Synthesis and Cardiovascular Activity of Phenylalkylamine Derivatives. I. Potential Specific Bradycardic Agents

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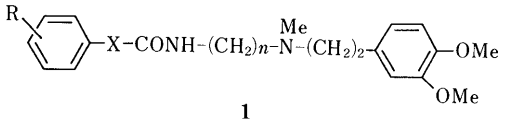
A series of acyclic amide derivatives of *N*-(ω-aminoalkyl)-*N*-methylhomoveratrylamine was synthesized and evaluated for their bradycardic activity in isolated guinea pig right atria. Among these compounds, (*E*)-*N*-[3-[*N'*-[2-(3,4-dimethoxyphenyl)ethyl]-*N'*-methylamino]propyl]-4-[3,4-(methylenedioxy)phenyl]-3-butenamide (35) was the most potent *in vitro* and was also found to show dose-dependent bradycardia without remarkable reduction of left ventricular dp/dt_{max} or mean aortic pressure in anesthetized dogs.

Keywords bradycardic activity; angina pectoris; structure–activity relationships; *N*-(ω-aminoalkyl)-*N*-methylhomoveratrylamine; 4-(substituted phenyl)-3-butenoic acid; (*E*)-*N*-[3-[*N'*-[2-(3,4-dimethoxyphenyl)ethyl]-*N'*-methylamino]propyl]-4-[3,4-(methylenedioxy)phenyl]-3-butenamide

Introduction

We have been studying cardiovascular activity of compounds having a phenylalkylamine structure like verapamil, and have recently found compounds of general formula **1** which decrease heart rate through their effect on the sinus node. Kobinger and Lillie[1] reported that the lactam derivatives **2**, **3** and **4** structurally similar to verapamil are specific bradycardic agents having a direct effect on the sinus node, which may offer new prospects in the therapy of angina pectoris in place of β-adrenoreceptor-blocking drugs having negative inotropy.



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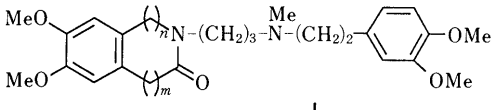


	m	*n*	
2	0	1	AQ-A39
3	1	1	AQ-AH208
4	1	2	UL-FS49

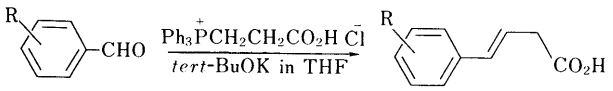
Chart 1

In addition to developing new agents for angina pectoris, we were extremely interested that acyclic amide derivagives **1** showed the same bradycardic activity as the lactam derivatives **2**, **3** and **4**. We investigated structure–activity relationships of compounds represented by general formula **1** by varying: 1) the type of link between the benzene ring and the amide group (x); 2) the properties and position of substituents on the benzene ring (R); and 3) the chain length between the amide group and the amino group (*n*).

We report here the synthesis and bradycardic activity of compounds **11**—**39**.

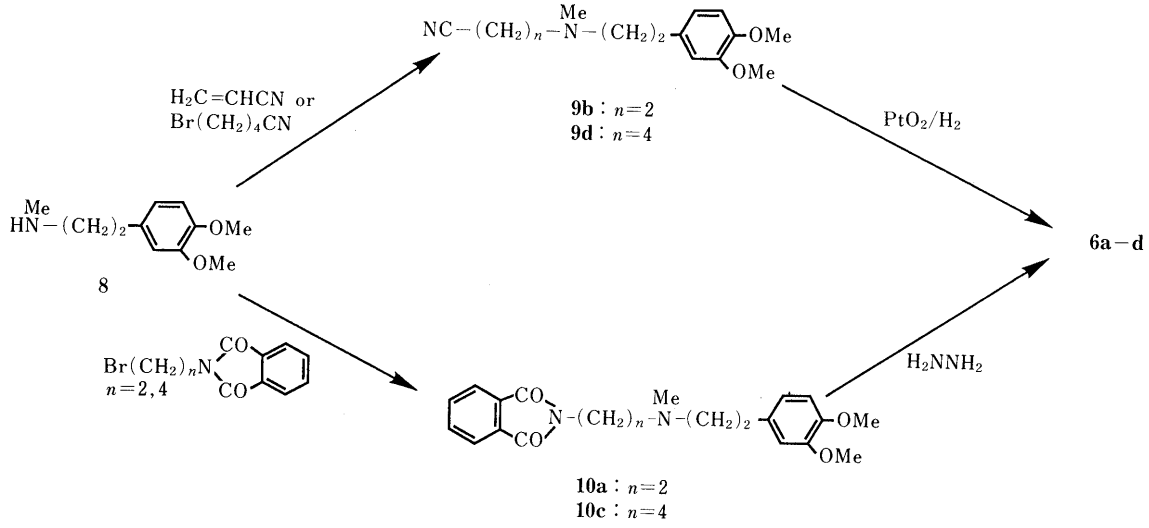
Chemistry

Most compounds of general formula **1** were obtained by condensation of carboxylic acid **5** with *N*-(ω-aminoalkyl)-



7 **5a–q**

Chart 2



10a : *n*=2
10c : *n*=4

Chart 3

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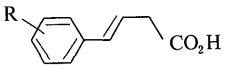
TABLE I. Physical Data of (*E*)-4-(Substituted Phenyl)-3-butenoic Acids **5a**—**q**



No.	R	Method[a] Yield (%)	mp (°C) Recryst. sol.[b]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$)
5a[c]	4-Cl	W 37	108—110 E-H_2O	$C_{10}H_9ClO_2$	61.08 (61.12)	4.61 4.67)		3.28 (2H, d, J=6 Hz), 6.19 (1H, dt, J=6, 16 Hz), 6.49 (1H, d, J=16 Hz), 7.1—7.4 (4H, m), 11.32 (1H, br)
5b[d]	4-Me	W 34	113—114 E-H_2O	$C_{11}H_{12}O_2$	74.97 (74.94	6.87 6.87)		2.32 (3H, s), 3.27 (2H, d, J=7.2 Hz), 6.18 (1H, dt, J=7.2, 16.2 Hz), 6.49 (1H, d, J=16.2 Hz), 7.0—7.4 (4H, m), 11.0 (1H, br)
5c[d]	4-OMe	W 45	102—104 E-H_2O	$C_{11}H_{12}O_3$	68.74 (68.84	6.30 6.20)		3.26 (2H, d, J=6.8 Hz), 3.78 (3H, s), 6.1 (1H, dt, J=6.8, 16.6 Hz), 6.45 (1H, d, J=16.6 Hz), 6.83 (2H, d, J=8.6 Hz), 7.3 (2H, d, J=8.6 Hz), 11.26 (1H, br)
5d	3-OMe	W 68	96.5—97.5 S-I	$C_{11}H_{12}O_3$	68.74 (68.92	6.30 6.23)		3.29 (2H, d, J=5.7 Hz), 3.8 (3H, s), 6.28 (1H, dt, J=5.7, 15.8 Hz), 6.45 (1H, d, J=15.8 Hz), 6.7—7.3 (4H, m), 9.8 (1H, br)
5e	2-OMe	W 56	Oil	$C_{11}H_{12}O_3$				3.31 (2H, dd, J=1, 7 Hz), 3.86 (3H, s), 6.27 (1H, dt, J=7, 16.3 Hz), 6.7—7.5 (5H, m), 10.5 (1H, br)
5f	4-F	W 50	114—115 E-H_2O	$C_{10}H_9O_2F$	66.64 (66.64	5.04 5.02	10.55 (F) 10.44 (F))	3.28 (2H, d, J=6.5 Hz), 6.16 (1H, dt, J=6.5, 16.2 Hz), 6.5 (1H, d, J=16.2 Hz), 7.2—7.5 (4H, m), 9.36 (1H, br)
5g	4-N(Me)$_2$	W 39	203—204 E-H_2O	$C_{12}H_{15}NO_2$	70.22 (70.36	7.37 7.21	6.82 6.73)	2.94 (6H, s), 3.25 (2H, d, J=7 Hz), 6.0 (1H, dt, J=7, 16 Hz), 6.4 (1H, d, J=16 Hz), 6.55—6.75 (2H, m), 7.16—7.35 (2H, m)
5h	4-CN	W 26	111—113 E-H_2O	$C_{11}H_9NO_2$	70.58 (70.61	4.85 4.96	7.48 7.41)	3.29 (2H, d, J=5.7 Hz), 6.34 (1H, dt, J=5.7, 15.8 Hz), 6.58 (1H, d, J=15.8 Hz), 7.3—7.7 (4H, m), 9.84 (1H, br)
5i	3-CN	W 81	81—83 S-H	$C_{11}H_9NO_2$	70.58 (70.58	4.85 4.95	7.48 7.43)	3.35 (2H, d, J=6 Hz), 6.33 (1H, dt, J=6, 16 Hz), 6.58 (1H, d, J=16 Hz), 7.3—7.7 (4H, m), 10.2 (1H, br)
5j	2-CN	W 7	Oil	$C_{11}H_9NO_2$				3.4 (2H, d, J=6 Hz), 6.48 (1H, dt, J=6, 16 Hz), 6.9 (1H, d, J=16 Hz), 7.2—7.8 (4H, m), 9.25 (1H, br)
5k	4-SMe	W 46	131—132 H-A	$C_{11}H_{12}O_2S$	63.43 (63.68	5.81 5.78	15.40 (S) 15.34 (S))	2.47 (3H, s), 3.28 (2H, d, J=7 Hz), 6.16 (1H, dt, J=7, 15 Hz), 6.44 (1H, d, J=15 Hz), 7.0—7.35 (4H, m), 9.9 (1H, br)
5l	4-CO_2Me	W 23	118—121 E-H_2O	$C_{12}H_{12}O_4$	65.44 (65.65	5.49 5.42)		3.3 (2H, d, J=6.1 Hz), 3.88 (3H, s), 6.33 (1H, dt, J=6.1, 15.5 Hz), 7.3—7.5 (2H, m), 7.8—8.1 (2H, m), 9.45 (1H, br)
5m	4-$CONH_2$	From 5h 84	247—249 E-H_2O	$C_{11}H_{11}NO_4$	64.38 (64.54	5.40 5.38	6.83 6.78)	3.2 (2H, d, J=5.8 Hz), 6.34 (1H, dt, J=5.8, 15.8 Hz), 6.66 (1H, d, J=15.8 Hz), 7.1—7.6 (3H, m), 7.6—8.1 (3H, m) (in DMSO-d_6)
5n	4-NHCOMe	W 72	216—217 E-H_2O	$C_{12}H_{13}NO_3$	65.74 (65.89	5.98 5.93	6.39 6.24)	2.02 (3H, s), 3.13 (2H, d, J=6 Hz), 6.12 (1H, dt, J=6, 16 Hz), 6.4 (1H, d, J=16 Hz), 7.14—7.6 (4H, m), 9.9 (1H, s) (in DMSO-d_6)
5o[e]	3,4-(OMe)$_2$	W 48	Oil	$C_{12}H_{14}O_4$				3.24 (2H, d, J=6.5 Hz), 3.82 (3H, s), 3.84 (3H, s), 6.06 (1H, dt, J=6.5, 16.2 Hz), 6.4 (1H, d, J=16.2 Hz), 6.8—7.0 (3H, m), 8.4 (1H, br)
5p[e]	3,4-OCH_2O	W 73	114—115 S-H	$C_{11}H_{10}O_4$	64.07 (64.28	4.89 4.95)		3.22 (2H, d, J=8 Hz), 5.9 (2H, s), 6.0 (1H, dt, J=8, 16 Hz), 6.36 (1H, d, J=16 Hz), 6.6—6.9 (3H, m), 8.5 (1H, br)
5q	3,4-(Cl)$_2$	W 65	77—78 H-D	$C_{10}H_8O_2Cl_2$	51.98 (52.21	3.49 3.47	30.68 (Cl) 30.57 (Cl))	3.3 (2H, d, J=6.5 Hz), 6.26 (1H, dt, J=6.5, 16 Hz), 6.46 (1H, d, J=16 Hz), 7.1—7.5 (3H, m), 9.8 (1H, br)

a) W, Wittig reaction. *b*) D, Et_2O; E, EtOH; H, *n*-hexane; I, isopropyl ether; S, AcOEt. *c*) Ref. 6. *d*) Ref. 7. *e*) Ref. 2.

N-methylhomoveratrylamine **6** as shown in Chart 4.

(*E*)-4-(Substituted phenyl)-3-butenoic acids **5a**—**q** as starting materials were synthesized by the Wittig reaction of substituted benzaldehyde **7** with $Ph_3P^+CH_2CH_2CO_2H$ Cl^-[2] in the presence of potassium *tert*-butoxide in tetrahydrofuran as shown in Chart 2. The Wittig reaction provided only (*E*)-isomer revealing a coupling constant of (*E*)-form in ^{1}H-NMR. (*E*)-4-(4-Carbamoylphenyl)-3-butenoic acid (**5m**) was obtained from (*E*)-4-(4-cyanophenyl)-3-butenoic acid (**5h**) by alkali hydrolysis. Physical data for compounds **5a**—**q** are shown in Table I.

The requisite diamines **6a**—**d**[3,4] were synthesized from *N*-methylhomoveratrylamine **8** as shown in Chart 3. Amine **8** was converted into the nitrile derivative **9b** by the Mi-

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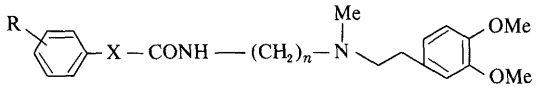
TABLE II. Physical Data and Bradycardic Activities of Compounds **11**—**39**[a]



No.	R	X	n	Yield (%) Method[b]	mp (°C) Oxalate Recryst. sol.[c]	Formula	Analysis (%) Calcd (Found) C	H	N	Bradycardic activity[d]
11	3,4-OMe	—	3	64 A	163—165 M–D	$C_{23}H_{32}N_2O_5 \cdot C_2H_2O_4$	59.27 (59.38)	6.76 (6.69)	5.54 (5.52)	5.9
12	3,4-OMe	CH_2	3	41 A	94—96 M–D	$C_{24}H_{34}N_2O_5 \cdot C_2H_2O_4 \cdot 1/2H_2O$	58.96 (58.95)	7.04 (6.89)	5.29 (5.25)	6.2
13	3,4-OMe	OCH_2	3	72 B	111—113 M–D–A	$C_{24}H_{34}N_2O_6 \cdot C_2H_2O_4$	58.20 (58.09)	6.76 (6.75)	5.22 (5.03)	6.1
14[e]	3,4-OMe	(*E*)-CH=CH	3	57 A	144—145 D–E	$C_{25}H_{34}N_2O_5 \cdot C_2H_2O_4$	60.89 (60.71)	6.81 (6.75)	5.26 (5.14)	5.8
15	3,4-OMe	CH_2CH_2	3	92 B	133—135 D–A	$C_{25}H_{36}N_2O_5 \cdot C_2H_2O_4$	60.66 (60.82)	7.16 (7.11)	5.24 (5.18)	5.4
16	3,4-OMe	(*E*)-CH=$CHCH_2$	3	49 A	96.5—98 D–A	$C_{26}H_{36}N_2O_5 \cdot C_2H_2O_4 \cdot 1/2H_2O$	60.52 (60.57)	7.08 (6.91)	5.04 (5.06)	6.4
17	3,4-OMe	$(CH_2)_3$	3	66 B	93.5—95 S–M	$C_{26}H_{38}N_2O_5 \cdot C_2H_2O_4 \cdot 1/2H_2O$	60.31 (60.07)	7.41 (7.13)	5.02 (5.13)	5.3
18	H	(*E*)-CH=$CHCH_2$	3	34 A	133—135 M–D	$C_{24}H_{32}O_3N_2 \cdot C_2H_2O_4$	64.18 (63.91)	7.04 (6.95)	5.76 (5.59)	5.8
19	4-Cl	(*E*)-CH=$CHCH_2$	3	95 B	107—108.5 D–A	$C_{24}H_{31}N_2ClO_3 \cdot C_2H_2O_4 \cdot 1/4H_2O$	59.42 (59.30)	6.43 (6.43)	5.33 (5.29)	6.7
20	4-Me	(*E*)-CH=$CHCH_2$	3	94 B	135.5—140 D–A	$C_{25}H_{34}N_2O_3 \cdot C_2H_2O_4$	64.78 (64.95)	7.25 (7.29)	5.60 (5.60)	6.0
21	4-OMe	(*E*)-CH=$CHCH_2$	3	75 B	125—126 E–D–A	$C_{25}H_{34}N_2O_4 \cdot C_2H_2O_4$	62.77 (62.83)	7.03 (6.89)	5.42 (5.32)	6.6
22	3-OMe	(*E*)-CH=$CHCH_2$	3	60 B	85.5—87.5 M–S	$C_{25}H_{34}N_2O_4 \cdot C_2H_2O_4 \cdot 1/2H_2O$	61.70 (61.48)	7.10 (6.85)	5.33 (5.46)	6.6
23	2-OMe	(*E*)-CH=$CHCH_2$	3	56 B	89—90.5 M–S	$C_{25}H_{34}N_2O_4 \cdot C_2H_2O_4 \cdot 1/2H_2O$	61.70 (61.92)	7.10 (6.82)	5.33 (5.45)	6.3
24	4-F	(*E*)-CH=$CHCH_2$	3	68 A	101 (2HCl) M–D	$C_{24}H_{31}FN_2O_3 \cdot 2HCl$	59.13 (59.13)	6.82 (6.83)	5.75 (5.60)	6.6
25	4-$N(Me)_2$	(*E*)-CH=$CHCH_2$	3	78 B	121—122 E	$C_{26}H_{37}N_3O_3 \cdot C_2H_2O_4 \cdot 1/2H_2O$	62.44 (62.78)	7.49 (7.21)	7.80 (7.65)	6.5
26	4-CN	(*E*)-CH=$CHCH_2$	3	60 B	89—91 D–A	$C_{25}H_{31}N_3O_3 \cdot C_2H_2O_4$	63.39 (63.29)	6.50 (6.50)	8.21 (8.16)	6.4
27	3-CN	(*E*)-CH=$CHCH_2$	3	47 A	Oil	$C_{25}H_{31}N_3O_3 \cdot C_2H_2O_4$				6.2
28	2-CN	(*E*)-CH=$CHCH_2$	3	25 A	Oil	$C_{25}H_{31}N_3O_3 \cdot C_2H_2O_4$				6.0
29	4-SMe	(*E*)-CH=$CHCH_2$	3	69 B	128—129 E	$C_{25}H_{34}N_2O_3S \cdot C_2H_2O_4$	60.88 (60.99)	6.81 (6.68)	5.26 (5.16)	6.5
30	4-SO_2Me	(*E*)-CH=$CHCH_2$	3	36 (from **29**)	144—145 E	$C_{25}H_{34}N_2O_5S \cdot C_2H_2O_4 \cdot 1/4H_2O$	56.98 (56.94)	6.46 (6.47)	4.92 (4.63)	5.3
31	4-CO_2Me	(*E*)-CH=$CHCH_2$	3	30 A	123—125 M–D–A	$C_{26}H_{34}N_2O_5 \cdot C_2H_2O_4 \cdot 1/2H_2O$	60.74 (60.88)	6.74 (6.54)	5.06 (5.02)	6.8
32	4-$CONH_2$	(*E*)-CH=$CHCH_2$	3	63 B	143—147 M–D	$C_{25}H_{33}N_3O_4 \cdot C_2H_2O_4$	60.21 (60.36)	6.74 (6.69)	7.80 (7.60)	5.7
33	4-CO_2H	(*E*)-CH=$CHCH_2$	3	91 (from **31**)	Oil (free)	$C_{25}H_{32}N_2O_5$				<4
34	4-$NHCOCH_3$	(*E*)-CH=$CHCH_2$	3	76 B	154—155 E	$C_{26}H_{35}N_3O_4 \cdot C_2H_2O_4 \cdot 1/4H_2O$	61.36 (61.44)	6.90 (6.77)	7.67 (7.54)	6.2
35	3,4-OCH_2O	(*E*)-CH=$CHCH_2$	3	46 B	84—85 S–M	$C_{25}H_{32}N_2O_5 \cdot 2HCl$	58.48 (58.27)	6.67 (6.51)	5.46 (5.37)	6.8
36	3,4-Cl_2	(*E*)-CH=$CHCH_2$	3	92 B	131—133 M–D	$C_{24}H_{30}N_2O_3Cl_2 \cdot C_2H_2O_4 \cdot 1/2H_2O$	55.32 (55.19)	5.89 (5.78)	4.96 (5.04)	5.7
37	3,4-OCH_2O	(*E*)-CH=$CHCH_2$	2	100 B	142—144 M–D	$C_{24}H_{30}N_2O_5 \cdot C_2H_2O_4 \cdot 1/4H_2O$	59.93 (60.10)	6.29 (6.19)	5.38 (5.49)	5.8
38	3,4-OCH_2O	(*E*)-CH=$CHCH_2$	4	89 B	102—104 M–D–A	$C_{26}H_{34}N_2O_5 \cdot C_2H_2O_4 \cdot 1/2H_2O$	60.75 (60.88)	6.74 (6.49)	5.06 (5.14)	6.1
39	3,4-OCH_2O	(*E*)-CH=$CHCH_2$	5	96 B	76—78 M–D	$C_{27}H_{36}N_2O_5 \cdot C_2H_2O_4 \cdot H_2O$	60.40 (60.51)	6.99 (6.71)	4.89 (4.99)	6.1
2	AQ-A39									5.3
3	AQ-AH208									6.3
4	UL-FS49									6.9

a) Structures of all compounds were confirmed by NMR spectra. For typical example, see Experimental. *b*) A, 1) $SOCl_2$, 2) $N(Et)_3$; B, DCC/HBT. *c*) A, acetone; D, Et_2O; E, EtOH; M, MeOH; S, AcOEt. *d*) See Experimental. *e*) Ref. 5.

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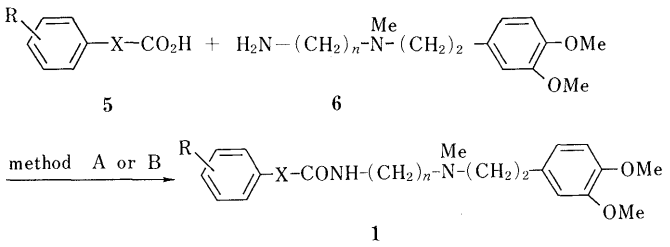

Chart 4

chael reaction with acrylnitrile, and **8** was also treated with 5-bromovaleronitrile in the presence of K_2CO_3 to give the nitrile derivative **9d**. Nitrile derivatives **9b** and **9d** were hydrogenated over PtO_2 in HCl–EtOH to give diamines **6b** and **6d**, respectively. On the other hand, **8** was reacted with *N*-(2-bromoethyl)phthalimide and *N*-(4-bromobutyl)phthalimide in the presence of K_2CO_3 to yield imides **10a** and **10c**, respectively, which were treated with hydrazine to give diamine **6a** and **6c**, respectively.

The condensation was carried out using two methods as shown in Chart 4: A) the acid chloride method [1) $SOCl_2$, and 2) $N(Et)_3$]; B) dicyclohexylcarbodiimide(DCC)/1-hydroxybenztriazole. Amide **30** was obtained from **29** by *m*-chloroperbenzoic acid oxidation, and carboxylic acid **33** was prepared from methyl ester **31** by alkali hydrolysis. Most of the amides were converted into oxalate salt for crystallization, but a few of them did not crystallize. Physical data of compounds **11**—**39** are shown in Table II.

Results and Discussion

Compounds **2**, **3**, **4** and **11**—**39** were tested for bradycardic activity in isolated guinea pig right atria. The cologarithm of the concentration of a test compound at which the heart rate was reduced by 30% is shown in Table II.

From the test results of compounds **11**—**17**, it was suggested that the activity of acyclic derivatives was generally stronger than that of the lactam derivative **2** and the (*E*)-CH=CHCH$_2$ group was preferable as a type of linkage (X) as in **16**.

Based on these results, (*E*)-4-(substituted phenyl)-3-butenoic acid derivatives **18**—**36** were synthesized to look for the preferable position and nature of substituents on the benzene ring. About half of them were more active than lactam **3** and the activity of compounds **19**, **31** and **35** was comparable to that of lactam **4**. In general, the effect of the position of the ring substituents (R) on the activity increased in the order *para* > *meta* > *ortho* (**21**—**23**, **26**—**28**), although not remarkably. No correlation was observed between the electronic effects (resonance and inductive) or the Hammett's σ substituent constants on the aromatic system of the substituents and the bradycardic activity.

As the 3,4-methylenedioxy group was the best substituent on the benzene ring as shown in **35**, the effect of the chain length (*n*) was examined in the amide derivatives (**35**, **37**, **38** and **39**) of (*E*)-4-[3,4-(methylenedioxy)phenyl]-3-butenoic acid. As shown in Table II, the most suitable length was $n=3$ (compound **35**).

We selected compound **35** from the test result in *in vitro*, physical and metabolic properties, and further evaluated it

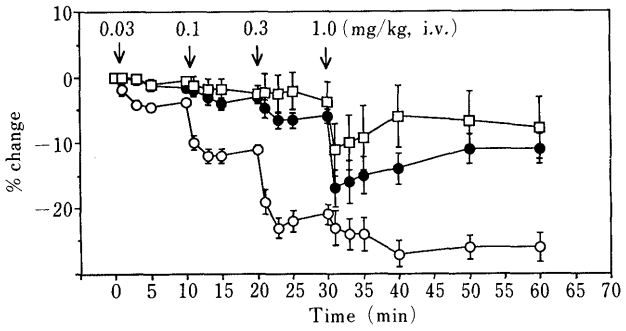

Fig. 1. Effects of Compound **35** on Haemodynamics in Anesthetized Dogs

Data are mean values ± S.E. ($n=8$). —□—, left ventricular dp/dt_{max}; —●—, mean aortic pressure; —○—, heart rate.

in vivo. Effects of compound **35** on haemodynamics were tested in anesthetized dogs. As shown in Fig. 1, dose-dependent bradycardia was observed without remarkable reduction of left ventricular dp/dt_{max} and mean aortic pressure. The compounds **2**, **3** and **4** showed similar effects on haemodynamics in anesthetized dogs, but bradycardic activity of verapamil was accompanied by reduction of left ventricular dp/dt_{max} and mean aortic pressure. These results suggest that compound **35** should be effective for angina pectoris as well as compounds **2**, **3** and **4**.

In conclusion, we found **35** to be a promising candidate, an acyclic amide compound different from the lactam derivatives **2**, **3** and **4** and offering new potential in the therapy of angina pectoris.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were measured on a JEOL-JNM-FX90Q (90 MHz) instrument. Chemical shifts are given in ppm using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, br = broad, m = multiplet. Column chromatography was performed on silica gel (Merck, particle size 0.063—0.200 mm for normal chromatography). Elemental analyses were performed at the Analytical Chemistry Section of Eisai Tsukuba Research Laboratories. The yields were not optimized.

Typical Procedure of (*E*)-4-(Substituted Phenyl)-3-butenoic Acids (5a—q) (Wittig Reaction). (*E*)-4-(4-Fluorophenyl)-3-butenoic Acid (5f) A solution of potassium *tert*-butoxide (141.4 g, 1.26 mol) in tetrahydrofuran (500 ml) was added portionwise to a mixture of 4-fluorobenzaldehyde (74.4 g, 0.60 mol) and (2-carboxyethyl)triphenylphosphonium chloride (233.6 g, 0.63 mol) in tetrahydrofuran (700 ml) under cooling with ice-water over a period of 1 h. The reaction mixture was stirred at the same temperature for 30 min and then brought to room temperature. After stirring for 10 h, the reaction mixture was poured into ice-water and washed with ether. The aqueous layer was adjusted to pH 2 with conc. HCl and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and then evaporated under reduced pressure. The solid residue was recrystallized from H_2O–EtOH to give **5f** (54 g, 50%). Physical data are shown in Table I.

(*E*)-4-(4-Carbamoylphenyl)-3-butenoic Acid (5m) A mixture of 4-(4-cyanophenyl)-3-butenoic acid (**5h**) (2.5 g, 13.4 mmol) and KOH (2.64 g, 40.1 mmol) in *tert*-BuOH (30 ml) was refluxed for 2 h. The reaction mixture was poured into ice-water and adjusted to pH 2 with conc. HCl. The precipitate was filtered and recrystallized from H_2O–EtOH to give **5m** (2.3 g, 84%). The physical data are shown in Table I.

Typical Procedure of Condensation A. (*E*)-*N*-[3-[*N'*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-methylamino]propyl]-4-(4-fluorophenyl)-3-butenamide (24) A mixture of **5f** (30 g, 0.17 mol) and thionyl chloride (14.6 ml, 0.2 mol) in benzene (350 ml) was refluxed for 2 h and evaporated under reduced pressure. The residue dissolved in CH_2Cl_2 (200 ml) was added portionwise to a mixture of *N*-[2-(3,4-dimethoxyphenyl)ethyl]-*N*-methyl-1,3-propanedi-

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amine (**6b**) (47.1 g, 0.19 mol) and K_2CO_3 (26.3 g, 0.19 mol) in CH_2Cl_2 (400 ml) under cooling with ice-water and the reaction mixture was stirred for 30 min; the mixture was stirred at room temperature for another 30 min and poured into ice-water. After extraction with CH_2Cl_2, the organic layer was washed with water, dried over $MgSO_4$ and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 25 : 1) to give **24** as a yellow oil (55.3 g, 79%). NMR ($CDCl_3$) δ: 1.5—1.8 (2H, m), 2.18 (3H, s), 2.3—2.8 (6H, m), 3.04 (2H, d, J = 6.8 Hz), 3.2—3.5 (2H, m), 3.84 (3H, s), 3.86 (3H, s), 6.12 (1H, d, J = 15.2 Hz), 7.6—7.8 (3H, m), 7.8—8.1 (2H, m), 8.1—8.4 (3H, m). Compound **24** (55.3 g) was dissolved in a methanolic HCl solution and crystallized from MeOH–Et_2O to give HCl salt (56.1 g, 86%), mp 101 °C. *Anal.* Calcd for $C_{24}H_{31}FN_2O_3 \cdot 2HCl$: C, 59.13; H, 6.82; F, 3.89; N, 5.75. Found: C, 59.13; H, 6.83; F, 3.91; N, 5.60.

Typical Procedure of Condensation B. (*E*)-*N*-[3-[*N'*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-methylamino]propyl]-4-(4-cyanophenyl)-3-butenamide (26) A mixture of **5h** (0.72 g, 3.9 mmol), **6b** (1.07 g, 4.2 mmol), *N*,*N'*-dicyclohexylcarbodiimide (0.87 g, 4.2 mmol) and 1-hydroxybenzotriazole (0.57 g, 4.2 mmol) in acetonitrile (13 ml) was stirred at 70 °C for 30 min. After cooling to room temperature, the reaction mixture was filtered to remove the precipitates and concentrated. The residue was dissolved in $CHCl_3$ and washed with 10% K_2CO_3. The organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 20 : 1) to give **26** as a yellow oil (1.52 g, 93%). NMR ($CDCl_3$) δ: 1.5—1.8 (2H, m), 2.14 (3H, s), 2.4—2.8 (6H, m), 3.01 (2H, d, J = 7 Hz), 3.2—3.5 (2H, m), 3.84 (3H, s), 3.86 (3H, s), 6.1—6.5 (2H, m), 6.6—6.8 (3H, m), 7.1—7.0 (5H, m). A solution of **26** (1.52 g) and oxalic acid (325 mg, 3.6 mmol) in EtOH (20 ml) was concentrated and the residue was recrystallized from Et_2O–acetone to give oxalate of **26** (1.19 g, 65%), mp 89—91 °C. *Anal.* Calcd for $C_{25}H_{31}N_3O_3 \cdot C_2H_2O_4$: C, 63.39; H, 6.50; N, 8.21. Found: C, 63.29; H, 6.50; N, 8.21.

(*E*)-*N*-[3-[*N'*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-methylamino]propyl]-4-(4-methylsulfonylphenyl)-3-butenamide (30) To a solution of (*E*)-*N*-[3-[*N'*-[2-(3,4-dimethoxyphenyl)ethyl]-*N'*-methyl]aminopropyl]-4-(4-methylthiophenyl)-3-butenamide (**29**) (1.0 g, 2.26 mmol) in CH_2Cl_2 (20 ml) was added *m*-chloroperbenzoic acid (860 mg, 4.98 mmol) under cooling with ice-water. After stirring at room temperature for 1 h, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (CH_2Cl_2 : MeOH = 30 : 1) to give **30** as a yellow oil (460 mg, 43%). NMR ($CDCl_3$) δ: 1.4—1.9 (2H, m), 2.22 (3H, s), 2.3—2.8 (6H, m), 3.00 (3H, s), 3.02 (2H, d, J = 4 Hz), 3.1—3.5 (2H, m), 3.81 (3H, s), 3.84 (3H, s), 6.3—6.9 (5H, m), 7.0—7.9 (5H, m). Oxalate (460 mg, 84%) was prepared from **30** (460 mg, 0.97 mmol) and oxalic acid (90 mg, 1 mmol) by a procedure similar to that described for **26**, mp 144—145 °C (EtOH). *Anal.* Calcd for $C_{25}H_{34}N_2O_5S \cdot C_2H_2O_4 \cdot 1/4H_2O$: C, 56.98; H, 6.46; N, 4.92. Found: C, 56.94; H, 6.47; N, 4.63.

(*E*)-*N*-[3-[*N'*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-methylamino]propyl]-4-(4-carboxyphenyl)-3-butenamide (33) A solution of methylester **31** (420 mg, 0.92 mmol) and 1 N-NaOH (2.0 ml, 2.0 mmol) in MeOH (2 ml) was stirred at room temperature for 12 h and then refluxed for 4 h. The reaction mixture was diluted with water, washed with Et_2O, adjusted to pH 7 with diluted HCl and then evaporated under reduced pressure. The residue was purified by Sephadex LH-20 (MeOH) to give **33** (370 mg, 91%) as an amorphous solid. NMR ($CDCl_3$) δ: 1.7—2.2 (2H, m), 2.62 (3H, s), 2.7—3.6 (10H, m), 3.81 (3H, s), 3.82 (3H, s), 6.3—6.8 (5H, m), 7.18 (2H, d, J = 10 Hz), 7.5 (1H, br), 7.82 (2H, d, J = 10 Hz), 9.0 (1H, br).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-1,2-ethylenediamine (6a)** A mixture of *N*-methyl-[2-(3,4-dimethoxyphenyl)ethyl]amine hydroiodide (**8**) (8.08 g, 25 mmol), *N*-(2-bromoethyl)phthalimide (7.63 g, 30 mmol) and K_2CO_3 (8.29, 60 mmol) in *N*,*N*-dimethylformamide (DMF) (50 ml) was stirred at 80 °C for 6 h. The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$: MeOH = 200 : 1) to give *N*-[2-[*N'*-[2-(3,4-dimethoxyphenyl)ethyl]-*N'*-methylamino]ethyl]-phthalimide (**10a**) (2.36 g, 26%) as a yellow oil. NMR ($CDCl_3$) δ: 7.6—7.9 (4H, m), 6.5—6.8 (3H, m), 3.6—3.9 (8H, m), 2.5—2.9 (6H, m), 2.37 (3H, s). A solution of phthalimide **10a** (2.36 g, 6.4 mmol) and hydrazine hydrate (0.34 ml, 7.1 mmol) in MeOH (10 ml) was refluxed for 2 h and then evaporated under reduced pressure. The residue was dissolved in 6 N HCl (20 ml) and the reaction mixture was refluxed for 1 h. The precipitate was filtered off and the filtrate was washed with Et_2O, made alkaline with 10% K_2CO_3 and then extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give diamine **6a** (1.35 g, 87%) as a yellow oil. NMR ($CDCl_3$) δ: 6.5—6.9 (3H, m), 3.84 (3H, s), 3.82 (3H, s), 2.2—2.9 (11H, m), 1.33 (2H, s).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-1,3-propanediamine (6b)** To a solution of **8** (630 mg, 3.3 mmol) in EtOH (5 ml) was added acrylnitrile (130 mg, 2.5 mmol) and the mixture was stirred at room temperature for 3 h. Conc. HCl (0.6 ml, 7.5 mmol) and EtOH (15 ml) was added to the above reaction mixture (nitrile derivative **9b**) and the mixture was hydrogenated over PtO_2 (50 mg) under 3 atmospheric pressure of H_2 at room temperature. After removal of the catalyst by filtration, the filtrate was concentrated under reduced pressure to give the residue, which was dissolved in 10% K_2CO_3 and extracted with $CHCl_3$. The organic layer was washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$: MeOH : NH_4OH = 100 : 10 : 1) to give **6b** (550 mg, 87%) as a yellow oil. NMR ($CDCl_3$) δ: 1.4—1.9 (4H, m), 2.2—2.9 (11H, m), 3.83 (3H, s), 3.86 (3H, s), 6.5—6.8 (3H, m).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-1,4-butanediamine (6c)** *N*-[4-[*N'*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N'*-methylamino]butyl]phthalimide (**10c**) (9.44 g, 95%) was obtained as a yellow oil from **8** hydroiodide (8.08 g, 25 mmol), *N*-(4-bromobutyl)phthalimide (8.46 g, 30 mmol) and K_2CO_3 (8.29 g, 60 mmol) by a similar procedure to that described in **10a**. NMR ($CDCl_3$) δ: 1.3—1.9 (4H, m), 2.2—2.8 (9H, m), 3.68 (2H, t, J = 7 Hz), 3.80 (3H, s), 3.84 (3H, s), 6.5—6.8 (3H, m), 7.5—7.8 (4H, m). Butane diamine **6c** (5.21 g, 82%) was obtained as a yellow oil from **10c** (9.44 g, 23.8 mmol) by a similar procedure to that described in **6a**. NMR ($CDCl_3$) δ: 1.3—1.8 (4H, m), 2.2—2.9 (11H, m), 3.26 (2H, s), 3.84 (3H, s), 3.87 (3H, s), 6.5—6.9 (3H, m).

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-*N*-methyl-1,5-pentanediamine (6d)** A solution of **8** (2.5 g, 12.8 mmol), 5-bromovaleronitrile (1.65 ml, 14.1 mmol) and K_2CO_3 (1.95 g, 14.1 mmol) in DMF (25 ml) was stirred at room temperature for 16 h. The reaction mixture was diluted with water and extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure to give the residue (**9d**). Pentanediamine **6d** (1.95 g, 55%) was obtained as a yellow oil from the residue (**9d**) by a similar procedure to that described in **6d**. NMR ($CDCl_3$) δ: 1.2—1.9 (8H, m), 2.2—2.9 (11H, m), 3.83 (3H, m), 3.86 (3H, s), 6.8—6.9 (3H, m).

Biology 1) Effects of Compounds 2, 3, 4 and 11—39 upon Cardiac Muscle Extirpated from Guinea Pigs Male guinea pigs of Hartley strain, weighing 300—500 g, were stunned with a blow on the head and exsanguinated. The heart was excised, and the right atrium was rapidly isolated. The tissues were mounted in organ baths of 6 ml capacity which were filled with a modified Krebs solution of the following composition (mmol/l): NaCl, 118.4; KCl, 4.7; $CaCl_2$, 2.5; $MgSO_4$, 1.3; KH_2PO_4, 1.2; $NaHCO_3$, 25.0 and glucose, 11.0. The solution was maintained at 37 °C and equilibrated with a mixture of 95% O_2 and 5% CO_2 to make pH 7.4. Spontaneous beating rate of the atrium was counted with a heart rate tachometer (AT-601G; Nihon-Kohden) which was triggered by tension signals. An equilibration time of at least 60 min preceded the commencement of each experiment. Concentration–response curves were constructed by adding cumulative concentrations of test compounds to the bath. The cologarithm of the concentration of a test compound at which the heart rate was reduced by 30% was defined as bradycardic activity and shown in Table II.

2) Effects of Compound 35 on Haemodynamics of Anesthetized Dogs Mongrel dogs of either sex, weighing 8—15 kg, were used. Anesthesia was initiated with ketamine hydrochloride (10 mg/kg i.m.) and thiopental sodium (20 mg/kg i.v.). After orotracheal intubation, respiration was controlled by an anesthesia ventilator (Anesthesia Apparatus EM-2, Fluotec-3, Acoma, Tokyo, Japan). Anesthesia was maintained with a 2 : 1 mixture of N_2O and O_2 as a carrier of enflurane (0.8—1.5%), and thoracotomy was performed. Aortic blood pressure and left ventricular pressure (LVP) were recorded by means of catheter-tip pressure transducers (MPC-500, Millar Instruments, U.S.A.). The maximum rate of rise in LVP ($LVdp/dt_{max}$) was determined through electronic differentiation of the LVP pulse. Heart rate was measured by a cardiotachometer triggered by LVP. Drug (0.03, 0.1, 0.3, 1.0 mg/kg, i.v.) was administered *via* a cannula inserted into the femoral vein.

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