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Synthesis and Spasmolytic Activity of Aminoalkyl 2-Substituted-2-(1,2-benzisoxazol-3-yl)acetates

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Several aminoalkyl esters of 2-(1,2-benzisoxazol-3-yl)-2-cyclohexylacetic acid, 1-(1,2-benzisoxazol-3-yl)-1-cyclopentanecarboxylic acid, and 1-(1,2-benzisoxazol-3-yl)-1-cyclohexanecarboxylic acid and their quaternary ammonium salts were synthesized. The anticholinergic (anti-Ach) and musculotropic (anti-KCl) activities of these compounds were examined. Among them, 3-(*N*,*N*-diethylamino)-propyl 2-(1,2-benzisoxazol-3-yl)-2-cyclohexylacetate (**8b**) showed potent anti-Ach and anti-KCl activities.

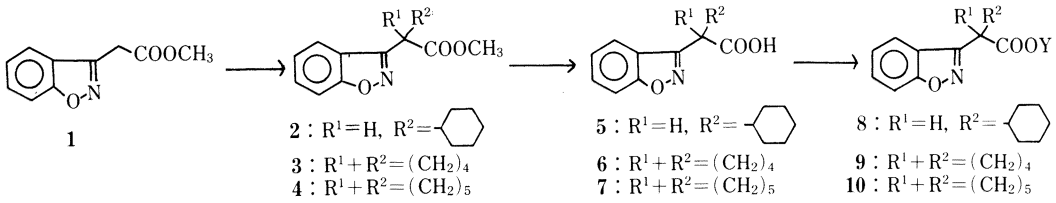
Keywords——1,2-benzisoxazole derivative; aminoalkyl ester; musculotropic activity; antimuscarinic activity; antispasmodic; structure–activity relationship

Although a number of compounds having antimuscarinic activity are used clinically as antispasmodics, there is an unavoidable problem of their undesirable anticholinergic side effects such as blurred vision, dry mouth, and tachycardia. As one approach to reducing these side effects, Toson *et al.* mentioned that an antispasmodic agent with balanced antimuscarinic and papaverine-like musculotropic activities exerts antispasmodic action with less side effects than a pure antimuscarinic agent and with less cardiovascular effect than a typical smooth muscle relaxant such as papaverine.[1] They claimed that 2-diethylamino-1-methylethyl *cis*-2-cyclohexyl-2-hydroxy-1-cyclohexanecarboxylate (rociverine) is the first antispasmodic agent with balanced antimuscarinic activity (sometimes referred to as anticholinergic or anti-Ach activity) and musculotropic activity (sometimes referred to as papaverine-like or anti-KCl activity).

As a part of our search for new antispasmodic agents, we reported the syntheses and spasmolytic activities of 3-substituted-1,2-benzisoxazole derivatives in previous papers.[2] Since we were interested in agents having both antimuscarinic and musculotropic activities, and considering that rociverine has two cyclohexyl rings, we prepared aminoalkyl esters of 1,2-benzisoxazole-3-acetic acid having a cycloalkyl ring such as cyclohexyl, tetramethylene, and pentamethylene at the α-position in the hope of finding new antispasmodics having dual modes of action. This paper deals with the synthesis of these compounds and the results of their primary pharmacological evaluations.

Chemistry

The target esters (**8**, **9**, and **10**) were synthesized as shown in Chart 1. Methyl 1,2-benzisoxazole-3-acetate (**1**) was converted to **2** by treatment with sodium hydride (NaH) (1 eq) in dimethylformamide, followed by alkylation with cyclohexyl iodide (1.9 eq) in 33% yield. This reaction also afforded a small amount of 2*H*-azirine derivative as a by-product.[3] The carboxylic acid (**5**) was prepared by hydrolysis of **2** with sodium hydroxide (NaOH) (1.5 eq) in aqueous ethanol. The carboxylic acids (**6** and **7**) were also obtained on treatment of **1** with



1

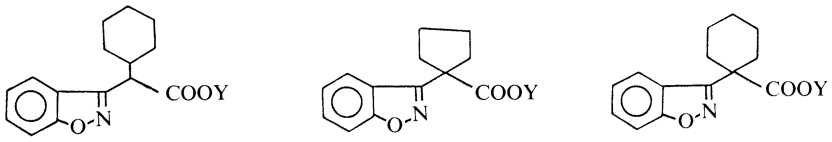
2 : R^1=H, R^2=⬡
3 : $R^1+R^2=(CH_2)_4$
4 : $R^1+R^2=(CH_2)_5$

5 : R^1=H, R^2=⬡
6 : $R^1+R^2=(CH_2)_4$
7 : $R^1+R^2=(CH_2)_5$

8 : R^1=H, R^2=⬡
9 : $R^1+R^2=(CH_2)_4$
10 : $R^1+R^2=(CH_2)_5$

Chart 1

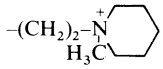
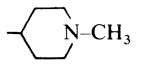
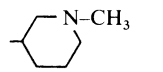
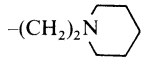
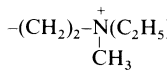
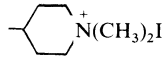
TABLE I. Pharmacological Data



8 **9** **10**

Compound No.	Y	anti-Ach[a] ID_{50} (mM)	anti-KCl[b] ID_{50} (mM)
8a	$-(CH_2)_2-N(C_2H_5)_2$	2.7×10^{-4}	2.3×10^{-3}
8b	$-(CH_2)_3-N(C_2H_5)_2$	3.5×10^{-4}	3.8×10^{-4}
8c	$-(CH_2)_4-N(C_2H_5)_2$	1.0×10^{-3}	NT
8d	$-CH(CH_3)-CH_2-N(C_2H_5)_2$	9.3×10^{-4}	5.5×10^{-3}
8e	$-CH(CH_3)-(CH_2)_3-N(C_2H_5)_2$	1.4×10^{-3}	NT
8f	⬡ N–CH_3	8.4×10^{-5}	1.0×10^{-2}
8g	⬡ N–Et	1.0×10^{-4}	NT
8h	$-(CH_2)_2-$⬡ N	8.9×10^{-4}	5.9×10^{-3}
8i	$-(CH_2)_2-\overset{+}{N}(CH_3)(C_2H_5)_2I^-$	5.2×10^{-4}	NT
8j	$-(CH_2)_3-\overset{+}{N}(CH_3)(C_2H_5)_2I^-$	4.0×10^{-4}	$>5.0\times10^{-2}$
8k	⬡ $\overset{+}{N}(CH_3)_2I^-$	2.3×10^{-5}	$>5.0\times10^{-2}$
9a	$-(CH_2)_2-N(C_2H_5)_2$	8.8×10^{-4}	NT
9b	$-(CH_2)_3-N(C_2H_5)_2$	7.8×10^{-4}	3.8×10^{-2}
9c	$-CH(CH_3)-CH_2-N(C_2H_5)_2$	3.3×10^{-3}	NT
9d	⬡ N–CH_3	1.1×10^{-4}	$>1.0\times10^{-1}$
9e	$-(CH_2)_2-$⬡ N	5.0×10^{-4}	$>5.0\times10^{-2}$
9f	$-(CH_2)_2-\overset{+}{N}(CH_3)(C_2H_5)_2I^-$	2.3×10^{-4}	$>1.0\times10^{-1}$
9g	⬡ $\overset{+}{N}(CH_3)_2I^-$	5.3×10^{-5}	NT

TABLE I. (continued)

Compound No.	Y	anti-Ach[a] ID_{50} (mM)	anti-KCl[b] ID_{50} (mM)
9h		6.6×10^{-4}	NT
10a	$-(CH_2)_2-N(C_2H_5)_2$	8.7×10^{-4}	NT
10b	$-(CH_2)_3N(C_2H_5)_2$	5.4×10^{-4}	8.5×10^{-3}
10c	$-CH(CH_3)-CH_2N(C_2H_5)_2$	3.9×10^{-4}	NT
10d		8.7×10^{-5}	$>5.0 \times 10^{-2}$
10e		2.1×10^{-3}	NT
10f		5.9×10^{-4}	NT
10g		3.7×10^{-4}	$>1.0 \times 10^{-1}$
10h		2.9×10^{-5}	$>1.0 \times 10^{-1}$
Scopolamine-*N*-butyl bromide		2.0×10^{-4}	$>5.0 \times 10^{-1}$
Papaverine hydrochloride		3.5×10^{-2}	3.5×10^{-3}

a) Concentration required to produce 50% inhibition of the response induced by acetylcholine (1.1×10^{-4} mM). *b*) Concentration required to produce 50% inhibition of the response induced by potassium chloride (40 mM). NT: Not tested.

NaH (2.2 eq) and 1,4-dibromobutane or 1,5-dibromopentane (1.2 eq) in dimethyl sulfoxide, followed by hydrolysis of the resulting esters **3** and **4** with an equimolar amount of NaOH in aqueous ethanol, in 76% and 50% yields, respectively. The aminoalkyl esters **8** were obtained by esterification of the aminoalkanols with **5** using *p*-toluenesulfonyl chloride in toluene. The esters **9** and **10** were obtained by reaction of the corresponding acid chloride with aminoalkanols. Quaternization was carried out in acetone using methyl iodide. The yields and physicochemical properties of **8**, **9**, and **10** are summarized in Table II.

Pharmacological Results and Discussion

The anticholinergic (anti-Ach) activity of the esters (**8**, **9**, and **10**) was examined by measuring the inhibitory effect on the response of isolated guinea pig ileum to acetylcholine (Ach) according to the method previously reported.[2a] The musculotropic (anti-KCl) activity of several compounds which showed relatively potent anti-Ach activity was measured in terms of the inhibitory effect on the response induced by potassium chloride using isolated guinea pig taenia coli. Based on the anti-Ach and anti-KCl activities shown in Table I, some structure–activity relationships of these esters may be summarized as follows. (a) When the aminoalkanol part of the esters was fixed, anti-Ach activity increased according to the kind of α-substituent in the order $-(CH_2)_4- < -(CH_2)_5- <$ cyclohexyl. (b) The order of increasing anti-Ach activity for the aminoalkanol part was as follows: linear aminoalkanol < cyclic aminoalkanol < quaternized cyclic aminoalkanol. However, the reverse order was found for the anti-KCl activity. As shown in Table I, several compounds showed remarkable anti-Ach activity. Among these esters, quaternary ammonium salts (**8k** and **10h**) exhibited about ten times more potency than scopolamine-*N*-butyl bromide, but these salts lacked musculotropic activity. The initially designed linear aminoalkanol esters having a cyclohexyl substituent

showed not only a significant antimuscarinic activity, but also a potent musculotropic activity. Of these compounds, the anti-KCl activities of **8a** or **8b** were equal to or ten times stronger than that of papaverine hydrochloride, respectively. Compound **8b** is of interest as a candidate antispasmodic having potent dual effects. An *in vivo* investigation of these compounds is in progress.

Experimental

Chemistry

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken with a Hitachi 260-10 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a Varian EM-360 instrument (60 MHz) with tetramethylsilane as an internal standard. Abbreviations used: s, singlet; d, doublet; m, multiplet. Mass spectra (MS) were recorded with a Hitachi RMU-6L spectrometer. For thin layer chromatography (TLC), Merck precoated silica gel $60F_{254}$ plates were used. Organic extracts were dried over anhydrous Na_2SO_4.

Methyl α-Cyclohexyl-1,2-benzisoxazole-3-acetate (2)——NaH (60% dispersion in mineral oil, 0.5 g, 10 mmol) was added portionwise to a solution of **1** (1.9 g, 10 mmol) and cyclohexyl iodide (4 g, 19 mmol) in dry dimethylformamide (15 ml) under ice cooling, and the mixture was stirred at room temperature for 0.5 h. Water (50 ml) was added to the reaction mixture and then the mixture was acidified with dil.HCl (pH 5—6). The solution was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and dried. After removal of the solvent, the residue was chromatographed on silica gel with hexane–$CHCl_3$ (1 : 1) as an eluent. The fractions were monitored by TLC developed with $CHCl_3$. Concentration of the fractions showing a spot at *Rf* 0.7 gave **2** (0.89 g, 33%) as a colorless oil. MS *m/z*: 273 (M^+). IR cm^{-1}: $\nu_{C=O}$ 1735 (film). ^{1}H-NMR ($CDCl_3$) δ: 0.7—2.6 (11H, m), 3.72 (3H, s), 3.98 (1H, d, J = 10 Hz), 7.2—8.2 (4H, m).

The next fractions (*Rf* 0.6) afforded the starting material (0.58 g, 31%) and the following fractions (*Rf* 0.2) afforded methyl 3-(2-hydroxyphenyl)-2-cyclohexyl-2*H*-azirine-2-carboxylate (0.07 g, 2.6%) as a by-product.[3]

α-Cyclohexyl-1,2-benzisoxazole-3-acetic Acid (5)——A solution of **2** (6.3 g, 23 mmol) and NaOH (1.4 g, 35 mmol) in water (8 ml) and EtOH (70 ml) was stirred at 60 °C for 0.5 h. After evaporation of the solvent, dil. HCl (5%, 100 ml) was added to the residue. The mixture was extracted with ethyl acetate. The organic layer was dried and evaporated. Recrystallization of the residue from ethyl acetate–hexane gave **5** as colorless needles (5 g, 84%), mp 135—137 °C. *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.07; H, 6.56; N, 5.37.

1-(1,2-Benzisoxazol-3-yl)-1-cyclopentanecarboxylic Acid (6)——NaH (6.9 g, 173 mmol) was added portionwise to a solution of **1** (15 g, 79 mmol) in dimethyl sulfoxide (120 ml). The mixture was stirred for 0.5 h at room temperature, then 1,4-dibromobutane (20.4 g, 98 mmol) was added to the mixture, and the solution was stirred for 4 h at room temperature. Water (100 ml) and conc. HCl (8 ml) were added to the solution and the mixture was extracted with toluene. The toluene layer was washed with water and dried. After removal of the solvent, the residue was chromatographed on silica gel. Elution with toluene gave **3** as a colorless oil (18 g). IR cm^{-1}: $\nu_{C=O}$ 1725 (film). ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.2 (4H, m), 2.2—2.9 (4H, m), 3.67 (3H, s), 7.1—7.8 (4H, m). A solution of **3** (18 g, 73 mmol) and NaOH (3 g, 75 mmol) in water (12 ml) and EtOH (150 ml) was stirred for 40 min at 60 °C. After evaporation of the solvent, dil. HCl (5%, 100 ml) was added to the residue. The mixture was extracted with ethyl acetate. The organic layer was dried and evaporated. The residue was recrystallized from ethyl acetate–hexane to give **6** as colorless needles (13.8 g, 76% from **1**), mp 124—126 °C. *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.50; H, 5.93; N, 6.17. IR cm^{-1}: $\nu_{C=O}$ 1680—1700 (KBr).

1-(1,2-Benzisoxazol-3-yl)-1-cyclohexanecarboxylic Acid (7)——Compound **7** was prepared from **1** (15 g, 79 mmol) and 1,5-dibromopentane (21.6 g, 94 mmol) by a procedure similar to that described for the preparation of **6**. **4**: A colorless oil (15 g). IR cm^{-1}: $\nu_{C=O}$ 1720 (film). ^{1}H-NMR ($CDCl_3$) δ: 1.3—2.7 (10H, m), 3.67 (3H, s), 7.1—7.9 (4H, m). **7**: Colorless needles from toluene–hexane (9.63 g, 50% from **1**), mp 116—118 °C. *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.52; H, 6.36; N, 5.42. IR cm^{-1}: $\nu_{C=O}$ 1690 (KBr).

General Procedure for Preparation of the Esters (8a—h)——*p*-Toluenesulfonyl chloride (0.8 g, 4.2 mmol) was added to a solution of **5** (1 g, 3.9 mmol) in dry toluene (30 ml) and triethylamine (0.6 ml). The mixture was stirred for 1 h at room temperature and an appropriate aminoalkanol (1.2 eq) was added to the solution. The mixture was stirred for 3 h at 70 °C. The reaction mixture was diluted with toluene and washed with an aqueous solution of Na_2CO_3. The toluene layer was extracted with dil. HCl. The aqueous layer was made alkaline with conc. NH_4OH under ice cooling and extracted with toluene. The toluene layer was dried and evaporated to give the free base of **8** as an oil. The oily base was converted to the hydrobromide or oxalate, which was recrystallized from the solvent shown in Table II to give **8a—h**. The results are summarized in Table II.

General Procedure for Preparation of the Esters (9a—e, 10a—f)——A solution of **6** (1 g, 4.3 mmol) or **7** (1 g, 4.1 mmol) and thionyl chloride (5 eq) in dry toluene (30 ml) was stirred for 1 h at 100 °C. After evaporation of the

TABLE II. Physicochemical Properties of the Esters **8**, **9**, and **10**

Compd. No.	Salt	mp (°C) (Recrystn. solvent[a])	Yield (%)	Formula	Analysis (%) Calcd (Found)			
					C	H	Br or I	N
8a	HBr	133—135 (A–E)	77	$C_{21}H_{30}N_2O_3 \cdot HBr$	57.40 (57.39)	7.11 7.15	18.19 18.06	6.37 6.61)
8b	HBr	128—130 (A–E)	88	$C_{22}H_{32}N_2O_3 \cdot HBr$	58.28 (58.46)	7.34 7.36	17.62 17.92	6.18 5.90)
8c	HBr	119—121 (A–E)	47	$C_{23}H_{34}N_2O_3 \cdot HBr$	59.10 (58.86)	7.55 7.32	17.09 17.09	5.99 5.93)
8d	HBr	136—138 (A–E)	57	$C_{22}H_{32}N_2O_3 \cdot HBr$	58.28 (58.47)	7.34 7.43	17.62 17.59	6.18 6.16)
8e	HBr	153—156 (A–E)	78	$C_{24}H_{36}N_2O_3 \cdot HBr$	59.87 (59.57)	7.75 7.84	16.60 16.39	5.82 5.73)
8f	HBr	199—201 (A–E)	73	$C_{21}H_{28}N_2O_3 \cdot HBr \cdot 1/3\,H_2O$[b]	56.89 (56.87)	6.74 6.60	18.02 18.04	6.32 6.46)
8g	Ox	103—106 (A–E)	11	$C_{22}H_{30}N_2O_3 \cdot C_2H_2O_4 \cdot 1/2\,H_2O$	61.39 (61.29)	7.09 7.11		5.97 5.96)
8h	Ox	179—181 (A–E)	56	$C_{22}H_{30}N_2O_3 \cdot C_2H_2O_4$	62.59 (62.37)	7.00 7.07		6.08 6.12)
8i		118—124 (A–E)	81[c]	$C_{22}H_{33}IN_2O_3$	52.80 (52.88)	6.65 6.54	25.36 25.58	5.60 5.62)
8j		88—91 (A)	35[c]	$C_{23}H_{35}IN_2O_3 \cdot 3/4\,H_2O$	52.32 (52.16)	6.87 6.82	24.04 23.91	5.32 5.32)
8k		103—104 (THF)	20[c]	$C_{22}H_{31}IN_2O_3 \cdot 1/3\,C_4H_8O$[d]	53.61 (53.34)	6.51 6.63	24.31 24.04	5.37 5.10)
9a	HBr	150—151 (A–E)	73	$C_{19}H_{26}N_2O_3 \cdot HBr$	55.48 (55.50)	6.62 6.75	19.43 19.69	6.81 6.60)
9b	HBr	124—126 (A–E)	30	$C_{20}H_{28}N_2O_3 \cdot HBr$	56.47 (56.25)	6.87 6.90	18.79 19.07	6.59 6.57)
9c	HBr	139—141 (A–E)	44	$C_{20}H_{28}N_2O_3 \cdot HBr$	56.47 (56.74)	6.87 6.75	18.79 18.98	6.59 6.88)
9d	Ox	157—160 (A–E)	23	$C_{19}H_{24}N_2O_3 \cdot C_2H_2O_4 \cdot 3/4\,H_2O$	58.39 (58.59)	6.42 6.19		6.48 6.34)
9e	HBr	163—165 (A–E)	78	$C_{20}H_{26}N_2O_3 \cdot HBr$	56.74 (56.85)	6.43 6.68	18.87 18.68	6.62 6.65)
9f		138—141 (A–E)	86[c]	$C_{20}H_{29}IN_2O_3$	50.85 (50.82)	6.19 6.16	26.87 26.60	5.93 6.00)
9g		173—178 (A–E)	80[c]	$C_{20}H_{27}IN_2O_3$	51.07 (50.81)	5.79 5.82	26.98 27.01	5.96 6.04)
9h		146—149 (Ac–E)	76[c]	$C_{21}H_{29}IN_2O_3$	52.07 (52.35)	6.03 6.10	26.20 26.47	5.78 5.77)
10a	HBr	177—179 (A–E)	64	$C_{20}H_{28}N_2O_3 \cdot HBr$	56.47 (56.40)	6.87 6.94	18.79 18.95	6.58 6.59)
10b	HBr	122—124 (A–E)	33	$C_{21}H_{30}N_2O_3 \cdot HBr \cdot 1/4\,H_2O$	56.88 (56.91)	7.16 7.13		6.32 6.27)
10c	HBr	150—152 (A–E)	59	$C_{21}H_{30}N_2O_3 \cdot HBr$	57.40 (57.43)	7.11 7.04	18.19 18.31	6.37 6.64)
10d	Ox	126—130 (A–E)	43	$C_{20}H_{26}N_2O_3 \cdot C_2H_2O_4 \cdot 3/2\,H_2O$	57.50 (57.34)	6.79 6.58		6.10 6.09)
10e	Ox	156—158 (A–E)	14	$C_{20}H_{26}N_2O_3 \cdot C_2H_2O_4$	61.10 (60.84)	6.53 6.69		6.48 6.61)
10f	HBr	188—190 (A–E)	22	$C_{21}H_{28}N_2O_3 \cdot HBr$	57.67 (57.82)	6.68 6.61	18.27 18.26	6.40 6.21)
10g		130—133 (A–E)	78[c]	$C_{21}H_{31}IN_2O_3$	51.86 (51.56)	6.42 6.41	26.09 26.35	5.76 5.79)
10h		239—242 (A–W)	55[c]	$C_{21}H_{29}IN_2O_3$	52.07 (51.81)	6.03 5.84	26.20 26.04	5.78 5.77)

a) A = EtOH, E = ether, Ac = acetone, THF = tetrahydrofuran, W = water. Ox = oxalate. *b*) Compounds obtained as hydrates showed the presence of water in their IR and ^{1}H-NMR spectra even after being dried at 80—90 °C for 6—8 h under reduced pressure. *c*) Yields of quaternization. *d*) Tetrahydrofuran.

solvent, dry toluene (10 ml), triethylamine (5 eq) and an appropriate aminoalkanol (1.2 eq) were added to the residue. The mixture was stirred at 100 °C for 1 h and worked up in a similar manner to that used for the preparation of **8a**—**h**. Recrystallization of the hydrobromide or oxalate from the solvent shown in Table II gave **9a**—**e** and **10a**—**f**. The results are summarized in Table II.

General Procedure for Preparation of the Quaternary Salts (8i—k, 9f—h, 10g—h)——A solution of the free base of **8**, **9** or **10** and an excess of methyl iodide in acetone was stirred at room temperature for 2 d. After evaporation of the solvent, the residue was recrystallized from the solvent shown in Table II to give **8i**—**k**, **9f**—**h**, and **10g**—**h**. The results are summarized in Table II.

Pharmacology

Method for Assaying the Musculotropic (anti-KCl) Activity——From male, Hartley strain guinea pigs, weighing 300—350 g, sections of the taenia-coli about 3 cm in length were prepared and mounted in physiological solution kept at 35 °C and oxygenated with 95% O_2–5% CO_2. The physiological solution used had the following composition (mM): NaCl, 137; KCl, 2.7; $MgCl_2$, 1.0; $CaCl_2$, 1.80; NaH_2PO_4, 0.42; $NaHCO_3$, 11.9; glucose, 5.55. The contractile responses were recorded isometrically. Each preparation was adjusted to a tension of 1 g and was allowed to equilibrate for 30 min. Test compounds were applied 5 min before adding KCl (40 mM). Each compound was tested at three different concentrations. On the basis of the percent inhibition at each concentration, the ID_{50} value was determined by the usual graphical method. The results are shown in Table I.

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