40	7.37 (0.03)
III-7	*o*-Br	0.86	0	0	7.60	7.30 (0.30)
III-8	*m*-Me	0.56	0.462	0	7.80	7.77 (0.03)
III-9	*m*-OMe	−0.02	0.684	0	8.20	7.91 (0.29)
III-10	*m*-OEt	0.38	1.144	0	7.84	7.74 (0.10)
III-11	*m*-F	0.14	−0.011	0	7.35	7.48 (−0.13)
III-12	*m*-Cl	0.71	0.500	0	7.50	7.73 (−0.23)
III-13	*m*-$CONMe_2$	−1.05[d]	1.830[e]	0	6.64	6.67 (−0.03)
III-14	*p*-Me	0.56	0	0.81	7.71	7.82 (−0.11)
III-15	*p*-iso-Pr	1.53	0	2.05	7.26	7.13 (0.13)
III-16	*p*-OMe	−0.02	0	1.92	7.64	7.81 (−0.17)
III-17	*p*-OEt	0.38	0	2.74	7.32	7.24 (0.08)
III-18	*p*-F	0.14	0	0.59	8.25	7.83 (0.42)
III-19	*p*-Cl	0.71	0	1.46	8.04	7.80 (0.24)
III-20	*p*-Br	0.86	0	1.76	7.80	7.67 (0.13)
III-21	*p*-NO_2	−0.28	0	1.38	7.87	7.93 (−0.06)
III-22	*p*-NH_2	−1.23	0	0.72	7.15	7.47 (−0.32)
III-23	*p*-NHAc	−0.97	0	3.03	6.76	6.74 (0.02)
III-24	*p*-$CONMe_2$	−1.05[d]	0	2.71	6.93	7.01 (−0.08)
III-25	3,4-$(OMe)_2$	−0.04[f]	0.684	1.92	7.99	8.22 (−0.23)
III-26[g]	3,5-$(OMe)_2$	−0.04[f]	0.684	0	8.88	8.31 (0.57)[h]
I′-2[g]	3,4,5-$(OMe)_3$	−0.06[f]	0.684	1.92	9.00	8.61 (0.39)[h]

a) Taken from ref. 7 unless otherwise noted. *b*) Taken from a brochure distributed by Dr. A. Verloop. *c*) Δ, the difference between observed and calculated values. *d*) Estimated from the equation $\pi(CONMe_2)=\pi(CONHMe)+[\pi(CONHMe)-\pi(CONH_2)]$. *e*) Estimated from the equation $MR(CONMe_2)=MR(CONHMe)+[MR(CONHMe)-MR(CONH_2)]$. *f*) Values are the sum of the values for the substituents at each position. *g*) Omitted from the calculation. *h*) Estimated from the equation $pA_2=-0.27\pi^2-0.30\Delta L_{para}^2+0.73\Delta L_{para}+\sum(-0.77\Delta MR_{meta}^2+1.12\Delta MR_{meta})+7.50$.

TABLE V. Correlation Coefficient (r) Matrix for the Parameters of Eq. 4

	π^2	ΔL_{para}^2	ΔL_{para}	ΔMR_{meta}^2	ΔMR_{meta}
π^2	1.00				
ΔL_{para}^2	0.31	1.00			
ΔL_{para}	0.33	0.96	1.00		
ΔMR_{meta}^2	0.13	0.19	0.24	1.00	
ΔMR_{meta}	0.02	0.23	0.28	0.94	1.00

relative to that of H: $\Delta MR_{meta} = MR_{meta}(X) - MR(H)$, and $\Delta L_{para} = L_{para}(X) - L(H)$. MR was multiplied by 0.1 to place it on a scale similar to those of the other parameters. Using quadratic terms of these parameters, correlation equations were developed as shown in Table III. Equation 3 was the best equation, where the linear term of π is insignificant. The physicochemical parameters of each substituent used in this analysis are listed in Table IV. The stepwise development of Eq. 3 justified statistically for twenty-four monosubstituted derivatives is shown in Table III.

In Eq. 4 and Fig. 2, the 3,4-$(OMe)_2$ (III-25) derivative was included using $\Sigma\pi$ for substituents and position-specific steric parameters, but not the 3,5-$(OMe)_2$ (III-26) and 3,4,5-$(OMe)_3$ (I′-2) derivatives. The activities of 3,5-$(OMe)_2$ and 3,4,5-$(OMe)_3$ derivatives were in accord with Eq. 4 when $\Sigma\pi$ was used for hydrophobicity and the position-specific terms for *m*-OMe were counted twice ($2\times[-0.77\Delta MR^2_{meta}+1.12\Delta MR_{meta}]$) instead of using $\Sigma\Delta MR_{meta}$. This is reasonable, since the position-specific steric effect is accounted for not by the sum of steric parameters, but by the sum of the steric effects of substituents at the respective positions. Equations 3 and 4 were practically identical. The fact that the behavior of the di- and trisubstituted derivatives conforms to that of the monosubstituted derivatives indicates that the effect of substituents is almost additive. In Table V, the intercorrelation between independent variables for twenty-five derivatives was shown to be insignificant except for that between the linear and squared values of the same variable.

Equation 4 shows that substituents for which π is close to zero are favorable for the activity. It also indicates that the optimum steric conditions for *m*- and *p*-substituents are $\Delta MR_{meta}=0.73$ and $\Delta L_{para}=1.22$, respectively. The most favorable substituents are *m*-OMe ($\Delta MR_{meta}=0.68$, $\pi=-0.02$) and *p*-F ($\Delta L_{para}=0.59$, $\pi=0.14$) groups. The very high activities of the 3,5-$(OMe)_2$ (III-26) and 3,4,5-$(OMe)_3$ (I′-2) derivatives can be rationalized by Eq. 4.

In summary, the effects of various substitutions on the A ring indicated that the *m*-OMe (III-9), *p*-F (III-18), *p*-Cl (III-19), 3,4-$(OMe)_2$ (III-25) and 3,5-$(OMe)_2$ (III-26) derivatives were more potent than verapamil. In particular, the potency of the 3,5-$(OMe)_2$ derivative was almost equal to that of the 3,4,5-$(OMe)_3$ analog at $pA_2=8.88$, being about ten times more active than verapamil. From the quantitative structure–activity analysis, it could be concluded that the activity is indeed optimized in these compounds.

Analysis for the Whole Series of *N*-Me Analogs (I: $m=n=3$)

Our previous analyses[1] on the effects of substituents R_3 and R_4 are represented by Eqs. 5a, b and 6, respectively. In Eqs. 5a, b and 6, *MR* and B_5[9] (the STERIMOL width parameter) are steric parameters, *I* is an indicator variable for $(CH_2)_2OMe$ and $(CH_2)_2OEt$ groups, and σ^0[10] and *F*[11] are electronic parameters. *MR* was multiplied by 0.1 and ΔB_5 is the value relative to that of H.

$$pA_2 = -0.68MR^2 + 2.49MR - 0.97I + 5.48 \quad (5a)$$
$$(0.19)\quad (0.78)\quad (0.63)\quad (0.68)$$
$$(n=12,\ r=0.95,\ s=0.33,\ F=23.89)$$

$$pA_2 = -0.23\Delta B_5^2 + 1.40\Delta B_5 - 0.89I + 5.61 \quad (5b)$$
$$(0.07)\quad (0.47)\quad (0.67)\quad (0.69)$$
$$(n=12,\ r=0.94,\ s=0.35,\ F=20.92)$$

$$pA_2 = -0.39\pi^2 - 0.35\sigma^0 - 1.50F_{ortho} - 0.60\Delta B_5^{para} + 0.46\pi_{para} + 8.50 \quad (6)$$
$$(0.12)\quad (0.30)\quad (0.55)\quad (0.14)\quad (0.19)\quad (0.16)$$
$$(n=32,\ r=0.92,\ s=0.25,\ F=29.68)$$

The π^2 term is significant in both Eqs. 4 and 6 for the substituents R_2 and R_4, representing the participation of the hydrophobicity of the whole molecule in the transport

process. For the substituent R_3, the most significant correlation equations were Eqs. 5a and 5b without the π^2 term. However, a correlation with π instead of steric parameters as expressed in Eq. 7 was also found, although the quality of the correlation is poorer.

$$\begin{array}{l} pA_2 = -0.38\pi^2 + 1.37\pi + 6.28 \\ \qquad (0.20)\quad (0.82)\quad (0.70) \\ \qquad (n=12,\ r=0.82,\ s=0.56,\ F=9.23) \end{array} \tag{7}$$

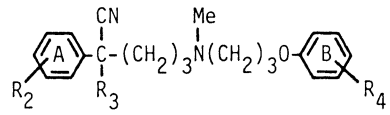
Since the regression coefficients of the π^2 term in Eqs. 4, 6 and 7 are similar, the analysis for the whole series of analogs (III-1—26, I′-2—44), where substituents on the A and B rings and the quaternary carbon atom were varied, was performed using the $\Sigma\pi$ and other position-specific parameters which were significant in the previous analyses for the individual series to give Eq. 8. In Eq. 9, compounds I′-45—50, where the combinations of substituents R_2, R_3 and R_4 are different from those of the compounds in Eq. 8, are included. The calculated pA_2 value of each compound is listed in Table VI.

$$\begin{array}{l} pA_2 = -0.31\Sigma\pi^2 + 0.93\Sigma\pi - 1.00\Delta MR^2_{meta}(\mathrm{A}) + 1.53\Delta MR_{meta}(\mathrm{A}) \\ \qquad (0.08)\quad (0.29)\quad (0.41)\quad (0.54) \\ \quad -0.29\Delta L^2_{para}(\mathrm{A}) + 0.71\Delta L_{para}(\mathrm{A}) - 1.41F_{ortho}(\mathrm{B}) - 0.60\Delta B_5^{para}(\mathrm{B}) \\ \qquad (0.15)\quad (0.37)\quad (0.63)\quad (0.17) \\ \quad +0.38\pi_{para}(\mathrm{B}) + 1.66\Delta B_1(\mathrm{Q}) + 5.33 \\ \qquad (0.25)\quad (0.60)\quad (0.53) \\ \qquad (n=69,\ r=0.91,\ s=0.31,\ F=27.40) \end{array} \tag{8}$$

$$\begin{array}{l} pA_2 = -0.31\Sigma\pi^2 + 0.95\Sigma\pi - 0.93\Delta MR^2_{meta}(\mathrm{A}) + 1.45\Delta MR_{meta}(\mathrm{A}) \\ \qquad (0.08)\quad (0.30)\quad (0.41)\quad (0.53) \\ \quad -0.30\Delta L^2_{para}(\mathrm{A}) + 0.76\Delta L_{para}(\mathrm{A}) - 1.74F_{ortho}(\mathrm{B}) - 0.59\Delta B_5^{para}(\mathrm{B}) \\ \qquad (0.16)\quad (0.37)\quad (0.59)\quad (0.17) \\ \quad +0.36\pi_{para}(\mathrm{B}) + 1.45\Delta B_1(\mathrm{Q}) + 5.45 \\ \qquad (0.26)\quad (0.61)\quad (0.54) \\ \qquad (n=75,\ r=0.89,\ s=0.33,\ F=24.97) \end{array} \tag{9}$$

In Eqs. 8 and 9 the signs A, B and Q in parentheses mean that the parameter term concerned is specific to substituents on the A ring (A), B ring (B) and quaternary carbon atom (Q), respectively. For the sake of simplicity, each steric parameter was set at the value relative to that of H, and MR was multiplied by 0.1. In Eqs. 8 and 9, the electronic σ^0 term, which was previously significant in the analysis for substituents on only the B ring (Eq. 6), was insignificant. Since the σ^0 term in Eq. 6 is least significant judging from the value of 95% confidence intervals, it seems reasonable that this term disappears for the more comprehensive set of compounds. We considered the possible significance of an indicator variable term I (A) for the effect of the 5-OMe group on the A ring in derivatives where R_2 = 3,5-$(OMe)_2$ and 3,4,5-$(OMe)_3$, because the effect of the 5-OMe group of these compounds was not considered in Eq. 4. The I (A) term, however, was insignificant. It seems that the effect of the 5-OMe group in 3,5-$(OMe)_2$ and 3,4,5-$(OMe)_3$ derivatives not incorporated in Eq. 4 was accounted for by the ΔMR_{meta}(A) term in Eqs. 8 and 9, since the effect of the 5-OMe group is considered as equivalent to that of the 3-OMe group, and also since the number of derivatives with R_2 = 3,4,5-$(OMe)_3$ is very large. In Eqs. 8 and 9, the ΔMR_{meta}(A) value for R_2 = 3,5-$(OMe)_2$ and 3,4,5-$(OMe)_3$ groups was not the sum of ΔMR values of two *m*-OMe groups but that of one *m*-OMe group. In Eqs. 8 and 9, ΔB_1[8] (the STERIMOL width parameter) was shown to describe best the steric effect of substituents on the quaternary carbon atom. The ΔB_1 term was not the best parameter in the analysis for the only substituent R_3. B_1 represents the minimum width of substituents from the axis connecting the α-atom to the rest of the

TABLE VI. Ca^{2+}-Antagonistic Activity of the *N*-Methylated Derivatives (III and I′)



Compd. No.	R_2	R_3	R_4	pA_2		
				Obsd.	Eq. 8	Eq. 9
					Calcd. (Δ)[a]	Calcd. (Δ)[a]
III-1	H	iso-Pr	*m*-OMe	7.59	7.53 (0.06)	7.48 (0.11)
III-2	*o*-Me	iso-Pr	*m*-OMe	7.25	7.43 (−0.18)	7.39 (−0.14)
III-3	*o*-OMe	iso-Pr	*m*-OMe	7.60	7.53 (0.07)	7.48 (0.12)
III-4	*o*-OEt	iso-Pr	*m*-OMe	7.53	7.48 (0.05)	7.44 (0.09)
III-5	*o*-F	iso-Pr	*m*-OMe	7.00	7.52 (−0.52)	7.48 (−0.48)
III-6	*o*-Cl	iso-Pr	*m*-OMe	7.40	7.37 (0.03)	7.34 (0.06)
III-7	*o*-Br	iso-Pr	*m*-OMe	7.60	7.30 (0.30)	7.27 (0.33)
III-8	*m*-Me	iso-Pr	*m*-OMe	7.80	7.92 (−0.12)	7.86 (−0.06)
III-9	*m*-OMe	iso-Pr	*m*-OMe	8.20	8.11 (0.09)	8.03 (0.17)
III-10	*m*-OEt	iso-Pr	*m*-OMe	7.84	7.93 (−0.09)	7.87 (−0.03)
III-11	*m*-F	iso-Pr	*m*-OMe	7.35	7.50 (−0.15)	7.46 (−0.11)
III-12	*m*-Cl	iso-Pr	*m*-OMe	7.50	7.89 (−0.39)	7.83 (−0.33)
III-13	*m*-$CONMe_2$	iso-Pr	*m*-OMe	6.64	6.64 (0.00)	6.65 (−0.01)
III-14	*p*-Me	iso-Pr	*m*-OMe	7.71	7.81 (−0.10)	7.82 (−0.11)
III-15	*p*-iso-Pr	iso-Pr	*m*-OMe	7.26	7.04 (0.22)	7.08 (0.18)
III-16	*p*-OMe	iso-Pr	*m*-OMe	7.64	7.82 (−0.18)	7.84 (−0.20)
III-17	*p*-OEt	iso-Pr	*m*-OMe	7.32	7.26 (0.06)	7.27 (0.05)
III-18	*p*-F	iso-Pr	*m*-OMe	8.25	7.84 (0.41)	7.83 (0.42)
III-19	*p*-Cl	iso-Pr	*m*-OMe	8.04	7.79 (0.25)	7.81 (0.23)
III-20	*p*-Br	iso-Pr	*m*-OMe	7.80	7.65 (0.15)	7.68 (0.12)
III-21	*p*-NO_2	iso-Pr	*m*-OMe	7.87	7.93 (−0.06)	7.94 (−0.07)
III-22	*p*-NH_2	iso-Pr	*m*-OMe	7.15	7.43 (−0.28)	7.40 (−0.25)
III-23	*p*-NHAc	iso-Pr	*m*-OMe	6.76	6.74 (0.02)	6.72 (0.04)
III-24	*p*-$CONMe_2$	iso-Pr	*m*-OMe	6.93	6.99 (−0.06)	6.98 (−0.05)
III-25	3,4-$(OMe)_2$	iso-Pr	*m*-OMe	7.99	8.40 (−0.41)	8.39 (−0.40)
III-26	3,5-$(OMe)_2$	iso-Pr	*m*-OMe	8.88	8.11 (0.77)	8.03 (0.85)
I′-2	3,4,5-$(OMe)_3$	iso-Pr	*m*-OMe	9.00	8.40 (0.60)	8.39 (0.61)
I′-3	3,4,5-$(OMe)_3$	iso-Pr	H	8.19	8.40 (−0.21)	8.39 (−0.20)
I′-4	3,4,5-$(OMe)_3$	iso-Pr	*o*-Me	8.31	8.40 (−0.09)	8.41 (−0.10)
I′-5	3,4,5-$(OMe)_3$	iso-Pr	*o*-*n*-Pr	7.79	7.93 (−0.14)	7.96 (−0.17)
I′-6	3,4,5-$(OMe)_3$	iso-Pr	*o*-OEt	8.10	8.08 (0.02)	8.00 (0.10)
I′-7	3,4,5-$(OMe)_3$	iso-Pr	*o*-F	7.95	7.79 (0.16)	7.64 (0.31)
I′-8	3,4,5-$(OMe)_3$	iso-Pr	*o*-Cl	7.69	7.68 (0.01)	7.54 (0.15)
I′-9	3,4,5-$(OMe)_3$	iso-Pr	*o*-NO_2	7.26	7.46 (−0.20)	7.22 (0.04)
I′-10	3,4,5-$(OMe)_3$	iso-Pr	*o*-NH_2	8.15	7.74 (0.41)	7.70 (0.45)
I′-11	3,4,5-$(OMe)_3$	iso-Pr	*m*-Me	8.48	8.34 (0.14)	8.33 (0.15)
I′-12	3,4,5-$(OMe)_3$	iso-Pr	*m*-*tert*-Bu	6.88	7.44 (−0.56)	7.46 (−0.58)
I′-13	3,4,5-$(OMe)_3$	iso-Pr	*m*-F	8.29	8.40 (−0.11)	8.38 (−0.09)
I′-14	3,4,5-$(OMe)_3$	iso-Pr	*m*-Cl	8.36	8.25 (0.11)	8.25 (0.11)
I′-15	3,4,5-$(OMe)_3$	iso-Pr	*m*-NO_2	8.17	8.40 (−0.23)	8.38 (−0.21)
I′-16	3,4,5-$(OMe)_3$	iso-Pr	*m*-NH_2	8.13	7.94 (0.19)	7.91 (0.22)
I′-17	3,4,5-$(OMe)_3$	iso-Pr	*m*-CF_3	8.06	8.16 (−0.10)	8.16 (−0.10)
I′-18	3,4,5-$(OMe)_3$	iso-Pr	*m*-CH_2OH	8.11	8.10 (0.01)	8.07 (0.04)
I′-19	3,4,5-$(OMe)_3$	iso-Pr	*p*-Me	7.61	7.92 (−0.31)	7.91 (−0.30)
I′-20	3,4,5-$(OMe)_3$	iso-Pr	*p*-*n*-Pr	6.88	6.89 (−0.01)	6.89 (−0.01)
I′-21	3,4,5-$(OMe)_3$	iso-Pr	*p*-*tert*-Bu	6.88	6.86 (0.02)	6.86 (0.02)

TABLE VI. (continued)

Compd. No.	R_2	R_3	R_4	pA_2		
				Obsd.	Eq. 8	Eq. 9
					Calcd. (Δ)[a]	Calcd. (Δ)[a]
I'-22	3,4,5-$(OMe)_3$	iso-Pr	*p*-OMe	7.64	7.12 (0.52)	7.12 (0.52)
I'-23	3,4,5-$(OMe)_3$	iso-Pr	*p*-F	8.02	8.27 (−0.25)	8.25 (−0.23)
I'-24	3,4,5-$(OMe)_3$	iso-Pr	*p*-Cl	7.73	8.07 (−0.34)	8.06 (−0.33)
I'-25	3,4,5-$(OMe)_3$	iso-Pr	*p*-NO_2	7.39	7.55 (−0.16)	7.54 (−0.15)
I'-26	3,4,5-$(OMe)_3$	iso-Pr	*p*-NH_2	6.50	6.67 (−0.17)	6.67 (−0.17)
I'-27	3,4,5-$(OMe)_3$	iso-Pr	*p*-CN	7.64	7.88 (−0.24)	7.87 (−0.23)
I'-28	3,4,5-$(OMe)_3$	iso-Pr	*p*-CH_2OH	6.56	6.63 (−0.07)	6.64 (−0.08)
I'-29	3,4,5-$(OMe)_3$	iso-Pr	2,3-$(OMe)_2$	8.23	8.03 (0.20)	7.93 (0.30)
I'-30	3,4,5-$(OMe)_3$	iso-Pr	2,4-Me_2	7.97	7.75 (0.22)	7.76 (0.21)
I'-31	3,4,5-$(OMe)_3$	iso-Pr	2,5-Me_2	8.68	8.17 (0.51)	8.18 (0.50)
I'-32	3,4,5-$(OMe)_3$	iso-Pr	2,6-$(OMe)_2$	7.57	7.65 (−0.08)	7.46 (0.11)
I'-33	3,4,5-$(OMe)_3$	iso-Pr	*o*-OMe	8.05	8.03 (0.02)	7.93 (0.12)
I'-34	3,4,5-$(OMe)_3$	H	*o*-OMe	5.56	5.70 (−0.14)	5.77 (−0.21)
I'-35	3,4,5-$(OMe)_3$	Me	*o*-OMe	6.76	7.02 (−0.26)	6.99 (−0.23)
I'-36	3,4,5-$(OMe)_3$	Et	*o*-OMe	7.44	7.30 (0.14)	7.28 (0.16)
I'-37	3,4,5-$(OMe)_3$	*n*-Pr	*o*-OMe	7.79	7.41 (0.38)	7.39 (0.40)
I'-38	3,4,5-$(OMe)_3$	*n*-Bu	*o*-OMe	7.21	7.33 (−0.12)	7.32 (−0.11)
I'-39	3,4,5-$(OMe)_3$	iso-Bu	*o*-OMe	7.53	7.36 (0.17)	7.35 (0.18)
I'-40	3,4,5-$(OMe)_3$	*n*-Hex	*o*-OMe	7.46	6.63 (0.83)	6.64 (0.82)
I'-41	3,4,5-$(OMe)_3$	*n*-Oct	*o*-OMe	5.06	5.22 (−0.16)	5.25 (−0.19)
I'-42	3,4,5-$(OMe)_3$	Benzyl	*o*-OMe	6.48	7.31 (−0.83)	7.30 (−0.82)
I'-43	3,4,5-$(OMe)_3$	$(CH_2)_2OMe$	*o*-OMe	6.80	6.52 (0.28)	6.48 (0.32)
I'-44	3,4,5-$(OMe)_3$	$(CH_2)_2OEt$	*o*-OMe	6.68	6.77 (−0.09)	6.73 (−0.05)
I'-45	H	iso-Pr	*o*-OMe	6.83		7.03 (−0.20)
I'-46	*o*-OMe	iso-Pr	*o*-OMe	6.87		7.03 (−0.16)
I'-47	*m*-OMe	iso-Pr	*o*-OMe	7.29		7.58 (−0.29)
I'-48	*p*-OMe	iso-Pr	*o*-OMe	7.46		7.38 (0.08)
I'-49	3,4-$(OMe)_2$	iso-Pr	*o*-OMe	7.41		7.93 (−0.52)
I'-50	2,3,4-$(OMe)_3$	iso-Pr	*o*-OMe	7.17		7.93 (−0.76)

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

molecule. The pA_2 value for derivatives of R_3 = iso-Pr with a relatively large B_1 value was observed generally as being higher than that calculated from Eq. 7. In Eqs. 8 and 9, including a large number of derivatives with R_3 = iso-Pr, the significance of the B_1 term was revealed. Equations 8 and 9 indicate that the greater is the smallest width of substituent R_3, the more potent is the activity. This means that the more symmetric and bulkier substituents such as *tert*-Bu are favorable for the activity. Since the *tert*-Bu derivatives are almost impossible to synthesize, the iso-Pr group could be practically the best as the substituent R_3 in terms of the steric effect. Equation 9 gave the optimum $\Sigma\pi = 1.53$ indicating the existence of an optimum in the total molecular hydrophobicity, presumably in connection with the transport process. It also indicates that optimum steric conditions for *m*- and *p*-substituents on the A ring, an importance of the electron-releasing effect of *o*-substituents as well as smaller and yet hydrophobic *p*-substituents on the B ring, and symmetric bulky substituents on the quaternary carbon atom are favorable for the activity.

The present quantitative analyses of the effects of substituents on the A and B rings and quaternary carbon atom seem adequate to allow us to identify the most effective structural features for the Ca^{2+}-antagonistic activity.

Experimental

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

Preparation of *N*-Unsubstituted α-Isopropyl-α-[3-[(3-phenoxypropyl)amino]propyl]-α-phenylacetonitriles (II): (Method A): α-Isopropyl-α-[3-[[3-(3-methoxyphenoxy)propyl]amino]propyl]-α-phenylacetonitrile (II-1)——A solution of α-(2-formylethyl)-α-isopropyl-α-phenylacetonitrile (VII-1, 3.50 g) and 3-(3-methoxyphenoxy)propylamine (2.33 g) in MeOH (80 ml) was refluxed for 2.5 h, then cooled with ice water, and $NaBH_4$ (0.62 g) was added. The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was acidified with aqueous HCl and washed with Et_2O. The aqueous layer and the insoluble oily layer were combined, made alkaline with K_2CO_3 and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ and $CHCl_3$–MeOH (98 : 2) as eluents to give II-1 (2.52 g, 51%) as a pale yellow oil. The free base thus obtained was converted into the fumarate in a usual manner and the resulting salt was recrystallized from EtOH–Et_2O to give colorless plates, mp 129—131 °C. IR ν_{max}^{KBr} cm^{-1}: 2230 (CN). ^{1}H-NMR (CD_3OD) δ: 0.74, 1.20 (each 3H, d, J=6.5 Hz, $CH(CH_3)_2$), 3.74 (3H, s, OCH_3), 4.01 (2H, t, J=6.0 Hz, $NCH_2CH_2CH_2O$), 6.62 (1H, s, olefinic proton). *Anal.* Calcd for $C_{24}H_{32}N_2O_2 \cdot 1/2C_4H_4O_4$: C, 71.21; H, 7.81; N, 6.39. Found: C, 70.81; H, 7.89; N, 6.28.

Compounds II-2—12, 14—20 and 25 were also prepared in a similar manner. The yields and characteristics of the products are listed in Table I.

(Method B): 3-[1-Cyano-1-isopropyl-4-[[3-(3-methoxyphenoxy)propyl]amino]butyl]-*N*,*N*-dimethylbenzamide (II-13)——A mixture of 3-(4-chloro-1-cyano-1-isopropylbutyl)-*N*,*N*-dimethylbenzamide (VIII-13, 1.60 g) and 3-(3-methoxyphenoxy)propylamine (1.89 g) was stirred at 90 °C for 2.5 h. After cooling, the mixture was acidified with aqueous HCl and washed with Et_2O. The aqueous layer was extracted with $CHCl_3$ and the $CHCl_3$ layer was washed with aqueous K_2CO_3. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ and $CHCl_3$–MeOH (95 : 5) as eluents to give II-13 (1.60 g, 68%) as a yellow oil. IR ν_{max}^{liq} cm^{-1}: 2236 (CN), 1632 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.78, 1.19 (each 3H, d, J=6.5 Hz, $CH(CH_3)_2$), 2.17 (1H, s, NH), 2.96, 3.09 (each 3H, s, $N(CH_3)_2$), 3.77 (3H, s, OCH_3), 3.98 (2H, t, J=6.0 Hz, $NCH_2CH_2CH_2O$). High MS m/z: 451.2840 (M^+) (Calcd for $C_{27}H_{37}N_3O_3$ 451.2835).

Compounds II-21, 23, 24 and 26 were also prepared in a similar manner. The yields and characteristics of the products are listed in Table I.

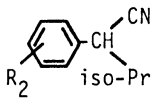
α-(4-Aminophenyl)-α-isopropyl-α-[3-[[3-(3-methoxyphenoxy)propyl]amino]propyl]acetonitrile (II-22)——A solution of α-isopropyl-α-[3-[[3-(3-methoxyphenoxy)propyl]amino]propyl]-α-(4-nitrophenyl)acetonitrile (II-21, 2.27 g) in MeOH (20 ml) was hydrogenated over PtO_2 (22 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified on a column of silica gel using $CHCl_3$–MeOH (98 : 2) and (95 : 5) as eluents to give II-22 (1.84 g, 87%) as a pale yellow oil. The free base thus obtained was converted into the oxalate in a usual manner and the resulting salt was recrystallized from EtOH to give pale yellowish brown crystals, mp 104.5—106 °C. IR ν_{max}^{KBr} cm^{-1}: 3450, 3380 (NH_2), 2230 (CN). ^{1}H-NMR (CD_3OD) δ: 0.76, 1.17 (each 3H, d, J=6.5 Hz, $CH(CH_3)_2$), 3.75 (3H, s, OCH_3), 4.03 (2H, t, J=5.5 Hz, $NCH_2CH_2CH_2O$), 6.92 (2H, d, J=8.5 Hz, aromatic protons), 7.25 (2H, d, J=8.5 Hz, aromatic protons). *Anal.* Calcd for $C_{24}H_{33}N_3O_2 \cdot 3/2C_2H_2O_4$: C, 61.12; H, 6.84; N, 7.92. Found: C, 61.01; H, 6.76; N, 7.87.

Preparation of *N*-Methylated α-Isopropyl-α-[3-[(3-phenoxypropyl)amino]propyl]-α-phenylacetonitriles (III): α-Isopropyl-α-[3-[*N*-[3-(3-methoxyphenoxy)propyl]-*N*-methylamino]propyl]-α-phenylacetonitrile (III-1)——A mixture of II-1 (1.60 g) and 37% formalin (4.15 ml) in MeOH (70 ml) was refluxed for 1.5 h, then cooled with ice water, and $NaBH_4$ (0.64 g) was added to the solution. The mixture was stirred at room temperature for 0.5 h, and then concentrated. The residue was diluted with water and extracted with Et_2O. The Et_2O layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ as an eluent to give III-1 (1.18 g, 71%) as a yellow oil. The free base thus obtained was converted into the fumarate in a usual manner and the resulting salt was recrystallized from EtOH–Et_2O to give colorless crystals, mp 105—106 °C. IR ν_{max}^{KBr} cm^{-1}: 2230 (CN). ^{1}H-NMR (CD_3OD) δ: 0.75, 1.20 (each 3H, d, J=6.5 Hz, $CH(CH_3)_2$), 2.73 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 4.00 (2H, t, J=5.5 Hz, $NCH_2CH_2CH_2O$), 6.67 (2H, s, olefinic protons). *Anal.* Calcd for $C_{25}H_{34}N_2O_2 \cdot C_4H_4O_4$: C, 68.21; H, 7.50; N, 5.49. Found: C, 68.02; H, 7.31; N, 5.24.

Compounds III-2—21 and 24—26 were also prepared in a similar manner. The yields and characteristics of the products are listed in Table II.

α-(4-Aminophenyl)-α-isopropyl-α-[3-[*N*-[3-(3-methoxyphenoxy)propyl]-*N*-methylamino]propyl]acetonitrile (III-22)——A solution of α-isopropyl-α-[3-[*N*-[3-(3-methoxyphenoxy)propyl]-*N*-methylamino]propyl]-α-(4-nitrophenyl)-acetonitrile (III-21, 2.12 g) in MeOH (20 ml) was hydrogenated over PtO_2 (22 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was

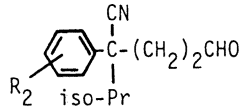
TABLE VII. Physicochemical Properties of α-Isopropyl-α-phenylacetonitriles (V)



Compd. No.	R_2	Yield (%)	bp (°C) (mmHg)	Formula	High MS m/z (M^+) Calcd (Found)
V-1[a]	H	93	98—100 (6)	$C_{11}H_{13}N$	159.1048 (159.1040)
V-2[b]	*o*-Me	49	125—126 (11)	$C_{12}H_{15}N$	173.1204 (173.1210)
V-3[c]	*o*-OMe	85	127—129 (8)	$C_{12}H_{15}NO$	189.1154 (189.1160)
V-4	*o*-OEt	83	110—114 (3)	$C_{13}H_{17}NO$	203.1310 (203.1312)
V-5[d]	*o*-F	62	98—99 (8)	$C_{11}H_{12}FN$	177.0954 (177.0961)
V-6[e]	*o*-Cl	77	120—121 (8)	$C_{11}H_{12}ClN$	193.0658 (193.0671) 195.0629 (195.0636)
V-7	*o*-Br	78	125—126 (9)	$C_{11}H_{12}BrN$	237.0153 (237.0145) 239.0133 (239.0145)
V-8	*m*-Me	81	109—112 (9)	$C_{12}H_{15}N$	173.1204 (173.1210)
V-9[f]	*m*-OMe	83	120—124 (6)	$C_{12}H_{15}NO$	189.1154 (189.1152)
V-10	*m*-OEt	78	140—152 (11)	$C_{13}H_{17}NO$	203.1310 (203.1307)
V-11[e]	*m*-F	80	98—102 (4)	$C_{11}H_{12}FN$	177.0954 (177.0950)
V-12[e]	*m*-Cl	77	100—102 (3)	$C_{11}H_{12}ClN$	193.0658 (193.0659) 195.0629 (195.0650)
V-13	*m*-$CONMe_2$	46	170—180 (3)	$C_{14}H_{18}N_2O$	230.1419 (230.1407)
V-14[g]	*p*-Me	77	105—107 (3)	$C_{12}H_{15}N$	173.1204 (173.1205)
V-15[e]	*p*-iso-Pr	80	141—146 (12)	$C_{14}H_{19}N$	201.1517 (201.1527)
V-16[e]	*p*-OMe	69	138—141 (8)	$C_{12}H_{15}NO$	189.1154 (189.1173)
V-17	*p*-OEt	77	145—148 (9)	$C_{13}H_{17}NO$	203.1310 (203.1317)
C-18[e]	*p*-F	73	97—98 (7)	$C_{11}H_{12}FN$	177.0954 (177.0951)
V-19[e]	*p*-Cl	77	108—112 (3)	$C_{11}H_{12}ClN$	193.0658 (193.0636) 195.0629 (195.0634)
V-20[e]	*p*-Br	72	148—151 (9)	$C_{11}H_{12}BrN$	237.0153 (237.0148) 239.0133 (239.0131)
V-24	*p*-$CONMe_2$	56	—	$C_{14}H_{18}N_2O$	230.1419 (230.1413)
V-25[h]	3,4-$(OMe)_2$	92	166—167 (7)	$C_{13}H_{17}NO_2$	219.1259 (219.1257)
V-26	3,5-$(OMe)_2$	67	169—171 (10)	$C_{13}H_{17}NO_2$	219.1259 (219.1262)

a) Ref. 12. *b*) Ref. 13. *c*) Ref. 4. *d*) Ref. 14. *e*) Ref. 15. *f*) Ref. 16. *g*) Ref. 17. *h*) Ref. 18.

TABLE VIII. Physicochemical Properties of α-(2-Formylethyl)-α-isopropyl-α-phenylacetonitriles (VII)



Compd. No.	R_2	Yield[a] (%)	Formula	High MS m/z (M^+) Calcd (Found)	Compd. No.	R_2	Yield[a] (%)	Formula	High MS m/z (M^+) Calcd (Found)
VII-1[b]	H	49	$C_{14}H_{17}NO$	215.1310 (215.1313)	VII-12	*m*-Cl	81	$C_{14}H_{16}ClNO$	249.0920 (249.0912)
VII-2	*o*-Me	86	$C_{15}H_{19}NO$	229.1467 (229.1472)					251.0891 (251.0895)
VII-3[b]	*o*-OMe	86	$C_{15}H_{19}NO_2$	245.1416 (245.1406)	VII-14	*p*-Me	79	$C_{15}H_{19}NO$	229.1467 (229.1470)
VII-4	*o*-OEt	94	$C_{16}H_{21}NO_2$	259.1572 (259.1585)	VII-15	*p*-iso-Pr	97	$C_{17}H_{23}NO$	257.1780 (257.1774)
VII-5	*o*-F	73	$C_{14}H_{16}FNO$	233.1216 (233.1224)	VII-16[b]	*p*-OMe	91	$C_{15}H_{19}NO_2$	245.1416 (245.1409)
VII-6	*o*-Cl	71	$C_{14}H_{16}ClNO$	249.0920 (249.0926)	VII-17	*p*-OEt	91	$C_{16}H_{21}NO_2$	259.1572 (259.1575)
				251.0891 (251.0870)	VII-18	*p*-F	75	$C_{14}H_{16}FNO$	233.1216 (233.1207)
VII-7	*o*-Br	83	$C_{14}H_{16}BrNO$	293.0415 (293.0424)	VII-19	*p*-Cl	82	$C_{14}H_{16}ClNO$	249.0920 (249.0928)
				295.0395 (295.0395)					251.0891 (251.0879)
VII-8	*m*-Me	74	$C_{15}H_{19}NO$	229.1467 (229.1448)	VII-20	*p*-Br	81	$C_{14}H_{16}BrNO$	293.0415 (293.0332)
VII-9[b]	*m*-OMe	58	$C_{15}H_{19}NO_2$	245.1416 (245.1406)					295.0395 (295.0386)
VII-10	*m*-OEt	96	$C_{16}H_{21}NO_2$	259.1572 (259.1562)	VII-25[c]	3,4-$(OMe)_2$	90	$C_{16}H_{21}NO_3$	275.1521 (275.1528)
VII-11	*m*-F	72	$C_{14}H_{16}FNO$	233.1216 (233.1216)					

a) Yield from α-isopropyl-α-phenylacetonitriles (VII). *b*) Ref. 4. *c*) Ref. 19.

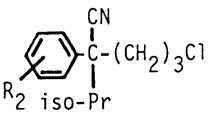
concentrated under reduced pressure and the residue was purified on a column of silica gel using $CHCl_3$–MeOH (98 : 2) and (95 : 5) as eluents to give III-22 (1.70 g, 86%) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 3464, 3384 (NH_2), 2236 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.77, 1.13 (each 3H, d, J=6.5 Hz, $CH(CH_3)_2$), 2.12 (3H, s, NCH_3), 3.64 (2H, br s, NH_2), 3.78 (3H, s, OCH_3), 3.95 (2H, t, J=6.0 Hz, $NCH_2CH_2CH_2O$), 6.63 (2H, d, J=8.5 Hz, aromatic protons), 7.11 (2H, d, J=8.5 Hz, aromatic protons). High MS m/z: 409.2727 (M^+) (Calcd for $C_{25}H_{35}N_3O_2$ 409.2729).

***N*-[4-[1-Cyano-1-isopropyl-4-[*N*-[3-(3-methoxyphenoxy)propyl]-*N*-methylamino]butyl]phenyl]acetamide (III-23)**——A mixture of III-22 (1.23 g) and Ac_2O (6 ml) was stirred at 55—60 °C for 0.5 h and concentrated. The residue was made alkaline with aqueous K_2CO_3 and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ and $CHCl_3$–MeOH (95 : 5) as eluents to give III-23 (1.08 g, 80%) as a yellow oil. IR ν_{max}^{liq} cm^{-1}: 2245 (CN), 1674 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.75, 1.15 (each 3H, d, J=6.5 Hz, $CH(CH_3)_2$), 2.11 (3H, s, NCH_3), 2.16 (3H, s, $COCH_3$), 3.79 (3H, s, OCH_3), 3.94 (2H, t, J=6.5 Hz, $NCH_2CH_2CH_2O$), 7.28 (2H, d, J=9.0 Hz, aromatic protons), 7.51 (2H, d, J=9.0 Hz, aromatic protons). High MS m/z: 451.2812 (M^+) (Calcd for $C_{27}H_{37}N_3O_3$ 451.2835).

Preparation of α-Isopropyl-α-phenylacetonitriles (V): α-Isopropyl-α-phenylacetonitrile (V-1)[12]——Compound V-1 was prepared by the method previously described.[4] Compounds V-2,[13] 3,[4] 4, 5,[14] 6,[15] 7, 8, 9,[16] 10, 11,[15] 12,[15] 13, 14,[17] 15,[15] 16,[15] 17, 18,[15] 19,[15] 20,[15] 24, 25[18] and 26 were also prepared in the same manner. The yields and characteristics of the products are listed in Table VII.

Preparation of α-(2-Formylethyl)-α-isopropyl-α-phenylacetonitriles (VII): α-(2-Formylethyl)-α-isopropyl-α-phenylacetonitrile (VII-1)——Compound VII-1 was prepared by the method previously described.[4] Compounds VII-

TABLE IX. Physicochemical Properties of α-(3-Chloropropyl)-α-isopropyl-α-phenylacetonitriles (VIII)



Compd. No.	R_2	Yield (%)	Formula	High MS *m/z* (M^+) Calcd (Found)
VIII-1	H	63	$C_{14}H_{18}ClN$	235.1128 (235.1111) 237.1098 (237.1090)
VIII-13	*m*-$CONMe_2$	72	$C_{17}H_{23}ClN_2O$	306.1499 (306.1495) 308.1469 (308.1468)
VIII-21	*p*-NO_2	93	$C_{14}H_{17}ClN_2O_2$	280.0978 (280.1004) 282.0949 (282.0958)
VIII-22	*p*-NH_2	76	$C_{14}H_{19}ClN_2$	250.1237 (250.1238) 252.1207 (252.1208)
VIII-23	*p*-NHAc	83	$C_{16}H_{21}ClN_2O$	292.1342 (292.1329) 294.1313 (294.1296)
VIII-24	*p*-$CONMe_2$	76	$C_{17}H_{23}ClN_2O$	306.1499 (306.1497) 308.1469 (308.1467)
VIII-26	3,5-$(OMe)_2$	48	$C_{16}H_{22}ClNO_2$	295.1339 (295.1340) 297.1309 (297.1313)

2, 3,[4] 4—8, 9,[4] 10—12, 14, 15, 16,[4] 17—20 and 25[19] were also prepared in the same manner. The yields and characteristics of the products are listed in Table VIII.

Preparation of α-(3-Chloropropyl)-α-isopropyl-α-phenylacetonitriles (VIII): α-(3-Chloropropyl)-α-isopropyl-α-phenylacetonitrile (VIII-1)——$NaNH_2$ (2.39 g) was added to a solution of α-isopropyl-α-phenylacetonitrile (V-1, 6.50 g) in anhydrous tetrahydrofuran (THF, 65 ml). The mixture was stirred at room temperature for 1 h, then 1-bromo-3-chloropropane (8.70 ml) was added and then the whole was stirred at 60 °C for 2 h. The mixture was poured into ice water and extracted with Et_2O. The Et_2O layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$–*n*-hexane (1 : 2) as an eluent to give VIII-1 (6.06 g, 63%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2236 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.79, 1.21 (each 3H, d, J=6.5 Hz, $CH(CH_3)_2$), 3.47 (2H, dd, J=6.5, 5.5 Hz, CH_2Cl). High MS *m/z*: 235.1111, 237.1090 (M^+) (Calcd for $C_{14}H_{18}ClN$ 235.1128, 237.1098).

Compounds V-13, 24 and 26 were also prepared in a similar manner. The yields and characteristics of the products are listed in Table IX.

α-(3-Chloropropyl)-α-isopropyl-α-(4-nitrophenyl)acetonitrile (VIII-21)——Compound VIII-1 (6.00 g) was added to a mixture of nitric acid (8.00 ml) and sulfuric acid (8.00 ml) at 8—13 °C and then the mixture was stirred at room temperature for 1 h. The mixture was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$–*n*-hexane (1 : 1) and (2 : 1) as eluents to give VIII-21 (6.65 g, 93%) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.81, 1.26 (each 3H, d, J=6.5 Hz, $CH(CH_3)_2$), 3.51 (2H, dd, J=6.5, 5.5 Hz,

CH_2Cl), 7.61 (2H, d, $J=9.0$ Hz, aromatic protons), 8.28 (2H, d, $J=9.0$ Hz, aromatic protons). High MS *m/z*: 280.1004, 282.0958 (M^+) (Calcd for $C_{14}H_{17}ClN_2O_2$ 280.0978, 282.0949).

α-(4-Aminophenyl)-α-(3-chloropropyl)-α-isopropylacetonitrile (VIII-22)——A solution of VIII-21 (2.50 g) in MeOH (10 ml) was hydrogenated over PtO_2 (25 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was purified on a column of silica gel using $CHCl_3$ as an eluent to give VIII-22 (1.69 g, 76%) as a yellow oil. IR ν_{max}^{liq} cm^{-1}: 3472, 3380 (NH_2), 2236 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.80, 1.17 (each 3H, d, $J=6.5$ Hz, $CH(C\underline{H}_3)_2$), 3.47 (2H, dd, $J=6.5$, 5.5 Hz, CH_2Cl), 3.63 (2H, br s, NH_2), 6.67 (2H, d, $J=8.5$ Hz, aromatic protons), 7.23 (2H, d, $J=8.5$ Hz, aromatic protons). High MS *m/z*: 250.1238, 252.1208 (M^+) (Calcd for $C_{14}H_{19}ClN_2$ 250.1237, 252.1207).

***N*-[4-[4-Chloro-1-cyano-1-isopropylbutyl]phenyl]acetamide (VIII-23)**——A mixture of VIII-22 (2.19 g) and Ac_2O (11 ml) was stirred at room temperature for 1 h and concentrated. The residue was made alkaline with aqueous K_2CO_3 and extracted with AcOEt. The AcOEt layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified on a column of silica gel using $CHCl_3$ and $CHCl_3$–MeOH (98 : 2) as eluents to give VIII-23 (2.13 g, 83%) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 2240 (CN), 1676 (CO). ^{1}H-NMR ($CDCl_3$) δ: 0.79, 1.19 (each 3H, d, $J=6.5$ Hz, $CH(C\underline{H}_3)_2$), 2.18 (3H, s, $COCH_3$), 3.47 (2H, dd, $J=6.5$, 5.5 Hz, CH_2Cl), 7.30 (2H, d, $J=9.0$ Hz, aromatic protons), 7.58 (2H, d, $J=9.0$ Hz, aromatic protons), 7.98 (1H, br s, NH). High MS *m/z*: 292.1329, 294.1296 (M^+) (Calcd for $C_{16}H_{21}ClN_2O$ 292.1342, 294.1313).

Ca^{2+}-Antagonistic Activity——Pharmacological procedures using KCl-depolarized guinea-pig taenia coli were described previously.[3]

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