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Novel Phenoxyalkylamine Derivatives. II.[1] Synthesis and Ca^{2+}-Antagonistic Activities of α-Alkyl-α-[(phenoxypropylamino)propyl]-benzeneacetonitrile Derivatives

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α-Alkyl-α-[(phenoxypropylamino)propyl]benzeneacetonitrile derivatives containing various substituents on the ring of the benzeneacetonitrile moiety (A), the quaternary carbon atom and the ring of the phenoxy moiety (B) were prepared, and their Ca^{2+}-antagonistic activities were evaluated. Among these compounds, the *N*-Me derivatives with a 3,4,5-$(OMe)_3$ group on the A ring, an iso-Pr group on the quaternary carbon atom, and a *m*-OMe, 3,5-$(OMe)_2$, 3,5-Me_2 or 3,4,5-$(OMe)_3$ group on the B ring were found to possess Ca^{2+}-antagonistic activity higher than $pA_2 = 9$. The effects of substitutions at the A ring, the quaternary carbon atom and the B ring are discussed.

Keywords——phenoxyalkylamine; α-alkyl-α-[(phenoxypropylamino)propyl]benzeneacetonitrile; calcium ion-antagonistic activity; structure–activity relationship

Previously,[1] we synthesized a series of novel phenoxyalkylamine derivatives (I) in which the phenethylamino moiety of verapamil was transformed to a phenoxyalkylamino moiety. We observed variations in their Ca^{2+}-antagonistic and α-blocking activities depending upon the structural modifications. The effects of the carbon chain length (m, n) and the R_1 substituent on the nitrogen atom on the activity were examined while the R_2 substituent on the A ring of the benzeneacetonitrile moiety was fixed as a 3,4,5-$(OMe)_3$ group, the R_3 substituent on the quaternary carbon atom as an iso-Pr group and the R_4 substituent on the B ring of the phenoxy moiety as an *o*-OMe group. We found that the compound (I′-2) with $m=3$, $n=3$ and R_1 = Me exhibited a potent Ca^{2+}-antagonistic activity and that (I′-3) with $m=3$, $n=2$ and R_1 = H exhibited a potent α-blocking activity.

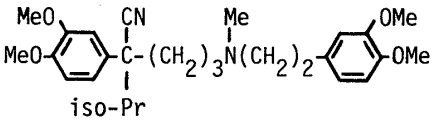
The aim of the present study was to investigate the effect of further structural modification of I on the Ca^{2+}-antagonistic activity. We examined the activity of compounds in which various modifications had been made in the R_2 substituent on the A ring (II-1—6, III-1—6), the R_3 substituent on the quaternary carbon atom (II-7—15, III-7—15) and the R_4 substituent on the B ring (II-16—50, III-16—50) while the carbon chains were fixed at $m=3$ and $n=3$, which were previously shown to be favorable for potent activity.[1]

Synthesis

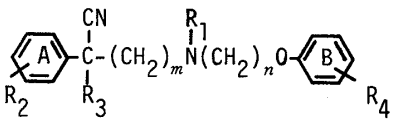
α-Alkyl-α-[(phenoxypropylamino)propyl]benzeneacetonitrile derivatives (II, III) were synthesized by the method shown in Chart 2.

The key intermediate aldehydes (IV) were obtained *via* α-alkylbenzeneacetonitriles (VIII) from benzeneacetonitriles (V) as shown in Chart 3. The physicochemical properties of VIII and IV are summarized in Tables IV and V in the experimental section.

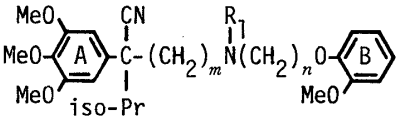
The aldehydes (IV) thus obtained were reductively condensed with the corresponding



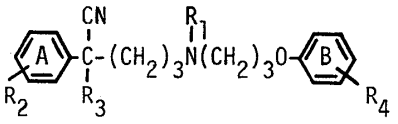
verapamil



I

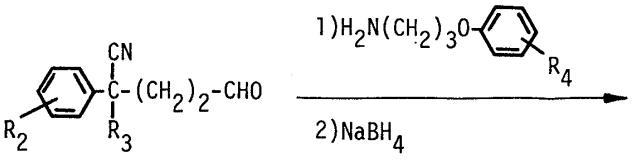


I'-1: R_1=H, m=n=3
I'-2: R_1=Me, m=n=3
I'-3: R_1=H, m=3, n=2



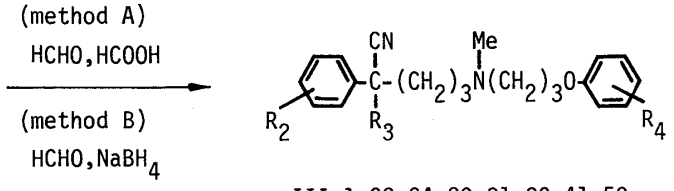
II-1-50 : R_1=H
III-1-50: R_1=Me

Chart 1

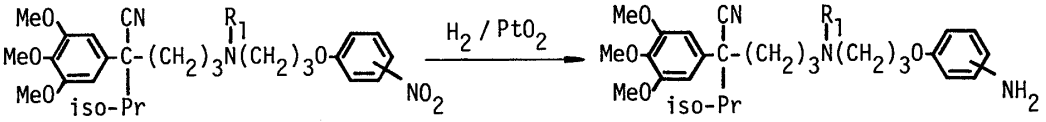


IV-1-16

II-1-22,24-29,31-39,41-50



III-1-22,24-29,31-39,41-50

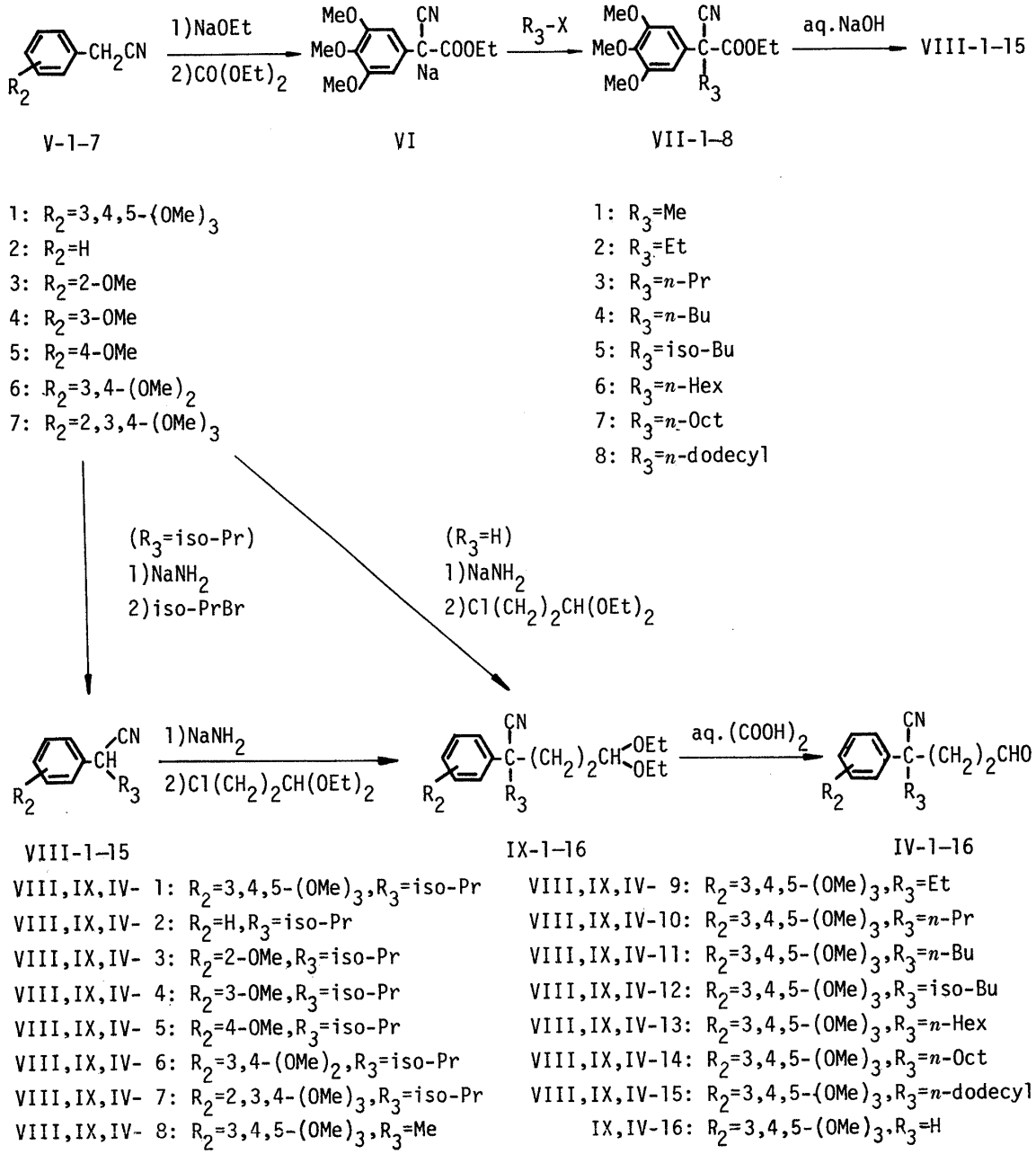


II-22,29,39 : R_1=H
III-22,29,39: R_1=Me

II-23,30,40 : R_1=H
III-23,30,40: R_1=Me

Chart 2

phenoxyalkylamines using sodium borohydride to yield the *N*-H derivatives (II), *N*-methylation of which was performed by two methods (A and B). Among them, *N*-methylation of the *m*-Me (II-24) and *m*-OMe (II-26) compounds by method A proceeded in low yields (19% and 0%, respectively). We considered that in the presence of an electron-releasing substituent such as a Me or OMe group at the *m*-position, hydroxymethylation with formalin occurred at the 2-, 4-, and 6-positions on the B ring. On the other hand, by method B, II-24 and 26 gave III-24 and 26 in relatively high yields (56% and 59%, respectively). Although



formalin was also employed in method B, no hydroxymethylation seemed to occur, since the reaction temperature (*ca.* 60 °C) in method B was lower than that (90—100 °C) in method A.

On the basis of the above results, *N*-methylation of the compounds having an electron-releasing substituent at the *m*-position of the B ring, including di- and trisubstituted derivatives, was performed by using method B, to give III-25, 32, 43, 45, 47—50.

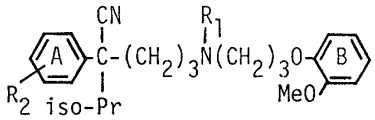
Both the *N*-H and *N*-Me derivatives with a nitro group (II-22, 29, 39, III-22, 29, 39) on the B ring were hydrogenated over PtO_2 to yield the corresponding derivatives with an amino group (II-23, 30, 40, III-23, 30, 40).

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

Results and Discussion

Pharmacological data for the compounds obtained here are summarized in Tables I—III.

TABLE I. Physicochemical and Pharmacological Data for R_2-Substituted α-Isopropyl-α-[(phenoxypropylamino)-propyl]benzeneacetonitriles (II, III)



Compd. No.	R_1	R_2	Yield[a] (%) (Method)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C H N	pA_2[b]
II-1	H	H	90	Free	Oil	—	$C_{24}H_{32}N_2O_2$	380.2464[c] (380.2435)	6.05
II-2	H	2-OMe	82	Free	Oil	—	$C_{25}H_{34}N_2O_3$	410.2569[c] (410.2550)	6.02
II-3	H	3-OMe	85	Free	Oil	—	$C_{25}H_{34}N_2O_3$	410.2569[c] (410.2588)	6.41
II-4	H	4-OMe	67	Free	Oil	—	$C_{25}H_{34}N_2O_3$	410.2569[c] (410.2539)	6.26
II-5	H	3,4-$(OMe)_2$	76	Free	Oil	—	$C_{26}H_{36}N_2O_4$	440.2675[c] (440.2680)	6.24
II-6	H	2,3,4-$(OMe)_3$	78	Oxalate	118—122	EtOH–iso-Pr_2O	$C_{27}H_{38}N_2O_5 \cdot C_2H_2O_4 \cdot 1/2\,H_2O$	61.15 7.25 4.92 (61.18 7.44 5.03)	6.19
I′-1[d]	H	3,4,5-$(OMe)_3$							6.24
III-1	Me	H	69 (A)	Free	Oil	—	$C_{25}H_{34}N_2O_2$	394.2620[c] (394.2615)	6.83
III-2	Me	2-OMe	90 (A)	Free	Oil	—	$C_{26}H_{36}N_2O_3$	424.2726[c] (424.2692)	6.87
III-3	Me	3-OMe	97 (A)	Oxalate	128—129	EtOH	$C_{26}H_{36}N_2O_3 \cdot C_2H_2O_4$	65.35 7.44 5.44 (65.33 7.53 5.31)	7.29
III-4	Me	4-OMe	68 (A)	Free	Oil	—	$C_{26}H_{36}N_2O_3$	424.2726[c] (424.2740)	7.46
III-5	Me	3,4-$(OMe)_2$	62 (A)	Free	Oil	—	$C_{27}H_{38}N_2O_4$	454.2832[c] (454.2852)	7.41
III-6	Me	2,3,4-$(OMe)_3$	65 (A)	Free	Oil	—	$C_{28}H_{40}N_2O_5$	484.2937[c] (484.2932)	7.17
I′-2[d]	Me	3,4,5-$(OMe)_3$							8.05

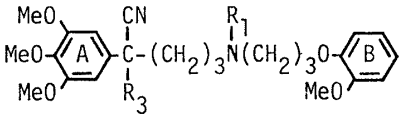
a) Yield of free base. *b*) pA_2 values in the KCl-depolarized guinea-pig taenia coli. *c*) High mass data. The upper values are calculated and the lower ones are those found. *d*) Ref. 1.

Ca^{2+}-Antagonistic activity was tested in KCl-depolarized guinea-pig taenia coli and the results are given as the pA_2 value.

First, we examined the effect of the R_2 substituent (Table I). As R_2-substituted compounds, the non-substituted (II-1, III-1), mono-OMe (II-2—4, III-2—4), di-$(OMe)_2$ (II-5, III-5) and 2,3,4-$(OMe)_3$ (II-6, III-6) derivatives, in addition to the 3,4,5-$(OMe)_3$ derivatives (I′-1, 2) reported in the previous paper,[1] were examined. The activity of the *N*-H derivatives (II-1—6, I′-1) was low and no marked difference was observed among them. On the other hand, the activities of the *N*-methylated derivatives (III-1—6, I′-2) were higher, but no compound was found to be superior to I′-2 having the 3,4,5-$(OMe)_3$ group.

Second, the effect of the R_3 substituent was examined (Table II). In the R_3-substituted compounds, in addition to the iso-Pr derivatives (I′-1, 2), the non-substituted (II-7, III-7) and alkyl (II-8—15, III-8—15) derivatives from Me to *n*-dodecyl were included. The activity of the *N*-H derivatives (II-7—15, I′-1) was low, similar to the findings for the R_2-substituted compounds. On the other hand, the activities of the *N*-methylated derivatives (III-7—15, I′-2)

TABLE II. Physicochemical and Pharmacological Data for R_3-Substituted α-[(Phenoxypropylamino)propyl]-benzeneacetonitriles (II, III)



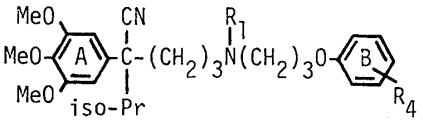
Compd. No.	R_1	R_3	Yield[a] (%) (Method)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C H N	pA_2[b]
II-7	H	H	31	Oxalate	163—165	MeOH	$C_{24}H_{32}N_2O_5 \cdot C_2H_2O_4$	60.22 6.61 5.40 (59.84 6.76 5.20)	5.39
II-8	H	Me	78	Oxalate	179—180	MeOH	$C_{25}H_{34}N_2O_5 \cdot C_2H_2O_4$	60.89 6.81 5.26 (60.54 6.93 5.23)	6.02
II-9	H	Et	84	Free	Oil	—	$C_{26}H_{36}N_2O_5$	456.2624[c] (456.2614)	6.46
II-10	H	*n*-Pr	69	Fumarate	99—100	EtOH–Et_2O	$C_{27}H_{38}N_2O_5 \cdot C_4H_4O_4 \cdot 1/2\,H_2O$	62.51 7.28 4.70 (62.28 7.42 4.55)	6.29
II-11	H	*n*-Bu	53	Free	Oil	—	$C_{28}H_{40}N_2O_5$	484.2937[c] (484.2914)	6.24
II-12	H	iso-Bu	69	Fumarate	106—108	EtOH–Et_2O	$C_{28}H_{40}N_2O_5 \cdot C_4H_4O_4 \cdot 1/2\,H_2O$	63.04 7.44 4.59 (62.82 7.42 4.49)	6.44
II-13	H	*n*-Hex	88	Free	Oil	—	$C_{30}H_{44}N_2O_5$	512.3250[c] (512.3269)	6.54
II-14	H	*n*-Oct	64	HCl	124—125	EtOH–Et_2O	$C_{32}H_{48}N_2O_5 \cdot HCl \cdot 1/4\,H_2O$	66.07 8.58 4.82 (65.82 8.47 4.75)	<5.0
II-15	H	*n*-Dodecyl	49	Free	Oil	—	$C_{36}H_{56}N_2O_5$	596.4189[c] (596.4210)	5.62
I′-1[d]	H	iso-Pr							6.24
III-7	Me	H	65 (A)	Free	Oil	—	$C_{25}H_{34}N_2O_5$	442.2468[c] (442.2457)	5.56
III-8	Me	Me	88 (A)	Oxalate	137—138	EtOH	$C_{26}H_{36}N_2O_5 \cdot C_2H_2O_4$	61.53 7.01 5.12 (61.07 7.12 5.03)	6.76
III-9	Me	Et	61 (A)	Free	Oil	—	$C_{27}H_{38}N_2O_5$	470.2781[c] (470.2751)	7.44
III-10	Me	*n*-Pr	92 (A)	Oxalate	113—114	EtOH–Et_2O	$C_{28}H_{40}N_2O_5 \cdot C_2H_2O_4$	62.70 7.37 4.87 (62.48 7.41 4.85)	7.79
III-11	Me	*n*-Bu	81 (A)	Free	Oil	—	$C_{29}H_{42}N_2O_5$	498.3094[c] (498.3102)	7.21
III-12	Me	iso-Bu	85 (A)	Free	Oil	—	$C_{29}H_{42}N_2O_5$	498.3094[c] (498.3079)	7.53
III-13	Me	*n*-Hex	91 (A)	Free	Oil	—	$C_{31}H_{46}N_2O_5$	526.3407[c] (526.3378)	7.46
III-14	Me	*n*-Oct	81 (A)	Free	Oil	—	$C_{33}H_{50}N_2O_5$	554.3720[c] (554.3734)	5.06
III-15	Me	*n*-Dodecyl	88 (A)	Free	Oil	—	$C_{37}H_{58}N_2O_5$	610.4346[c] (610.4316)	5.33
I′-2[d]	Me	iso-Pr							8.05

a) Yield of free base. *b*) pA_2 values in the KCl-depolarized guinea-pig taenia coli. *c*) High mass data. The upper values are calculated and the lower ones are those found. *d*) Ref. 1.

were enhanced, but no compound was found to be superior to I′-2 having the iso-Pr group. Among these compounds, the iso-Pr (C_3) derivative was the most potent, lengthening or shortening of the carbon chain leading to a decrease in activity.

Finally, the effect of the R_4 substituent was examined (Table III). Here, the activity of the

TABLE III. Physicochemical and Pharmacological Data for R_4-Substituted α-Isopropyl-α-[(phenoxypropylamino)propyl]benzeneacetonitriles (II, III)



Compd. No.	R_1	R_4	Yield[a] (%) (Method)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	pA_2[b]
II-16	H	H	45	Oxalate	182—184	EtOH–Et_2O	$C_{26}H_{36}N_2O_4 \cdot C_2H_2O_4$	63.38 (62.99)	7.22 (7.34)	5.28 (5.14)	6.35
II-17	H	*o*-Me	45	Free	Oil	—	$C_{27}H_{38}N_2O_4$	454.2832[c] (454.2819)			6.43
II-18	H	*o*-*n*-Pr	39	Fumarate	151—152	EtOH	$C_{29}H_{42}N_2O_4 \cdot C_4H_4O_4$	66.20 (66.19)	7.74 (7.76)	4.68 (4.68)	6.47
II-19	H	*o*-OEt	92	Free	Oil	—	$C_{28}H_{40}N_2O_5$	484.2937[c] (484.2975)			6.76
II-20	H	*o*-F	57	Fumarate	147—148	EtOH–iso-Pr_2O	$C_{26}H_{35}FN_2O_4 \cdot C_4H_4O_4$	62.70 (62.80)	6.84 (6.94)	4.87 (4.87)	6.23
II-21	H	*o*-Cl	47	Fumarate	123—125	EtOH–iso-Pr_2O	$C_{26}H_{35}ClN_2O_4 \cdot C_4H_4O_4$	60.96 (61.26)	6.65 (6.80)	4.74 (4.44)	6.36
II-22	H	*o*-NO_2	53	Oxalate	155—156	EtOH–iso-Pr_2O	$C_{26}H_{35}N_3O_6 \cdot 1/2\,C_2H_2O_4$	61.12 (60.80)	6.84 (6.90)	7.92 (7.83)	6.52
II-23	H	*o*-NH_2	97	Oxalate	118—122	EtOH–Et_2O	$C_{26}H_{37}N_3O_4 \cdot C_2H_2O_4 \cdot H_2O$	59.67 (59.39)	7.33 (7.11)	7.46 (7.16)	6.15
II-24	H	*m*-Me	58	Free	Oil	—	$C_{27}H_{38}N_2O_4$	454.2832[c] (454.2807)			6.78
II-25	H	*m*-*tert*-Bu	41	Free	Oil	—	$C_{30}H_{44}N_2O_4$	496.3301[c] (496.3303)			6.71
II-26	H	*m*-OMe	39	Oxalate	134—135	EtOH	$C_{27}H_{38}N_2O_5 \cdot C_2H_2O_4$	62.13 (61.80)	7.19 (7.26)	5.00 (4.75)	6.83
II-27	H	*m*-F	45	Fumarate	158.5—159.5	EtOH	$C_{26}H_{35}FN_2O_4 \cdot C_4H_4O_4$	62.70 (62.47)	6.84 (6.98)	4.87 (4.82)	6.64
II-28	H	*m*-Cl	83	Fumarate	160—161	EtOH–iso-Pr_2O	$C_{26}H_{35}ClN_2O_4 \cdot C_4H_4O_4$	60.96 (61.20)	6.65 (6.78)	4.74 (4.45)	6.28
II-29	H	*m*-NO_2	64	Fumarate	142—144	EtOH	$C_{26}H_{35}N_3O_6 \cdot C_4H_4O_4$	59.89 (59.79)	6.53 (6.72)	6.98 (6.93)	6.38
II-30	H	*m*-NH_2	99	Oxalate	132—134	DMF–EtOH	$C_{26}H_{37}N_3O_4 \cdot C_2H_2O_4 \cdot H_2O$	59.67 (59.68)	7.33 (7.34)	7.46 (7.31)	6.01
II-31	H	*m*-CF_3	83	Fumarate	142.5—145	EtOH–Et_2O	$C_{27}H_{35}F_3N_2O_4 \cdot C_4H_4O_4$	59.61 (59.60)	6.29 (6.46)	4.48 (4.24)	6.74
II-32	H	*m*-CH_2OH	97	Fumarate	145—148	EtOH–iso-Pr_2O	$C_{27}H_{38}N_2O_5 \cdot C_4H_4O_4$	63.47 (63.26)	7.22 (7.58)	4.77 (4.57)	6.80
II-33	H	*p*-Me	51	Oxalate	135—136	EtOH–iso-Pr_2O	$C_{27}H_{38}N_2O_4 \cdot C_2H_2O_4$	63.95 (63.60)	7.40 (7.61)	5.14 (4.75)	6.58
II-34	H	*p*-*n*-Pr	50	Fumarate	151.5—152.5	EtOH–iso-Pr_2O	$C_{29}H_{42}N_2O_4 \cdot C_4H_4O_4$	66.20 (66.35)	7.74 (7.82)	4.68 (4.65)	6.43
II-35	H	*p*-*tert*-Bu	70	HCl	121.5—123	EtOH–Et_2O	$C_{30}H_{44}N_2O_4 \cdot HCl \cdot 1/2\,H_2O$	66.46 (66.76)	8.55 (8.83)	5.17 (5.05)	6.78
II-36	H	*p*-OMe	60	Fumarate	143—143.5	EtOH–iso-Pr_2O	$C_{27}H_{38}N_2O_5 \cdot C_4H_4O_4$	63.47 (63.48)	7.22 (7.42)	4.77 (4.73)	6.83
II-37	H	*p*-F	49	Free	Oil	—	$C_{26}H_{35}FN_2O_4$	458.2581[c] (458.2579)			6.72
II-38	H	*p*-Cl	46	Free	Oil	—	$C_{26}H_{35}ClN_2O_4$	474.2285[c] (474.2309)			6.49

TABLE III. (continued)

Compd. No.	R_1	R_4	Yield[a] (%) (Method)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	pA_2[b]
								476.2256[c] (476.2250)			
II-39	H	*p*-NO_2	38	Fumarate	189—190	EtOH	$C_{26}H_{35}N_3O_6 \cdot C_4H_4O_4$	59.89 (59.67	6.53 6.70	6.98 6.87)	6.60
II-40	H	*p*-NH_2	96	Oxalate	177—180	DMF–EtOH	$C_{26}H_{37}N_3O_4 \cdot 2C_2H_2O_4$	56.69 (56.46	6.50 6.47	6.61 6.67)	5.60
II-41	H	*p*-CN	77	Fumarate	188—190	MeOH	$C_{27}H_{35}N_3O_4 \cdot C_4H_4O_4$	64.01 (63.84	6.76 6.88	7.22 7.07)	6.99
II-42	H	*p*-CH_2OH	80	Fumarate	148—149.5	EtOH–iso-Pr_2O	$C_{27}H_{38}N_2O_5 \cdot C_4H_4O_4 \cdot 1/4\,H_2O$	62.98 (62.92	7.25 7.27	4.74 4.66)	5.69
II-43	H	2,3-$(OMe)_2$	70	Fumarate	132—133	EtOH–Et_2O	$C_{28}H_{40}N_2O_6 \cdot C_4H_4O_4 \cdot 1/2\,H_2O$	61.43 (61.30	7.25 7.49	4.48 4.25)	6.48
II-44	H	2,4-Me_2	63	Fumarate	136—138	EtOH–Et_2O	$C_{28}H_{40}N_2O_4 \cdot C_4H_4O_4 \cdot 1/2\,H_2O$	64.74 (64.70	7.64 7.72	4.72 4.58)	7.11
II-45	H	2,5-Me_2	52	Fumarate	143—145	EtOH	$C_{28}H_{40}N_2O_4 \cdot C_4H_4O_4 \cdot 1/2\,H_2O$	64.74 (64.76	7.64 7.90	4.72 4.61)	6.48
II-46	H	2,6-$(OMe)_2$	47	HCl	162.5—166	EtOH	$C_{28}H_{40}N_2O_6 \cdot HCl \cdot 1/2\,H_2O$	61.58 (61.84	7.75 7.86	5.13 5.05)	6.61
II-47	H	3,4-$(OMe)_2$	81	Fumarate	114.5—116.5	EtOH–Et_2O	$C_{28}H_{40}N_2O_6 \cdot C_4H_4O_4$	62.32 (62.03	7.19 7.58	4.54 4.27)	6.86
II-48	H	3,5-$(OMe)_2$	80	HCl	129—130	EtOH–Et_2O	$C_{28}H_{40}N_2O_6 \cdot HCl \cdot 1/2\,H_2O$	61.58 (61.32	7.75 7.64	5.13 4.84)	7.83
II-49	H	3,5-Me_2	90	Fumarate	131.5—132	EtOH–Et_2O	$C_{28}H_{40}N_2O_4 \cdot C_4H_4O_4 \cdot 1/2\,H_2O$	64.74 (64.80	7.64 7.67	4.72 4.48)	7.24
II-50	H	3,4,5-$(OMe)_3$	91	HCl	191—194	EtOH	$C_{29}H_{42}N_2O_7 \cdot HCl$	61.42 (61.20	7.64 7.68	4.94 4.75)	7.79
I′-1[d]	H	*o*-OMe									6.24
III-16	Me	H	77 (A)	Free	64—65	iso-Pr_2O	$C_{27}H_{38}N_2O_4$	71.34 (71.41	8.43 8.44	6.16 6.10)	8.19
III-17	Me	*o*-Me	57 (A)	Oxalate	132—133	EtOH	$C_{28}H_{40}N_2O_4 \cdot C_2H_2O_4$	64.50 (64.28	7.58 7.70	5.01 4.94)	8.31
III-18	Me	*o*-*n*-Pr	63 (A)	Free	Oil	—	$C_{30}H_{44}N_2O_4$	496.3301[c] (496.3296)			7.79
III-19	Me	*o*-OEt	84 (A)	Free	Oil	—	$C_{29}H_{42}N_2O_5$	498.3094[c] (498.3115)			8.10
III-20	Me	*o*-F	53 (A)	Oxalate	155—156	EtOH	$C_{27}H_{37}FN_2O_4 \cdot C_2H_2O_4$	61.91 (61.94	6.99 7.12	4.98 5.00)	7.95
III-21	Me	*o*-Cl	70 (A)	Free	Oil	—	$C_{27}H_{37}ClN_2O_4$	488.2442[c] (488.2424) 490.2412[c] (490.2395)			7.69
III-22	Me	*o*-NO_2	54 (A)	Free	Oil	—	$C_{27}H_{37}N_3O_6$	499.2682[c] (499.2699)			7.26
III-23	Me	*o*-NH_2	99	Oxalate	108—110	CH_3CN–Et_2O	$C_{27}H_{39}N_3O_4 \cdot 2C_2H_2O_4$	57.31 (57.15	6.67 6.87	6.47 6.41)	8.15
III-24	Me	*m*-Me	56[e] (B)	HCl	156—160	EtOH–Et_2O	$C_{28}H_{40}N_2O_4 \cdot HCl$	66.58 (66.50	8.18 8.38	5.55 5.47)	8.48
III-25	Me	*m*-*tert*-Bu	48 (B)	Free	Oil	—	$C_{31}H_{46}N_2O_4$	510.3458[c] (510.3470)			6.88
III-26	Me	*m*-OMe	59[f] (B)	Free	Oil	—	$C_{28}H_{40}N_2O_5$	484.2937[c] (484.2934)			9.00
III-27	Me	*m*-F	49 (A)	Oxalate	121.5—122.5	EtOH–iso-Pr_2O	$C_{27}H_{37}FN_2O_4 \cdot C_2H_2O_4$	61.91 (61.67	6.99 7.10	4.98 4.93)	8.29

TABLE III. (continued)

Compd. No.	R_1 R_4	Yield[a] (%) (Method)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C H N	pA_2[b]
III-28	Me *m*-Cl	87 (A)	Free	Oil	—	$C_{27}H_{37}ClN_2O_4$	488.2442[c] (488.2444) 490.2412[c] (490.2410)	8.36
III-29	Me *m*-NO_2	35 (A)	Free	Oil	—	$C_{27}H_{37}N_3O_6$	499.2682[c] (499.2662)	8.17
III-30	Me *m*-NH_2	92	Oxalate	94—97	CH_3CN–Et_2O	$C_{27}H_{39}N_3O_4 \cdot 3/2\,C_2H_2O_4$	59.59 7.00 6.95 (59.12 6.98 6.80)	8.13
III-31	Me *m*-CF_3	95 (A)	Fumarate	103—104.5	EtOH–Et_2O	$C_{28}H_{37}F_3N_2O_4 \cdot C_4H_4O_4$	60.18 6.47 4.39 (60.30 6.71 4.16)	8.06
III-32	Me *m*-CH_2OH	26 (B)	Free	Oil	—	$C_{28}H_{40}N_2O_5$	484.2937[c] (484.2958)	8.11
III-33	Me *p*-Me	97 (A)	Free	Oil	—	$C_{28}H_{40}N_2O_4$	468.2988[c] (468.2964)	7.61
III-34	Me *p*-*n*-Pr	85 (A)	Oxalate	135—136	EtOH–Et_2O	$C_{30}H_{44}N_2O_4 \cdot C_2H_2O_4$	65.51 7.90 4.77 (65.45 8.01 4.81)	6.88
III-35	Me *p*-*tert*-Bu	88 (A)	Free	Oil	—	$C_{31}H_{46}N_2O_4$	510.3458[c] (510.3497)	6.88
III-36	Me *p*-OMe	50 (A)	Oxalate	132—133.5	EtOH–iso-Pr_2O	$C_{28}H_{40}N_2O_5 \cdot C_2H_2O_4$	62.70 7.37 4.87 (62.51 7.40 4.74)	7.64
III-37	Me *p*-F	71 (A)	Free	Oil	—	$C_{27}H_{37}FN_2O_4$	472.2737[c] (472.2720)	8.02
III-38	Me *p*-Cl	61 (A)	Free	Oil	—	$C_{27}H_{37}ClN_2O_4$	488.2442[c] (488.2422) 490.2412[c] (490.2395)	7.73
III-39	Me *p*-NO_2	80 (A)	Free	Oil	—	$C_{27}H_{37}N_3O_6$	499.2682[c] (499.2684)	7.39
III-40	Me *p*-NH_2	94	Oxalate	87—90	CH_3CN–Et_2O	$C_{27}H_{39}N_3O_4 \cdot 2C_2H_2O_4 \cdot 1/2\,H_2O$	56.53 6.73 6.38 (56.69 6.75 6.10)	6.50
III-41	Me *p*-CN	84 (A)	Free	Oil	—	$C_{28}H_{37}N_3O_4$	479.2784[c] (479.2781)	7.64
III-42	Me *p*-CH_2OH	44 (A)	Free	Oil	—	$C_{28}H_{40}N_2O_5$	484.2937[c] (484.2949)	6.56
III-43	Me 2,3-$(OMe)_2$	82 (B)	Free	Oil	—	$C_{29}H_{42}N_2O_6$	514.3043[c] (514.3041)	8.23
III-44	Me 2,4-Me_2	83 (A)	Free	Oil	—	$C_{29}H_{42}N_2O_4$	482.3145[c] (482.3117)	7.97
III-45	Me 2,5-Me_2	84 (B)	Free	Oil	—	$C_{29}H_{42}N_2O_4$	482.3145[c] (482.3119)	8.68
III-46	Me 2,6-$(OMe)_2$	71 (A)	Free	Oil	—	$C_{29}H_{42}N_2O_6$	514.3043[c] (514.3027)	7.57
III-47	Me 3,4-$(OMe)_2$	79 (B)	Free	Oil	—	$C_{29}H_{42}N_2O_6$	514.3043[c] (514.3034)	8.35
III-48	Me 3,5-$(OMe)_2$	83 (B)	HCl	126—129	EtOH–Et_2O	$C_{29}H_{42}N_2O_6 \cdot HCl$	63.20 7.86 5.08 (62.90 8.22 5.01)	10.20[g]
III-49	Me 3,5-Me_2	61 (B)	Free	Oil	—	$C_{29}H_{42}N_2O_4$	482.3145[c] (482.3131)	9.53[g]
III-50	Me 3,4,5-$(OMe)_3$	77 (B)	HCl	117—118.5	EtOH–Et_2O	$C_{30}H_{44}N_2O_7 \cdot HCl \cdot H_2O$	60.14 7.91 4.68 (60.32 7.99 4.47)	9.32[g]
I′-2[d]	Me *o*-OMe Verapamil							8.05 7.88

a) Yield of free base. *b*) pA_2 values in the KCl-depolarized guinea-pig taenia coli. *c*) High mass data. The upper values are calculated and the lower ones are those found. *d*) Ref. 1. *e*) The yield by method A is 19%. *f*) The yield by method A is 0%. *g*) pA_2 values in the KCl-depolarized rabbit thoracic aorta.

N-H derivatives was also lower than that of the *N*-methylated derivatives. Of the *N*-Me derivatives, the non-substituted derivative (III-16) showed potent activity, $pA_2 = 8.19$. Among those in which a mono-substituent was introduced at the *o*-, *m*- or *p*-position on the B ring, the *o*-Me (III-17), *m*-Me (III-24), *m*-OMe (III-26), *m*-F (III-27) and *m*-Cl (III-28) derivatives were more potent than the non-substituted derivative. In particular, the activity of III-26 was $pA_2 = 9.00$, about ten times more potent than that of verapamil. Since the OMe and Me groups were thought to be favorable substituents for potent activity, di- or tri-substituted analogs (II-43—50, III-43—50) were synthesized. Among the *N*-H derivatives, the activities of II-48 and 50 were especially potent, being almost equal to that of verapamil. Furthermore, the activities of the corresponding *N*-methylated derivatives (III-43—50) were higher than those of the *N*-H derivatives. The derivatives having 3,5-$(OMe)_2$ (III-48), 3,5-Me_2 (III-49) and 3,4,5-$(OMe)_3$ (III-50) groups exhibited very high activities of more than $pA_2 = 9$ in the rabbit thoracic aorta, although their pA_2 values could not be calculated in the test using guinea-pig taenia coli owing to their non-competitive mode of action.

As a result of various conversions of the R_2, R_3 and R_4 substituents of I, especially the R_4 substituent, we found that III-26, 48, 49 and 50 showed potent Ca^{2+}-antagonistic activities of more than $pA_2 = 9$.

Investigations of the pharmacological activities of these compounds are in progress. The effects of the R_3 and R_4 substituents on the Ca^{2+}-antagonistic activity were quantitatively analyzed by using substituent parameters and regression analysis. The results will be reported in a later paper.

Experimental

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. Mass spectra (MS) were obtained on a Hitachi RMU-6M or JEOL DX-300 mass spectrometer. High-resolution 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-[3-[(3-Phenoxypropyl)amino]propyl]benzeneacetonitriles (II). α-Isopropyl-α-[3-[[3-(2-methoxyphenoxy)propyl]amino]propyl]benzeneacetonitrile (II-1)——A solution of α-(2-formylethyl)-α-isopropylbenzeneacetonitrile (IV-2, 2.85 g) and 3-(2-methoxyphenoxy)propylamine (2.00 g) in EtOH (100 ml) was refluxed for 1.5 h, then cooled with ice water, and $NaBH_4$ (0.51 g) was added. The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was acidified with 10% 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 (95 : 5) as eluents to give II-1 (3.80 g, 90%) as a colorless oil. IR ν_{max}^{liq} cm^{-1}: 2230 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.77, 1.19 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 3.79 (3H, s, OCH_3), 4.07 (2H, t, J=6.0 Hz, $NCH_2CH_2C\underline{H}_2O$), 6.88 (4H, s, aromatic protons). High MS *m/z*: 380.2435 (M^+) (Calcd for $C_{24}H_{32}N_2O_2$ 380.2464).

Compounds II-2—22, 24—29, 31—39 and 41—50 were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Tables I—III.

α-[3-[[3-(2-Aminophenoxy)propyl]amino]propyl]-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (II-23)——A solution of α-isopropyl-3,4,5-trimethoxy-α-[3-[[3-(2-nitrophenoxy)propyl]amino]propyl]benzeneacetonitrile (II-22, 4.78 g) in MeOH (100 ml) was hydrogenated over PtO_2 (50 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 to give II-23 (4.36 g, 97%) 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–Et_2O to give colorless crystals, mp 118—122 °C. IR ν_{max}^{KBr} cm^{-1}: 2210 (CN). ^{1}H-NMR (DMSO-d_6) δ: 0.71, 1.13 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 3.67 (3H, s, OCH_3), 3.80 (6H, s, 2×OCH_3), 3.96 (2H, t, J=6.0 Hz, $NCH_2CH_2C\underline{H}_2O$), 6.67 (2H, s, aromatic protons). *Anal.* Calcd for $C_{26}H_{37}N_3O_4 \cdot C_2H_2O_4 \cdot H_2O$: C, 59.67; H, 7.33; N, 7.46. Found: C, 59.39; H, 7.11; N, 7.16.

Compounds II-30 and 40 were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Table III.

Preparation of *N*-Methylated α-[3-[(3-Phenoxypropyl)amino]propyl]benzeneacetonitriles (III) (Method A). α-Isopropyl-α-[3-[*N*-[3-(2-methoxyphenoxy)propyl]-*N*-methylamino]propyl]benzeneacetonitrile (III-1)——A mixture of

II-1 (2.50 g), 37% formalin (6 ml) and HCOOH (6 ml) was stirred at 90—100 °C for 1 h. After cooling, the mixture 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 $CHCl_3$ as the eluent to give III-1 (1.80 g, 69%) as a pale yellow oil. IR ν_{max}^{liq} cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.76, 1.17 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 2.09 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 4.03 (2H, t, J=6.5 Hz, $NCH_2CH_2C\underline{H}_2O$), 6.89 (4H, s, aromatic protons). High MS m/z: 394.2615 (M^+) (Calcd for $C_{25}H_{34}N_2O_2$ 394.2620).

Compounds III-2—22, 27—29, 31, 33—39, 41—42, 44, and 46 were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Tables I—III.

(Method B). α-Isopropyl-3,4,5-trimethoxy-α-[3-[*N*-[3-(3-methoxyphenoxy)propyl]-*N*-methylamino]propyl]benzeneacetonitrile (III-26)——Formalin (37%, 3.54 ml) was added to a solution of α-isopropyl-3,4,5-trimethoxy-α-[3-[[3-(3-methoxyphenoxy)propyl]amino]propyl]benzeneacetonitrile (II-26, 1.90 g) in MeOH (40 ml) and the mixture was refluxed for 2 h, then cooled with ice water, and $NaBH_4$ (1.50 g) was added. The mixture was stirred at room temperature for 1 h, and then concentrated. The residue was acidified with aqueous HCl and extracted with AcOEt. The AcOEt layer was washed with aqueous NaOH and then 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 (97 : 3) as eluents to give III-26 (1.16 g, 59%) as a yellow oil. IR ν_{max}^{liq} cm^{-1}: 2230 (CN). ^{1}H-NMR ($CDCl_3$) δ: 0.79, 1.17 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 2.13 (3H, s, NCH_3), 3.78 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.86 (6H, s, 2×OCH_3), 3.97 (2H, t, J=6.5 Hz, $NCH_2CH_2C\underline{H}_2O$), 6.57 (2H, s, aromatic protons). High MS m/z: 484.2934 (M^+) (Calcd for $C_{28}H_{40}N_2O_5$ 484.2937).

Compounds III-24, 25, 32, 43, 45, and 47—50 were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Table III.

α-[3-[*N*-[3-(2-Aminophenoxy)propyl]-*N*-methylamino]propyl]-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (III-23)——A solution of α-isopropyl-3,4,5-trimethoxy-α-[3-[*N*-[3-(2-nitrophenoxy)propyl]-*N*-methylamino]propyl]-benzeneacetonitrile (III-22, 0.92 g) in MeOH (20 ml) was hydrogenated over PtO_2 (10 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 to give III-23 (0.86 g, 99%) 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 CH_3CN–Et_2O to give colorless crystals, mp 108—110 °C. IR ν_{max}^{KBr} cm^{-1}: 2240 (CN). ^{1}H-NMR (CD_3OD) δ: 0.79, 1.21 (each 3H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 2.80 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 3.85 (6H, s, 2×OCH_3), 4.11 (2H, t, J=5.5 Hz, $NCH_2CH_2C\underline{H}_2O$), 6.72 (2H, s, aromatic protons). *Anal.* Calcd for $C_{27}H_{39}N_3O_4 \cdot 2C_2H_2O_4$: C, 57.31; H, 6.67; N, 6.47. Found: C, 57.15; H, 6.87; N, 6.41.

Compounds III-30 and 40 were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Table III.

Preparation of α-Alkylbenzeneacetonitriles (VIII). α-Isopropyl-3,4,5-trimethoxybenzeneacetonitrile (VIII-1)[2]——$NaNH_2$ (10.00 g) was added to a solution of 3,4,5-trimethoxybenzeneacetonitrile (V-1, 50.00 g) in anhydrous tetrahydrofuran (THF, 500 ml). The mixture was stirred at room temperature for 0.5 h, then iso-PrBr (30.80 g) was added. The whole was stirred at room temperature for 4 h, 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 distilled to give VIII-1 (54.44 g, 90%) as a colorless oil, bp 170—173 °C (8 mmHg). IR ν_{max}^{liq} cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 1.06 (6H, d, J=6.5 Hz, $CH(C\underline{H}_3)_2$), 3.58 (1H, d, J=6.5 Hz, CHCN), 3.85 (3H, s, OCH_3), 3.87 (6H, s, 2×OCH_3), 6.50 (2H, s, aromatic protons). High MS m/z: 249.1367 (M^+) (Calcd for $C_{14}H_{19}NO_3$ 249.1365).

Compounds VIII-2,[3] 3, 4,[4] 5,[5] 6[6] and 7 were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Table IV.

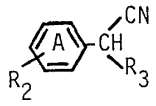
α-Methyl-3,4,5-trimethoxybenzeneacetonitrile (VIII-8)——NaOEt in absolute EtOH (prepared from Na (6.90 g) and absolute EtOH (150 ml)) was added to a mixture of 3,4,5-trimethoxybenzeneacetonitrile (V-1, 62.10 g) and $CO(OEt)_2$ (354.40 g) and the solvent was distilled away at 120—140 °C. After cooling, the residue was taken up in Et_2O and the precipitate was filtered off to give ethyl α-cyano-3,4,5-trimethoxybenzeneacetate sodium salt (VI, 105.00 g) as pale brown crystals.

MeI (128.00 g) was added to a solution of the above crystals in EtOH (1 l) and the mixture was refluxed for 1 h. The solvent was evaporated off under reduced pressure. 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 to give ethyl α-cyano-3,4,5-trimethoxy-α-methylbenzeneacetate (VII-1, 84.00 g) as a brown oil.

A solution of NaOH (8.20 g) in water (35 ml) was added to a solution of VII-1 (46.14 g) in MeOH (400 ml) and then the mixture was refluxed for 2 h. The solvent was evaporated off under reduced pressure. 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 distilled to give VIII-8 (31.50 g, 86% (from V-1)) as a pale yellow oil, bp 141—143 °C (5 mmHg). IR ν_{max}^{liq} cm^{-1}: 2240 (CN). ^{1}H-NMR ($CDCl_3$) δ: 1.64 (3H, d, J=7.0 Hz, CH_3), 3.84 (3H, s, OCH_3), 3.88 (6H, s, 2×OCH_3), 6.55 (2H, s, aromatic protons). High MS m/z: 221.1056 (M^+) (Calcd for $C_{12}H_{15}NO_3$ 221.1052).

Compounds VIII-9—15 were also prepared in the same manner as described above. The yields and

TABLE IV. Physicochemical Properties of α-Alkylbenzeneacetonitriles (VIII)



Compd. No.	R_2	R_3	Yield[a] (%)	bp (°C) (mmHg)	Formula	IR ν_{max}^{liq} cm^{-1} C≡N	Analysis (%) Calcd (Found) C H N
VIII-1[b]	3,4,5-$(OMe)_3$	iso-Pr	90	170—173 (8)	$C_{14}H_{19}NO_3$	2240	249.1365[c] (249.1367)
VIII-2[d]	H	iso-Pr	93	98—100 (6)	$C_{11}H_{13}N$	2240	159.1048[c] (159.1040)
VIII-3	2-OMe	iso-Pr	85	127—129 (8)	$C_{12}H_{15}NO$	2240	189.1154[c] (189.1160)
VIII-4[e]	3-OMe	iso-Pr	83	120—124 (6)	$C_{12}H_{15}NO$	2244	189.1154[c] (189.1152)
VIII-5[f]	4-OMe	iso-Pr	69	138—141 (8)	$C_{12}H_{15}NO$	2240	189.1154[c] (189.1173)
VIII-6[g]	3,4-$(OMe)_2$	iso-Pr	92	166—167 (7)	$C_{13}H_{17}NO_2$	2236	219.1259[c] (219.1257)
VIII-7	2,3,4-$(OMe)_3$	iso-Pr	65	135—149 (5)	$C_{14}H_{19}NO_3$	2240	249.1365[c] (249.1345)
VIII-8	3,4,5-$(OMe)_3$	Me	86	141—143 (5)	$C_{12}H_{15}NO_3$	2240	221.1052[c] (221.1056)
VIII-9	3,4,5-$(OMe)_3$	Et	86	155—163 (7)	$C_{13}H_{17}NO_3$	2240	235.1208[c] (235.1201)
VIII-10	3,4,5-$(OMe)_3$	*n*-Pr	81	159—160 (3)	$C_{14}H_{19}NO_3$	2230	249.1365[c] (249.1373)
VIII-11	3,4,5-$(OMe)_3$	*n*-Bu	81	150—161 (9)	$C_{15}H_{21}NO_3$	2220	263.1521[c] (263.1533)
VIII-12	3,4,5-$(OMe)_3$	iso-Bu	59	168—170 (8)	$C_{15}H_{21}NO_3$	2225	263.1521[c] (263.1527)
VIII-13	3,4,5-$(OMe)_3$	*n*-Hex	72	196—200 (5)	$C_{17}H_{25}NO_3$	2230	291.1834[c] (291.1821)
VIII-14	3,4,5-$(OMe)_3$	*n*-Oct	82	mp 43—44	$C_{19}H_{29}NO_3$	2245[h]	71.44 9.15 4.38 (71.11 9.50 4.32)
VIII-15	3,4,5-$(OMe)_3$	*n*-Dodecyl	63	mp 64—65	$C_{23}H_{37}NO_3$	2220[h]	73.56 9.93 3.73 (73.17 10.00 3.63)

a) Yield from benzeneacetonitriles (V). *b*) Ref. 2. *c*) High mass data. The upper values are calculated and the lower ones are those found. *d*) Ref. 3. *e*) Ref. 4. *f*) Ref. 5. *g*) Ref. 6. *h*) KBr disc.

characteristics of the products are listed in Table IV.

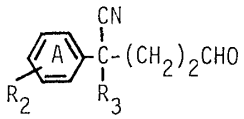
Preparation of α-(2-Formylethyl)benzeneacetonitriles (IV). α-(2-Formylethyl)-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (IV-1)——IV-1 was prepared *via* α-(3,3-diethoxypropyl)-α-isopropyl-3,4,5-trimethoxybenzeneacetonitrile (IX-1) from VIII-1 by the method previously described.[1]

Compounds IV-2—5, 6[2] and 7—15 were also prepared in the same manner. The yields and characteristics of the products are listed in Table V.

α-(2-Formylethyl)-3,4,5-trimethoxybenzeneacetonitrile (IV-16)——$NaNH_2$ (1.69 g) was added to a solution of 3,4,5-trimethoxybenzeneacetonitrile (V-1, 10.00 g) in ahydrous THF (100 ml). The mixture was stirred at room temperature for 0.5 h, then 3-chloropropionaldehyde diethylacetal (7.27 ml) was added and the whole was refluxed for 1.5 h. The reaction mixture was then 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 Al_2O_3 using benzene as the eluent to give α-(3,3-diethoxypropyl)-3,4,5-trimethoxybenzeneacetonitrile (IX-16, 10.50 g) as a pale yellow oil.

A mixture of IX-16 (7.50 g), $(COOH)_2 \cdot 2H_2O$ (3.36 g), acetone (50 ml) and water (24 ml) was refluxed for 1.5 h.

TABLE V. Physicochemical Properties of α-(2-Formylethyl)benzeneacetonitriles (IV)



Compd. No.	R_2	R_3	Yield[a] (%)	Formula	IR ν_{max}^{liq} cm^{-1} C≡N	IR C=O	High MS m/z (M^+) Calcd (Found)
IV-1[b]	3,4,5-$(OMe)_3$	iso-Pr	91	$C_{17}H_{23}NO_4$	2240	1726	305.1627 (305.1605)
IV-2	H	iso-Pr	49	$C_{14}H_{17}NO$	2230	1725	215.1310 (215.1313)
IV-3	2-OMe	iso-Pr	86	$C_{15}H_{19}NO_2$	2230	1725	245.1416 (245.1406)
IV-4	3-OMe	iso-Pr	58	$C_{15}H_{19}NO_2$	2230	1725	245.1416 (245.1406)
IV-5	4-OMe	iso-Pr	91	$C_{15}H_{19}NO_2$	2230	1725	245.1416 (245.1409)
IV-6[c]	3,4-$(OMe)_2$	iso-Pr	90	$C_{16}H_{21}NO_3$	2236	1722	275.1521 (275.1528)
IV-7	2,3,4-$(OMe)_3$	iso-Pr	77	$C_{17}H_{23}NO_4$	2220	1725	305.1627 (305.1617)
IV-8	3,4,5-$(OMe)_3$	Me	95	$C_{15}H_{19}NO_4$	2230	1725	277.1314 (277.1333)
IV-9	3,4,5-$(OMe)_3$	Et	71	$C_{16}H_{21}NO_4$	2230	1725	291.1471 (291.1489)
IV-10	3,4,5-$(OMe)_3$	*n*-Pr	86	$C_{17}H_{23}NO_4$	2225	1725	305.1627 (305.1646)
IV-11	3,4,5-$(OMe)_3$	*n*-Bu	97	$C_{18}H_{25}NO_4$	2225	1725	319.1784 (319.1796)
IV-12	3,4,5-$(OMe)_3$	iso-Bu	94	$C_{18}H_{25}NO_4$	2230	1725	319.1784 (319.1771)
IV-13	3,4,5-$(OMe)_3$	*n*-Hex	76	$C_{20}H_{29}NO_4$	2230	1725	347.2097 (347.2083)
IV-14	3,4,5-$(OMe)_3$	*n*-Oct	60	$C_{22}H_{33}NO_4$	2230	1725	375.2410 (375.2396)
IV-15	3,4,5-$(OMe)_3$	*n*-Dodecyl	91	$C_{26}H_{41}NO_4$	2225	1720	431.3036 (431.3020)
IV-16	3,4,5-$(OMe)_3$	H	60[d]	$C_{14}H_{17}NO_4$	2230	1725	263.1158 (263.1163)

a) Yield from α-alkylbenzeneacetonitriles (VIII). *b*) Ref. 1. *c*) Ref. 2. *d*) Yield from 3,4,5-trimethoxybenzeneacetonitrile (V-1).

The mixture was neutralized with aqueous K_2CO_3 and 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 to give IV-16 (5.40 g, 60% (from V-1)) as a yellow oil. IR ν_{max}^{liq} cm^{-1}: 2230 (CN), 1725 (CO). ^{1}H-NMR ($CDCl_3$) δ: 3.84 (3H, s, OCH_3), 3.87 (6H, s, $2 \times OCH_3$), 6.53 (2H, s, aromatic protons), 9.80 (1H, s, CHO). High MS m/z: 263.1163 (M^+) (Calcd for $C_{14}H_{17}NO_4$ 263.1158).

Pharmacology

Ca^{2+}-Antagonistic Activity in Isolated Guinea-Pig Taenia Coli——The procedure was carried out in the manner previously described.[1]

Ca^{2+}-Antagonistic Activity in Isolated Rabbit Thoracic Aorta——The procedure was performed according to the method of Campbell *et al.*[7] Briefly, the rabbit thoracic aorta was suspended under a resting tension of 3.0 g in an organ bath maintained at 37 ± 1 °C. After depolarization, the contraction induced by cumulative application of $CaCl_2$ was recorded isometrically. Compounds were applied 30 min before $CaCl_2$ application and their pA_2 values were calculated from dose ratios estimated graphically from the parallel shifts of concentration-response curves to $CaCl_2$.

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