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Novel Phenoxyalkylamine Derivatives. I. Synthesis and Pharmacological Activities of α -Isopropyl- α -[(phenoxyalkylamino)alkyl]-benzeneacetonitrile Derivatives

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Novel α -isopropyl- α -[(phenoxyalkylamino)alkyl]benzeneacetonitrile derivatives, the phenoxyalkylamino moiety of which was introduced in place of the phenethylamino moiety of verapamil (known to be an excellent Ca^{2+} -antagonist), were synthesized and their pharmacological activities were evaluated. These compounds exhibited α -blocking activity along with Ca^{2+} -antagonistic activity, and their activities were influenced by the substituent on the amino nitrogen atom and by the number of carbons between the nitrogen atom and the benzeneacetonitrile moiety (m) as well as that between it and the phenoxy moiety (n). Among these compounds, the N -methyl derivative (**2h**) where $m=n=3$, was found to possess a high Ca^{2+} -antagonistic activity and the N -H derivative (**2c**) in which $m=3$ and $n=2$ possessed a high α -blocking activity.

Keywords—calcium ion-antagonistic activity; α -blocking activity; phenoxyalkylamine; structure-activity relationship; α -isopropyl- α -[(phenoxyalkylamino)alkyl]benzeneacetonitrile

We have been interested in variations of each activity of compounds exhibiting several types of pharmacological actions as a result of structural modifications. As a part of our studies on cardiovascular agents, we have focused our attention on verapamil,¹⁾ which is a Ca^{2+} -antagonist widely used in clinical practice, and planned a number of structural modifications starting from verapamil. We designed some novel phenoxyalkylamine derivatives (**1**) having the phenoxyalkylamino moiety, which is known to be a mother structure of α -blockers,²⁾ instead of the phenethylamino moiety present in verapamil, with the aim of investigating their Ca^{2+} -antagonistic and/or α -blocking activities.

The α,β -blockers such as labetalol³⁾ or amosulalol⁴⁾ are regarded as being representative of compounds having dual types of pharmacological activity in one type of structure. However, hardly any investigations of paired Ca^{2+} -antagonistic and α -blocking activity have been carried out up to the present.

Our designed compound (**1**) possesses several substructures which can be modified, namely, the carbon chains (m, n), the substituents on the nitrogen atom (R_1), the A ring of the benzeneacetonitrile moiety (R_2), the quaternary carbon atom (R_3), the B ring of the phenoxy moiety (R_4) and the CN group. First, we investigated the effects of changing the carbon chains (m, n) and N -substituent (R_1) of **1** on its Ca^{2+} -antagonistic and α -blocking activities. We fixed the other positions in the molecule as follows. The A ring structure was kept as 3,4,5-trimethoxyphenyl, which showed a more potent action in a Ca^{2+} -antagonist than the 3,4-dimethoxyphenyl moiety.⁵⁾ The R_3 substituent on the quaternary C and the CN group were held as iso-Pr and CN groups, as in verapamil. The R_4 substituent on the phenoxy benzene ring (B ring) was the *o*-OMe group, which is one of the substituents expected to show potent

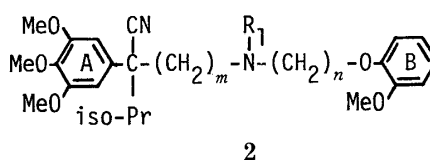
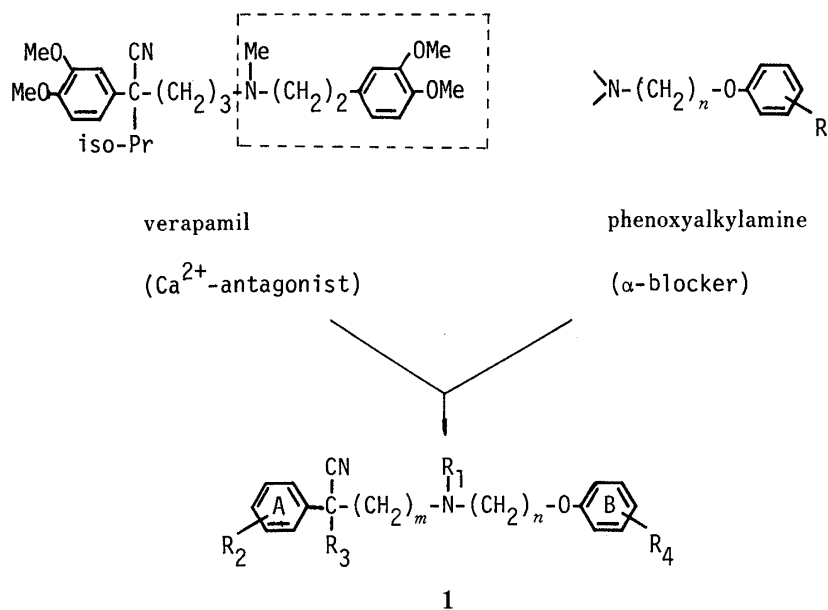


Chart 1

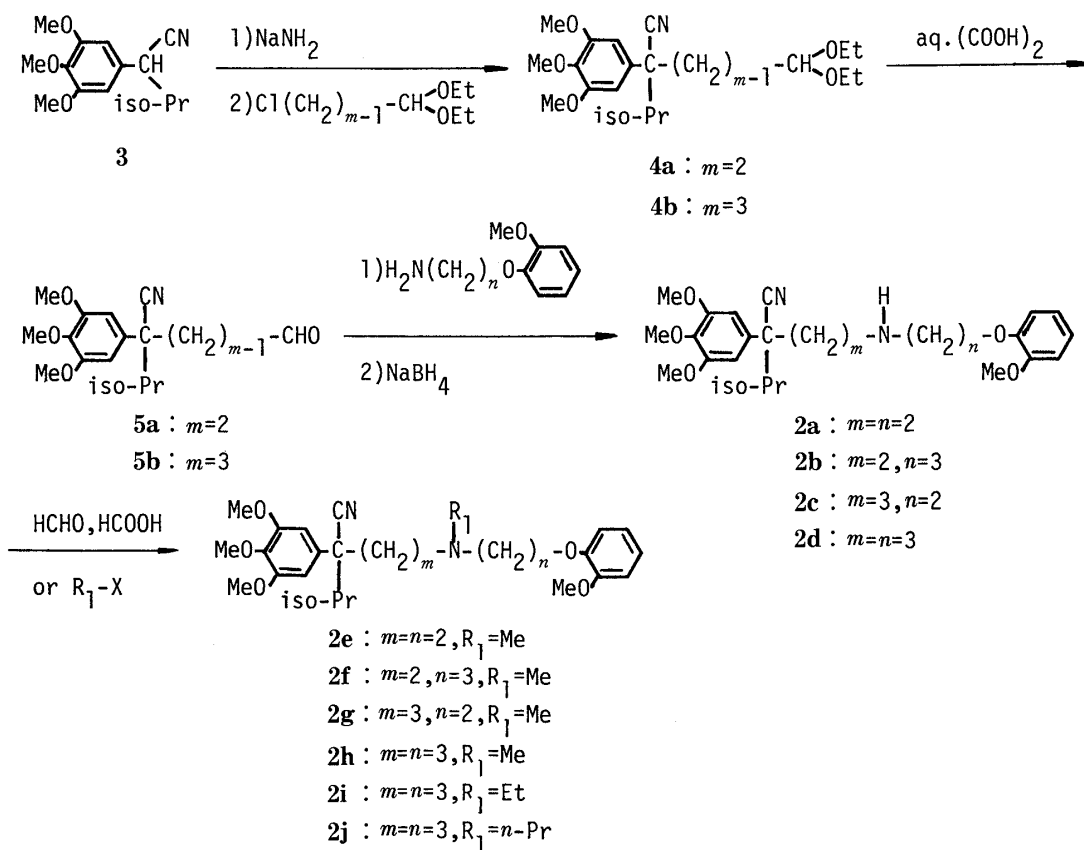


Chart 2

α -blocking activity.^{2a)} We report here the synthesis and the pharmacological activities of these novel α -isopropyl- α -[(phenoxyalkylamino)alkyl]benzeneacetonitrile derivatives (**2**).

Synthesis

α -Isopropyl- α -[(phenoxyalkylamino)alkyl]benzeneacetonitrile derivatives (**2a—j**) were prepared as shown in Chart 2.

Of the two key intermediate aldehydes (**5a, b**), **5b** was obtained by the method of Ferdinand,⁶⁾ that is, α -isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**3**) was alkylated with 3-chloropropionaldehyde diethylacetal to give the acetal (**4b**), which was subsequently hydrolyzed with aqueous oxalic acid to yield the aldehyde (**5b**). The novel aldehyde (**5a**) was also obtained in the same manner from **3** in an almost equivalent yield. The reaction of **5a** or **5b** with *o*-methoxyphenoxyalkylamines⁷⁾ gave the desired *N*-H derivatives (**2a—d**), which were reacted with formalin and formic acid or alkyl halide to give the *N*-alkyl derivatives (**2e—j**).

The physicochemical properties of the obtained compounds (**2a—j**) are summarized in Table I.

TABLE I. Physicochemical and Pharmacological Data for α -Isopropyl- α -[(phenoxyalkylamino)alkyl]-benzeneacetonitriles

Compd. No.	<i>m</i>	<i>n</i>	<i>R</i> ₁	Yield ^{a)} (%)	Salt	mp (°C)	Recrystn. solvent	Formula	Analysis (%)			Ca ²⁺ + ^{b)} pA ₂	α^c pA ₂
									Calcd	Found	N		
									C	H			
2a	2	2	H	46	Free	Oil	—	C ₂₅ H ₃₄ N ₂ O ₅	442.2468 ^{d)} (442.2475)			5.79	7.09
2b	2	3	H	36	HCl	174—175	EtOH	C ₂₆ H ₃₆ N ₂ O ₅ ·HCl	63.34 7.56 5.68 (63.26 7.55 5.57)			6.59	6.65
2c	3	2	H	32	Fumarate	149—150	EtOH— iso-Pr ₂ O	C ₂₆ H ₃₆ N ₂ O ₅ ·C ₄ H ₄ O ₄	62.92 7.04 4.89 (62.62 7.30 4.76)			6.59	8.42
2d	3	3	H	88	Fumarate	112—113	EtOH— Et ₂ O	C ₂₇ H ₃₈ N ₂ O ₅ ·C ₄ H ₄ O ₄	63.47 7.22 4.77 (63.07 7.30 4.70)			6.24	6.61
2e	2	2	Me	84	Oxalate	147—148	EtOH— iso-Pr ₂ O	C ₂₆ H ₃₆ N ₂ O ₅ ·C ₂ H ₂ O ₄	61.53 7.01 5.12 (61.43 7.22 5.01)			6.76	6.15
2f	2	3	Me	57	Free	Oil	—	C ₂₇ H ₃₈ N ₂ O ₅	470.2781 ^{d)} (470.2779)			6.36	6.19
2g	3	2	Me	36	HCl	146—148	EtOH— iso-Pr ₂ O	C ₂₇ H ₃₈ N ₂ O ₅ ·HCl	63.96 7.75 5.52 (63.75 8.01 5.42)			7.20	7.04
2h	3	3	Me	90	Free	Oil	—	C ₂₈ H ₄₀ N ₂ O ₅	484.2937 ^{d)} (484.2935)			8.05	6.73
2i	3	3	Et	74	Free	Oil	—	C ₂₉ H ₄₂ N ₂ O ₅	498.3094 ^{d)} (498.3081)			7.36	6.72
2j	3	3	<i>n</i> -Pr	78	Free	Oil	—	C ₃₀ H ₄₄ N ₂ O ₅	512.3250 ^{d)} (512.3238)			6.33	6.60
Verapamil												7.88	5.79
Prazosin ^{e)}												<5	8.63

a) Yield of free base. b) pA₂ values in the KCl-depolarized guinea-pig taenia coli. c) pA₂ values in the rabbit thoracic aorta. d) High mass data. The upper values are calculated and the lower ones are those found. e) A representative α -blocker.⁸⁾

Results and Discussion

The Ca^{2+} -antagonistic activity was tested by using KCl-depolarized guinea-pig taenia coli and is expressed as the pA_2 value. The α -blocking activity was tested using rabbit thoracic aorta and is also shown as the pA_2 value. The data obtained are listed in Table I.

First, our attention was drawn to the resulting Ca^{2+} -antagonistic activities. The $\text{R}_1 = \text{H}$ derivatives (**2a—d**) were less potent than verapamil, the pA_2 values being 5.8—6.6, but *N*-methylation of these compounds increased these activities, except for **2b** with $m=2$, $n=3$. Among these compounds with the $\text{R}_1 = \text{Me}$ group, the most potent compound was **2h** with $m=3$, $n=3$, the pA_2 value of which was 8.05 (higher than that of verapamil), followed by **2g** with $m=3$, $n=2$, and then by **2e** with $m=2$, $n=2$. The extension of the $\text{R}_1 = \text{Me}$ group of **2h** to an Et (**2i**) or *n*-Pr group (**2j**) somewhat decreased the activity. This result indicates that the $\text{R}_1 = \text{Me}$ derivative with $m=3$ and $n=3$ in the carbon chains is the most favorable in terms of Ca^{2+} -antagonistic activity.

Next, our attention was focused on the α -blocking activities. The $\text{R}_1 = \text{H}$ derivatives (**2a—d**) were more potent than verapamil, and **2c** with $m=3$, $n=2$ was the most effective, with a pA_2 value of 8.42. The order of activity was **2c** ($m=3$, $n=2$), **2a** ($m=2$, $n=2$), **2b** ($m=2$, $n=3$) and **2d** ($m=3$, $n=3$). *N*-Methylation of these compounds decreased the activity, except in the case of **2d** with $m=3$, $n=3$. This shows that the most favorable substructure for α -blocking activity is the $\text{R}_1 = \text{H}$ one with $m=3$ and $n=2$ in the carbon chains.

In summary, the replacement of the phenethylamino moiety of verapamil by the phenoxyalkylamino moiety was shown to introduce α -blocking activity as well as the Ca^{2+} -antagonistic activity into the molecule, and these activities were influenced by changes in the carbon chain lengths (m , n) and the *N*-substituent (R_1).

In subsequent papers, we will report on the qualitative and quantitative structure-activity relationships for Ca^{2+} -antagonistic activity in this series of compounds with the highly favorable $m=3$ and $n=3$ carbon chains and with $\text{R}_1 = \text{H}$ or Me as the *N*-substituent, where the substituents on the A ring (R_2), the quaternary carbon atom (R_3) and the B ring (R_4) are variously changed.

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 ($^1\text{H-NMR}$) spectra were measured with a JEOL FX-90Q spectrometer using tetramethylsilane as an internal standard.

α -Isopropyl-3,4,5-trimethoxy- α -[2-[[2-(2-methoxyphenoxy)ethyl]amino]ethyl]benzeneacetonitrile (2a**)**—A solution of α -(formylmethyl)- α -isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**5a**, 6.00 g) and 2-(2-methoxyphenoxy)ethylamine (2.75 g) in MeOH (50 ml) was refluxed for 1 h, then cooled with ice water, and NaBH_4 (0.76 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 was made alkaline with K_2CO_3 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 as the eluent to give **2a** (3.34 g, 46%) as a pale yellow oil. IR $\nu_{\text{max}}^{\text{liq}}$ cm^{-1} : 2230 (CN). $^1\text{H-NMR}$ (CDCl_3) δ : 0.81, 1.21 (each 3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.93 (2H, t, $J=5.0$ Hz, $\text{NCH}_2\text{CH}_2\text{O}$), 3.84, 3.85 (each 3H, s, $2 \times \text{OCH}_3$), 3.87 (6H, s, $2 \times \text{OCH}_3$), 4.05 (2H, t, $J=5.0$ Hz, $\text{NCH}_2\text{CH}_2\text{O}$), 6.59 (2H, s, aromatic protons), 6.89 (4H, s, aromatic protons). High MS m/z : 442.2475 (M^+) (Calcd for $\text{C}_{25}\text{H}_{34}\text{N}_2\text{O}_5$ 442.2468).

Compounds **2b—d** were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Table I.

α -Isopropyl-3,4,5-trimethoxy- α -[2-[*N*-[2-(2-methoxyphenoxy)ethyl]-*N*-methylamino]ethyl]benzeneacetonitrile (2e**)**—A mixture of **2a** (2.34 g), 37% formalin (7 ml) and HCOOH (14 ml) was stirred at 90 °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 **2e** (2.03 g, 84%) as a pale yellow oil. IR $\nu_{\text{max}}^{\text{liq}} \text{ cm}^{-1}$: 2240 (CN). $^1\text{H-NMR}$ (CDCl_3) δ : 0.81, 1.21 (each 3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.33 (3H, s, NCH_3), 2.80 (2H, t, $J=6.0$ Hz, $\text{NCH}_2\text{CH}_2\text{O}$), 3.84 (3H, s, OCH_3), 3.85 (9H, s, $3 \times \text{OCH}_3$), 4.03 (2H, t, $J=6.0$ Hz, $\text{NCH}_2\text{CH}_2\text{O}$), 6.58 (2H, s, aromatic protons), 6.88 (4H, s, aromatic protons).

The obtained free base was converted into the oxalate in a usual manner, and the resulting salt was recrystallized from $\text{EtOH-iso-Pr}_2\text{O}$ to give colorless needles, mp 147–148 °C. Anal. Calcd for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_5 \cdot \text{C}_2\text{H}_2\text{O}_4$: C, 61.53; H, 7.01; N, 5.12. Found: C, 61.43; H, 7.22; N, 5.01.

Compounds **2f–h** were also prepared in the same manner as described above. The yields and characteristics of the products are listed in Table I.

α -Isopropyl-3,4,5-trimethoxy- α -[3-[*N*-[3-(2-methoxyphenoxy)propyl]-*N*-ethylamino]propyl]benzeneacetonitrile (2i**)**—A suspension of α -isopropyl-3,4,5-trimethoxy- α -[3-[3-(2-methoxyphenoxy)propyl]amino]propyl]benzeneacetonitrile (**2d**, 2.00 g), K_2CO_3 (0.39 g) and EtI (0.72 g) in EtOH (25 ml) was refluxed for 4 h and then concentrated. Water was added to the residue and the mixture was 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 $\text{CHCl}_3\text{-MeOH}$ (98:2) as eluents to give **2i** (1.56 g, 74%) as a pale yellow oil. IR $\nu_{\text{max}}^{\text{liq}} \text{ cm}^{-1}$: 2220 (CN). $^1\text{H-NMR}$ (CDCl_3) δ : 0.80, 1.18 (each 3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.95 (3H, t, $J=7.0$ Hz, NCH_2CH_3), 2.44 (2H, q, $J=7.0$ Hz, NCH_2CH_3), 3.84 (6H, s, $2 \times \text{OCH}_3$), 3.85 (6H, s, $2 \times \text{OCH}_3$), 4.03 (2H, t, $J=6.5$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{O}$), 6.57 (2H, s, aromatic protons), 6.89 (4H, s, aromatic protons). High MS m/z : 498.3081 (M^+) (Calcd for $\text{C}_{29}\text{H}_{42}\text{N}_2\text{O}_5$ 498.3094).

α -Isopropyl-3,4,5-trimethoxy- α -[3-[*N*-[3-(2-methoxyphenoxy)propyl]-*N*-propylamino]propyl]benzeneacetonitrile (2j**)**—A suspension of **2d** (2.04 g), K_2CO_3 (0.40 g) and *n*-PrBr (0.64 g) in EtOH (25 ml) was refluxed for 11.5 h, and then treated by the same procedure as **2i** to give **2j** (1.73 g, 78%) as a pale yellow oil. IR $\nu_{\text{max}}^{\text{liq}} \text{ cm}^{-1}$: 2225 (CN). $^1\text{H-NMR}$ (CDCl_3) δ : 0.80, 1.18 (each 3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 0.82 (3H, t, $J=7.0$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_3$), 3.85 (6H, s, $2 \times \text{OCH}_3$), 3.86 (6H, s, $2 \times \text{OCH}_3$), 4.03 (2H, t, $J=6.5$ Hz, $\text{NCH}_2\text{CH}_2\text{CH}_2\text{O}$), 6.57 (2H, s, aromatic protons), 6.89 (4H, s, aromatic protons). High MS m/z : 512.3238 (M^+) (Calcd for $\text{C}_{30}\text{H}_{44}\text{N}_2\text{O}_5$ 512.3250).

α -(2-Formylethyl)- α -isopropyl-3,4,5-trimethoxybenzeneacetonitrile (5b**)**—**5b** was prepared by the method of Ferdinand.⁶ NaNH_2 (44.90 g) and then 3-chloropropionaldehyde diethylacetal (95.30 g) were added to a solution of α -isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**3**, 118.60 g) in anhydrous tetrahydrofuran (THF, 1000 ml) at room temperature with stirring. The mixture was refluxed for 3.5 h, 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 to give α -(3,3-diethoxypropyl)- α -isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**4b**, 180.45 g) as a brown oil.

The obtained **4b** was dissolved in acetone (1200 ml) and $(\text{COOH})_2 \cdot 2\text{H}_2\text{O}$ (72.00 g) in water (510 ml) was added to the solution. The mixture was refluxed for 1.5 h, then 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 **5b** (132.16 g, 91%) as a brown oil. IR $\nu_{\text{max}}^{\text{liq}} \text{ cm}^{-1}$: 2240 (CN), 1726 (CO). $^1\text{H-NMR}$ (CDCl_3) δ : 0.83, 1.23 (each 3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 3.85 (3H, s, OCH_3), 3.86 (6H, s, $2 \times \text{OCH}_3$), 6.55 (2H, s, aromatic protons), 9.68 (1H, s, CHO). High MS m/z : 305.1605 (M^+) (Calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4$ 305.1627).

α -(Formylmethyl)- α -isopropyl-3,4,5-trimethoxybenzeneacetonitrile (5a**)**— NaNH_2 (16.80 g) and then α -chloroacetaldehyde diethylacetal (39.80 g) were added to a solution of **3** (53.40 g) in anhydrous THF (500 ml) at room temperature with stirring. The mixture was refluxed for 4 h, and then treated by the same procedure as **4b** to give α -(2,2-diethoxyethyl)- α -isopropyl-3,4,5-trimethoxybenzeneacetonitrile (**4a**, 78.00 g) as a brown oil.

The obtained **4a** was dissolved in acetone (580 ml) and aqueous 10% $(\text{COOH})_2$ (240 ml) was added to the solution. The mixture was refluxed for 6 h, and then treated by the same procedure as **5b** to give **5a** (62.20 g, quant.) as a brownish yellow oil. IR $\nu_{\text{max}}^{\text{liq}} \text{ cm}^{-1}$: 2230 (CN), 1730 (CO). $^1\text{H-NMR}$ (CDCl_3) δ : 0.89, 1.20 (each 3H, d, $J=6.5$ Hz, $\text{CH}(\text{CH}_3)_2$), 2.97 (2H, d, $J=2.0$ Hz, CH_2CHO), 3.85 (3H, s, OCH_3), 3.87 (6H, s, $2 \times \text{OCH}_3$), 6.60 (2H, s, aromatic protons), 9.55 (1H, br s, CHO). High MS m/z : 291.1454 (M^+) (Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4$ 291.1471).

Pharmacology

Ca^{2+} -Antagonistic Activity in Isolated Taenia Coli—The taenia coli was isolated from Hartley guinea-pig and suspended under a resting tension of 0.5 g in an organ bath maintained at 38 ± 1 °C. The preparation was depolarized by Ca^{2+} -free, high- K^+ solution aerated with 95% O_2 and 5% CO_2 . Ca^{2+} -free, high- K^+ solution was prepared by removing CaCl_2 from Locke Ringer solution and increasing the concentration of KCl to 100 mM. After an equilibration period, the contractions induced by cumulative applications of CaCl_2 were recorded isototically. Compounds were applied 30 min before CaCl_2 application and their pA_2 values (pA_2 is the negative log of the antagonist concentration required to maintain a constant response when the concentration of the agonist is doubled) were calculated from dose ratios estimated graphically from the parallel shifts of concentration-response curves to CaCl_2 .

α -Adrenoceptor-Blocking Activity in Isolated Aorta—The thoracic aorta was isolated from rabbit and suspended under a resting tension of 2.0 g in an organ bath maintained at 37 ± 1 °C. After equilibration in Krebs-Henseleit solution aerated with 95% O_2 and 5% CO_2 , the contraction induced by cumulative application of

noradrenaline was recorded isometrically. Compounds were applied 30 min before noradrenaline application and their pA_2 values were calculated from dose ratios estimated graphically from the parallel shifts of concentration-response curves to noradrenaline.

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