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Benzylpiperazine Derivatives. I.[1] Syntheses and Biological Activities of 1-(2,3,4-Trimethoxybenzyl)piperazine Derivatives

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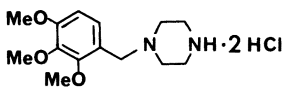
A series of 1-(2,3,4-trimethoxybenzyl)piperazine (trimetazidine) derivatives were prepared and tested for cerebral vasodilating activity. Almost all the compounds possess stronger activity than trimetazidine and among them, the γ-amino tertiary alcohols **6e—j** exhibit potent cerebral vasodilating activities which are superior to those of cinnarizine and papaverine. Moreover, these compounds show a selective vasodilating effect on vertebral arteries.

Keywords——piperazine; trimetazidine; Mannich reaction; Grignard reaction; cerebral vasodilator

1-(2,3,4-Trimethoxybenzyl)piperazine dihydrochloride (trimetazidine dihydrochloride; **1**) is one of a few monosubstituted piperazines used clinically, and there are some patents concerning 4-substituted derivatives of this coronary vasodilator.[2] It is of interest to note that trimetazidine was reported to be distributed in the brain as well as in the heart,[3] and to relax dog basilar arteries more effectively than coronary arteries after contraction with prostaglandin $F_{2\alpha}$.[4] Trimetazidine seems to be more hydrophilic than cinnarizine (CNZ, **2**), a well known cerebral vasodilator, and therefore we thought it pertinent to prepare a group of lipophilic trimetazidine derivatives, with the aim of finding a new cerebral vasodilator. The structure of the trimetazidine derivatives was designed taking the structure of **2** into consideration. This paper describes the synthesis of a group of trimetazidine derivatives (**3**—**6**), as well as the cerebral vasodilating activities of the compounds.



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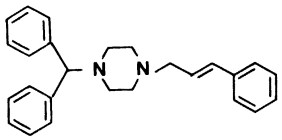

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Chart 1

Most of the trimetazidine derivatives listed in Table I were prepared by the methods shown in Chart 2. Thus, acetophenone was subjected to the Mannich reaction with trimetazidine dihydrochloride and paraformaldehyde in refluxing ethanol, and the product, 1-(2-benzoylethyl)-4-(2,3,4-trimethoxybenzyl)piperazine (**3a**), was precipitated as its dihydrochloride from the cooled reaction mixture. As for the substituent on the phenyl ring, we applied Topliss's method,[5] which was a practical application of the Hansch theory,[6] to obtain the highly active compound, and synthesized a further four compounds, the 4-methyl,

4-methoxy, 4-chloro and 3,4-dichloro derivatives, **3b**—**e**. The resulting Mannich bases **3a**—**e** were reduced with sodium borohydride in methanol to give the γ-amino secondary alcohols **4a**—**e**. The alcohols were dehydrated to provide the cinnamylpiperazines **5a**—**e** by treatment with 50% phosphoric acid solution. Some cinnamylpiperazines (**5a**, **e**, **f**) were prepared by the reaction of trimetazidine with substituted cinnamyl chlorides[7] in the presence of triethylamine as shown in Chart 2.

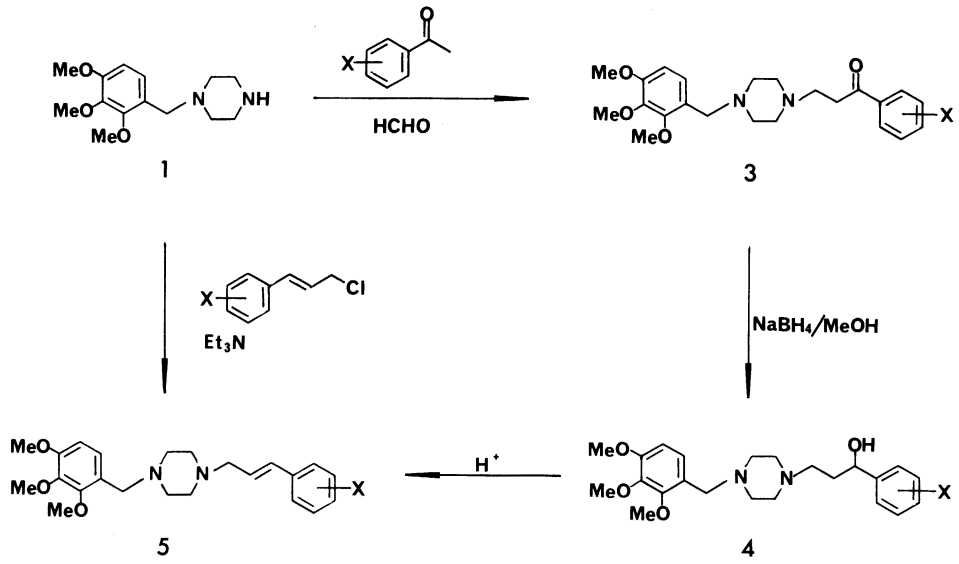

Chart 2

From the biological test results obtained with the above trimetazidine derivatives in dogs, it was found that two of the γ-amino secondary alcohols, **4d**, **e**, induced a considerable increase in vertebral blood flow, indicative of cerebral vasodilating action. The benzoylethyl derivatives (**3**) and the cinnamyl derivatives (**5**) were less potent than cinnarizine and the effects of the substituents on the potency were less and unclear in these derivatives. These results suggest that the benzylic hydroxy group is a prerequisite for high cerebral vasodilating activity, and in a series of γ-amino secondary alcohols the activity depends positively on the lipophilicity (π) of the substituent. To clarify this point we synthesized some further γ-amino secondary alcohols **4f**—**i** by the method described above. The nitro derivative, **4f**, was practically insoluble in many solvents and could not be recrystallized or tested. The results for the other compounds supported the above hypothesis.

Thus the γ-amino tertiary alcohols **6a**—**n** (Table II) were synthesized by the methods shown in Chart 3 in order to obtain more lipophilic compounds.

One method was to convert the Mannich base **3c** into the γ-amino tertiary alcohol **6c** by means of the Grignard reaction. This method required a large excess (about 10-fold excess) of methylmagnesium iodide, otherwise a mixture of the γ-amino tertiary alcohol **6c** and the starting Mannich base **3c** was obtained. The naphthyl derivative, **6f**, was also prepared by this method.

As the other method, substituted ω-chloropropiophenones **7a**—**e**[8] were subjected to the Grignard reaction and the resulting tertiary alcohols **8a**—**l** were allowed to react with trimetazidine to give the γ-amino tertiary alcohols **6a**, **b**, **d**, **e**, **g**—**n**. In this method, equimolar Grignard reagent was sufficient.

Topliss's method was applied to introduce the alkyl group at the benzylic position, but

TABLE I. Trimetazidine Derivatives (**3**, **4** and **5**)

Compd. No.	X	Yield[a] (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Potency[b]
3a	H	40	201—203 (dec.)	MeOH	$C_{23}H_{30}N_2O_4 \cdot 2HCl$	58.60 (58.56	6.84 6.83	5.94 5.90)	0.49
3b	4-Me	32	207—211 (dec.)	MeOH	$C_{24}H_{32}N_2O_4 \cdot 2HCl$	59.38 (59.08	7.06 7.04	5.77 5.67)	0.37
3c	4-OMe	54	210—214 (dec.)	MeOH	$C_{24}H_{32}N_2O_5 \cdot 2HCl \cdot 0.25H_2O$	56.97 (56.88	6.87 6.76	5.54 5.57)	0.50
3d	4-Cl	38	214—216 (dec.)	MeOH	$C_{23}H_{29}ClN_2O_4 \cdot 2HCl$	54.61 (54.26	6.18 6.13	5.54 5.47)	0.46
3e	3,4-Cl_2	35	205—209 (dec.)	MeOH	$C_{23}H_{38}Cl_2N_2O_4 \cdot 2HCl$	51.13 (50.97	5.60 5.67	5.18 5.08)	0.48
4a	H	76	214—217	MeOH	$C_{23}H_{32}N_2O_4 \cdot 2HCl$	58.35 (58.16	7.24 7.39	5.92 5.87)	0.28
4b	4-Me	82	225—228 (dec.)	MeOH	$C_{24}H_{34}N_2O_4 \cdot 2HCl$	59.14 (58.90	7.44 7.48	5.75 5.76)	0.44
4c	4-OMe	53	227—229 (dec.)	MeOH	$C_{24}H_{34}N_2O_5 \cdot 2HCl$	57.26 (57.54	7.21 7.27	5.56 5.39)	N.T.
4d	4-Cl	56	204—206 (dec.)	MeOH	$C_{23}H_{31}ClN_2O_4 \cdot 2HCl$	54.40 (54.16	6.55 6.46	5.52 5.42)	0.61
4e	3,4-Cl_2	81	228—232 (dec.)	MeOH	$C_{23}H_{30}Cl_2N_2O_4 \cdot 2HCl$	50.94 (50.88	5.95 5.96	5.16 5.24)	0.79
4f	4-NO_2	89	250—254 (dec.)	—	$C_{23}H_{31}N_3O_6 \cdot 2HCl$	53.29 (53.55	6.42 6.58	8.11 8.18)	N.T.
4g	4-NHAc	62	200—203 (dec.)	MeOH–EtOH	$C_{25}H_{35}N_3O_5 \cdot 2HCl$	56.60 (56.46	7.03 7.14	7.92 7.91)	Inact.
4h	3,4-Me_2	28	228—230 (dec.)	EtOH	$C_{25}H_{36}N_2O_4 \cdot 2HCl$	59.88 (59.72	7.64 7.54	5.59 5.62)	0.63
4i	3,4-$(CH)_4$	43	223—227 (dec.)	MeOH–EtOH	$C_{27}H_{34}N_2O_4 \cdot 2HCl$	61.95 (61.81	6.93 7.14	5.35 5.38)	0.89
5a	H[c]	26[d]	205—208	EtOH	$C_{23}H_{30}N_2O_3 \cdot 2HCl$	60.66 (60.47	7.08 7.16	6.15 6.19)	0.44
5b	4-Me	16	235—238 (dec.)	CH_3CN	$C_{24}H_{32}N_2O_3 \cdot 2HCl \cdot 0.25H_2O$	60.82 (60.88	7.34 7.41	5.91 6.11)	0.17
5c	4-OMe	14	229—232 (dec.)	EtOH	$C_{24}H_{32}N_2O_4 \cdot 2HCl$	59.38 (59.19	7.06 6.91	5.77 5.70)	N.T.
5d	4-Cl	13	249—253 (dec.)	EtOH	$C_{23}H_{29}ClN_2O_3 \cdot 2HCl \cdot 0.75H_2O$	54.88 (54.86	6.51 6.21	5.57 5.55)	N.T.
5e	3,4-Cl_2	10[d]	240—243 (dec.)	CH_3CN	$C_{23}H_{28}Cl_2N_2O_3 \cdot 2HCl$	52.69 (52.45	5.77 5.88	5.34 5.31)	0.43
5f	2,4-Cl_2	29[d]	177—179 (dec.)	CH_3CN	$C_{23}H_{28}Cl_2N_2O_3 \cdot 2(C_4H_4O_4)$[e]	54.47 (54.43	5.31 5.28	4.10 4.09)	0.45

a) Yields are based on the preceding isolated intermediates. *b*) The potency is expressed as the ratio of cerebral vasodilating activity to that of papaverine taken as 1. The potency of trimetazidine is 0.06 and that of cinnarizine is 0.71. N.T. = not tested. Inact. = inactive. *c*) See refs. 2*f* and 2*g*. *d*) See experimental section. *e*) Maleate.

the attempt failed, because *sec*-alkylmagnesium halides (such as isopropylmagnesium bromide) did not afford the corresponding tertiary alcohols. The γ-chloro tertiary alcohols (**8**) were purified by column chromatography and yields and nuclear magnetic resonance (NMR) data are given in Table III.

Most of the γ-amino tertiary alcohols (**6**) were stable, but **6c** was dehydrated in the salt-forming step with hydrochloric acid to give **9**.

TABLE II. γ-Amino Tertiary Alcohols (**6**)

Compd. No.	R	X	Yield[a] (%)	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N	Potency[b]
6a	CH_3	H	20	214—215 (dec.)	CH_3CN–EtOH	$C_{24}H_{34}N_2O_4 \cdot 2HCl \cdot 0.25H_2O$	58.59 (58.48	7.48 7.53	5.69 5.71)	0.88
6b	CH_3	4-Me	19	165—171 (dec.)	EtOH	$C_{25}H_{36}N_2O_4 \cdot 2(C_4H_4O_4)$[c]	59.99 (59.82	6.71 6.58	4.24 4.19)	0.92
6c	CH_3	4-OMe	38	169—172 (dec.)	EtOH	$C_{25}H_{36}N_2O_5 \cdot 2(C_4H_4O_4) \cdot 0.5H_2O$	57.80 (57.80	6.61 6.61	4.09 4.12)	0.69
6d	CH_3	4-Cl	31	168—169 (dec.)	MeOH–EtOH	$C_{24}H_{33}ClN_2O_4 \cdot 2(C_4H_4O_4)$	56.43 (56.63	6.07 6.37	4.11 4.14)	0.94
6e	CH_3	3,4-Cl_2	57	220—224 (dec.)	MeOH–EtOH	$C_{24}H_{32}Cl_2N_2O_4 \cdot 2HCl$	51.81 (51.53	6.16 6.34	5.04 5.01)	1.36
6f	CH_3	3,4-$(CH)_4$	14	203—205 (dec.)	iso-PrOH	$C_{28}H_{36}N_2O_4 \cdot 2HCl \cdot H_2O$	60.53 (60.66	7.26 7.05	5.04 5.16)	1.17
6g	CH_3	2,4-Cl_2	14	231—233 (dec.)	EtOH	$C_{24}H_{32}Cl_2N_2O_4 \cdot 2HCl$	51.81 (51.71	6.16 6.20	5.04 5.04)	1.46
6h	C_2H_5	3,4-Cl_2	44	229—230 (dec.)	MeOH	$C_{25}H_{34}Cl_2N_2O_4 \cdot 2HCl$	52.64 (52.39	6.36 6.37	4.90 4.91)	1.77
6i	C_2H_5	2,4-Cl_2	55	232—237 (dec.)	EtOH	$C_{25}H_{34}Cl_2N_2O_4 \cdot 2HCl$	52.64 (52.48	6.36 6.45	4.90 4.93)	1.64
6j	*n*-C_3H_7	3,4-Cl_2	49	224—226 (dec.)	EtOH–Et_2O	$C_{26}H_{36}Cl_2N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	52.62 (52.78	6.62 6.60	4.72 4.86)	1.36
6k	*n*-C_4H_9	3,4-Cl_2	40	210—214 (dec.)	EtOH–Et_2O	$C_{27}H_{38}Cl_2N_2O_4 \cdot 2HCl \cdot H_2O$	52.61 (52.45	6.87 6.88	4.54 4.53)	0.81
6l	*n*-C_5H_{11}	3,4-Cl_2	11	212—215 (dec.)	EtOH–Et_2O	$C_{28}H_{40}Cl_2N_2O_4 \cdot 2HCl \cdot 1.5H_2O$	52.59 (52.66	7.09 6.88	4.38 4.52)	N.T.
6m	*n*-C_6H_{13}	3,4-Cl_2	16	205—208 (dec.)	EtOH–Et_2O	$C_{29}H_{42}Cl_2N_2O_4 \cdot 2HCl \cdot 1.5H_2O$	53.30 (53.41	7.24 7.25	4.29 4.33)	Inact.
6n	$CH_2C_6H_5$	3,4-Cl_2	29	223—226 (dec.)	MeOH	$C_{30}H_{36}Cl_2N_2O_4 \cdot 2HCl \cdot 0.5H_2O$	56.17 (56.07	6.13 6.03	4.37 4.26)	0.58

a, *b* and *c*) See footnotes *a*), *b*) and *c*), respectively, of Table I.

TABLE III. γ-Chloro Tertiary Alcohols **8**

Compd. No.	R	X	Yield (%)	^{1}H-NMR ($CDCl_3$)
8a[a)]	CH_3	H	91	1.53 (3H, s), 2.00 (1H, s), 2.23 (2H, t, J=8 Hz), 3.00—3.80 (2H, m), 7.0—7.6 (5H, m)
8b	CH_3	4-CH_3	90	1.52 (3H, s), 2.00 (1H, s), 2.27 (3H, s), 2.18 (2H, t, J=8 Hz), 3.00—3.70 (2H, m), 6.80—7.40 (4H, m)
8c	CH_3	4-Cl	95	1.53 (3H, s), 2.20 (1H, s), 2.20 (2H, t, J=8 Hz), 3.00—3.70 (2H, m), 7.17 (4H, s)
8d	CH_3	3,4-Cl_2	93	1.55 (3H, s), 2.14 (1H, s), 2.23 (2H, t, J=8 Hz), 3.00—3.70 (2H, m), 7.00—7.60 (3H, m)
8e	C_2H_5	3,4-Cl_2	98	0.74 (3H, t, J=7 Hz), 1.82 (2H, q, J=7 Hz), 1.97 (1H, s), 2.23 (2H, t, J=7 Hz), 3.00—3.70 (2H, m), 6.80—7.60 (3H, m)
8f	n-C_3H_7	3,4-Cl_2	32	0.50—2.00 (7H, m), 2.00 (1H, s), 2.23 (2H, t, J=7 Hz), 2.90—3.70 (2H, m), 6.90—7.60 (3H, m)
8g	n-C_4H_9	3,4-Cl_2	32	0.50—2.00 (9H, m), 2.00 (1H, s), 2.23 (2H, t, J=7 Hz), 6.95—7.60 (3H, m)
8h	n-C_5H_{11}	3,4-Cl_2	48	0.50—2.00 (11H, m), 2.10 (1H, s), 2.20 (2H, t, J=7 Hz), 2.90—3.70 (2H, m), 6.90—7.50 (3H, m)
8i	n-C_6H_{13}	3,4-Cl_2	47	0.50—2.00 (13H, m), 2.00 (1H, s), 2.20 (2H, t, J=7 Hz), 2.90—3.70 (2H, m), 6.90—7.50 (3H, m)
8j	$CH_2C_6H_5$	3,4-Cl_2	93	2.10 (1H, s), 2.00—2.40 (2H, m), 2.80—3.70 (4H, m), 6.70—7.50 (8H, m)
8k	CH_3	2,4-Cl_2	99	1.68 (3H, s), 2.50 (1H, s), 2.00—3.70 (4H, m), 7.00—7.80 (3H, m)
8l	C_2H_5	2,4-Cl_2	36	0.70 (3H, t, J=7 Hz), 2.33 (1H, s), 1.10—3.60 (6H, m), 6.90—7.70 (3H, m)

a) J. W. Baker, *J. Chem. Soc.*, **1948**, 89.

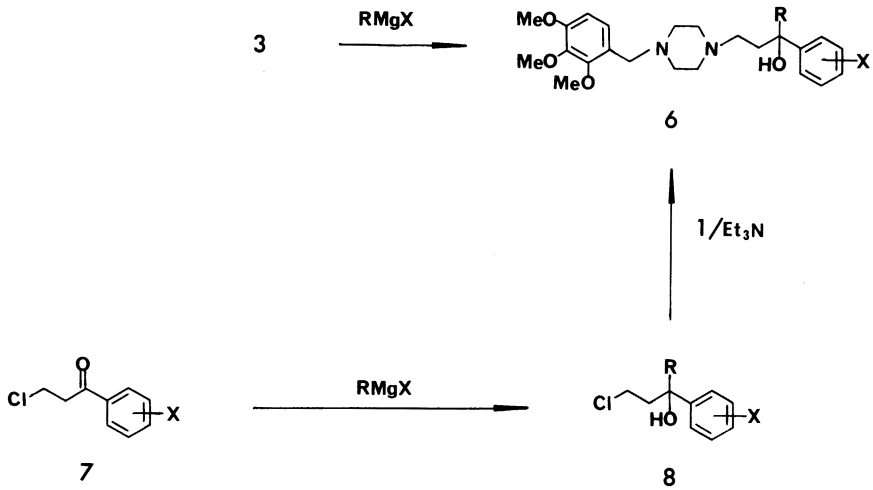

Chart 3

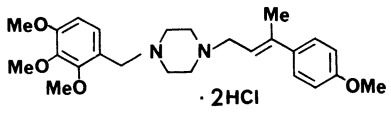

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Chart 4

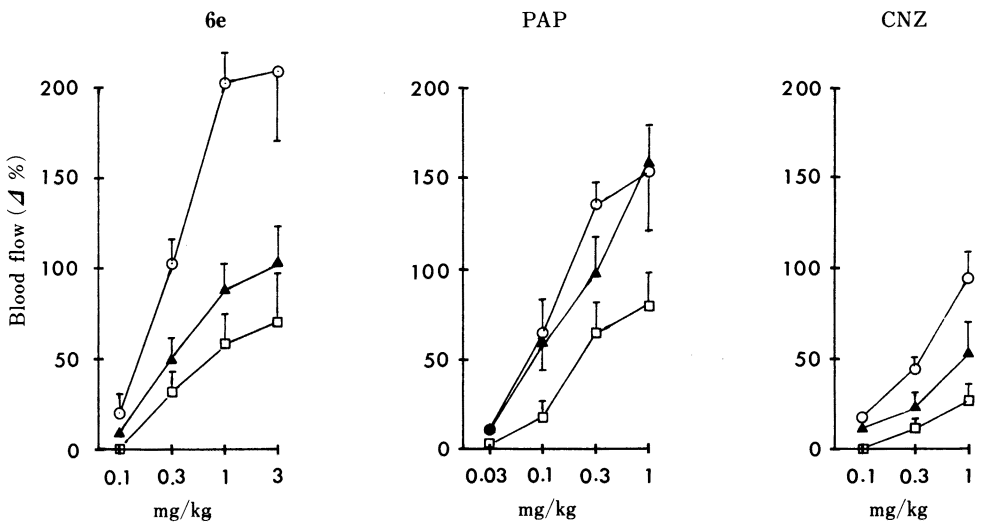

Fig. 1. Effect of Cerebral Vasodilators on Vertebral (○—○), Common Carotid (▲—▲) and Femoral (□—□) Blood Flows in Anesthetized Dog

Drugs were intravenously injected. CNZ, cinnarizine; PAP, papaverine. Means ± standard errors of 5 experiments.

Biological Testing

Most of the compounds **3a**—**6n** listed above were tested for cerebral vasodilating activity. The cerebral vasodilating activity was evaluated in dogs anesthetized with pentobarbital. The potency is expressed in terms of the ratio of the maximum change of blood flow in vertebral arteries after intravenous administration of the test compound (1 mg/kg) to that of papaverine (1 mg/kg). The results are summarized in Tables I and II. Almost all the compounds prepared possess stronger activity than trimetazidine. Potent cerebral vasodilating activity was observed in six compounds **6e**—**j**, which were superior in activity to cinnarizine and papaverine.

Moreover, in order to study the effects of these compounds on various arteries, **6e** was selected as a representative and its effect was compared with those of cinnarizine and papaverine. Figure 1 shows that **6e** exhibits a selective effect on vertebral arteries.

Experimental

Melting points were determined on a Yamato capillary melting point apparatus, model MP-21, and are uncorrected. ^{1}H-NMR spectra were determined on a Hitachi R-24A NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Silica gel 60 F_{254} (Merck) TLC plates were used for thin layer chromatography (TLC). For column chromatography, Silica gel 60 (Merck) was used. Trimetazidine dihydrochloride (**1**) was prepared according to the reported method.[9]

Preparation of the Mannich Bases 3a—e

1-(2-Benzoylethyl)-4-(2,3,4-trimethoxybenzyl)piperazine Dihydrochloride (3a)——A mixture of **1** (10 g), paraformaldehyde (4 g), acetophenone (7 g) and EtOH (100 ml) was refluxed for 6 h. After the mixture had cooled to room temperature, the precipitated solid was filtered off. Recrystallization of the solid from MeOH yielded 5.6 g (yield, 40%) of **3a** as colorless needles, mp 201—203 °C (dec.).

Compounds **3b**—**e** were obtained in the same manner as described for **3a**. The yields, melting points and elementary analytical data are given in Table I.

Preparation of the γ-Amino Secondary Alcohols 4a—i

1-[3-(3,4-Dichlorophenyl)-3-hydroxypropyl]-4-(2,3,4-trimethoxybenzyl)piperazine Dihydrochloride (4e)——A mixture of **3e** (11.6 g), 10% NaOH (50 ml) and AcOEt (100 ml) was stirred at room temperature. The organic layer was separated, washed with water and dried over Na_2SO_4. After removal of the solvent by evaporation,

the residue was suspended in MeOH (100 ml), and $NaBH_4$ (0.41 g) was added portionwise to the mixture. After being stirred for 30 min at room temperature, the mixture was poured into water and extracted with Et_2O (100 ml). The Et_2O layer was washed with water and dried over Na_2SO_4. HCl gas was bubbled into the solution and the precipitated solid was filtered off. Recrystallization of the solid from MeOH yielded 9.45 g (yield, 81%) of **4e** as colorless fine needles, mp 228—232 °C (dec.).

Compounds **4a—d** were obtained in the same manner as described for **4e**. The yields, melting points and elementary analytical data are given in Table I.

1-[3-Hydroxy-3-(2-naphthyl)propyl]-4-(2,3,4-trimethoxybenzyl)piperazine Dihydrochloride (4i)——A mixture of **1** (17 g), paraformaldehyde (6 g), 2-acetonaphthone (8.5 g) and CH_3NO_2 (200 ml) was refluxed for 4.5 h. After the mixture had cooled to room temperature, 10% NaOH (100 ml) was added and the organic layer was separated, washed with water and dried over Na_2SO_4. Removal of the solvent by evaporation gave crude 1-[2-(2-naphthoyl)ethyl]-4-(2,3,4-trimethoxybenzyl)piperazine. $NaBH_4$ (0.25 g) was added portionwise to the mixture of the Mannich base (3 g) and MeOH (30 ml). After being stirred for 2 h, the mixture was poured into water and extracted with AcOEt. The organic layer was washed with water and dried over $MgSO_4$. HCl–MeOH (5 ml) was added to the solution and the precipitated solid was filtered off. Recrystallization of the solid from MeOH–EtOH (1 : 1) yielded 1.34 g (yield, 43%) of **4i** as pale yellow fine prisms, mp 223—227 °C (dec.).

Compounds **4f—h** were obtained in the same manner as described for **4i**, though, **4f** could not be recrystallized because of its insolubility. The yields, melting points and elementary analytical data are given in Table I.

Preparation of the Cinnamylpiperazines 5a—f

1-(3,4-Dichlorocinnamyl)-4-(2,3,4-trimethoxybenzyl)piperazine Dihydrochloride (5e)——A mixture of **4e** (4.0 g), phosphoric acid (15 ml) and water (15 ml) was stirred at 90 °C for 7 h. After the mixture had cooled to room temperature, the mixture was poured into water and the solution was made basic by the addition of 10% NaOH and extracted with Et_2O. The Et_2O layer was washed with water. The dried extract was concentrated and the residue was chromatographed on a silica gel column with Et_2O. After concentration of the eluate, HCl–EtOH was added and precipitated solid was filtered off. Recrystallization of the solid from CH_3CN yielded 0.39 g (yield, 10%) of **5e** as colorless fine needles, mp 240—243 °C (dec.).

Compounds **5a—d** were obtained in the same manner as described for **5e**. The yields, melting points and elementary analytical data are given in Table I.

1-(2,4-Dichlorocinnamyl)-4-(2,3,4-trimethoxybenzyl)piperazine Dihydrochloride (5f)——A mixture of **1** (3.39 g), 2,4-dichlorocinnamyl chloride[7] (2.22 g), benzene (60 ml) and triethylamine (4 ml) was refluxed for 3 h. After the mixture had cooled to room temperature, water (50 ml) was added and the organic layer was separated, washed with water, dried over Na_2SO_4 and concentrated. The residue was diluted with MeOH (10 ml) and a MeOH solution of maleic acid (2.5 g) was added. The precipitated solid was filtered off and recrystallized from CH_3CN to yield 2 g (yield, 29%) of **5f**, mp 177—179 °C (dec.).

Compounds **5a** and **5e** were prepared in the same manner as described for **5f**. The yields were 30% and 29%, respectively.

Preparation of the γ-Amino Tertiary Alcohols 6a—n

1-[3-Hydroxy-3-(4-methoxyphenyl)butyl]-4-(2,3,4-trimethoxybenzyl)piperazine Dimaleate (6c)——A small portion of a solution of methyl iodide (33 g) in dry Et_2O (100 ml) was added dropwise to magnesium turnings (5.7 g) under a nitrogen atmosphere. After the spontaneous reaction had begun, residual methyl iodide solution was added at a rate sufficient to maintain gentle reflux. When the addition was complete, the mixture was stirred for 1 h at room temperature then cooled to ice-bath temperature. The free base of **3c** (10 g) in dry benzene (50 ml) was added dropwise, and the reaction mixture was stirred for 1 h. After the usual work-up, the product was chromatographed on silica gel with $CHCl_3$–MeOH (20 : 1). Concentration of the eluate gave 7.2 g of the free base of **6c** (yield, 70%) as a colorless oil.

HCl–MeOH (25 ml) was added to this oil (6 g) in EtOH (25 ml) and the precipitated solid was filtered off. The TLC and NMR analysis revealed that this solid was a mixture of **6c** and **9**. It was refluxed for 1 h in HCl–MeOH, then the solid was filtered off and recrystallized from water to yield 1.6 g (total yield, 24%) of **9**, mp 222—224 °C (dec.). NMR (D_2O–DMSO-d_6–CD_3OD): 2.0 (3H, s, allylic methyl). *Anal.* Calcd for $C_{25}H_{34}N_2O_4 \cdot 2HCl \cdot 0.5H_2O$: C, 59.05; H, 7.33. N, 5.51. Found: C, 58.90; H, 7.44; N, 5.54.

Maleic acid (0.62 g) in EtOH (10 ml) was added to a solution of the oil obtained by the Grignard reaction described above (1.2 g) in EtOH (10 ml) and the precipitated solid was filtered off. The solid was recrystallized from EtOH to give 1.0 g (total yield, 38%) of **6c**, mp 169—172 °C (dec.).

1-[3-(2,4-Dichlorophenyl)-3-hydroxypentyl]-4-(2,3,4-trimethoxybenzyl)piperazine Dihydrochloride (6i)——A small portion of a solution of ethyl iodide (24 g) in dry Et_2O (100 ml) was added dropwise to magnesium turnings (2.6 g) under a nitrogen atmosphere. After the spontaneous reaction had begun, residual ethyl iodide solution was added at a rate sufficient to maintain gentle reflux. When the addition was complete, the mixture was stirred for 1 h at room temperature and then cooled to ice-bath temperature. Then **7e**[8c] (24.5 g) in dry benzene (100 ml) was added dropwise and the reaction mixture was stirred for 1 h. After the usual work-up, the product was chromatographed on silica gel with *n*-hexane–AcOEt (10 : 1). Concentration of the eluate gave 9.6 g of **8l** (yield, 36%) as a pale brown oil. A

mixture of **8l** (9.5 g), **1** (11 g), triethylamine (11 g) and xylene (150 ml) was refluxed overnight. The cooled mixture was washed with water and dried over $MgSO_4$. After removal of the solvent by evaporation, conc. HCl (6 ml) and EtOH (60 ml) were added to the residue. The precipitated solid was filtered off and recrystallization from EtOH yielded 10 g (yield, 55%) of **6i** as colorless crystals, mp 232—237 °C (dec.).

Compounds **6a**, **b**, **d**, **e**, **g**—**n** were obtained in the same manner as described for **6i**. The yields, melting points and elementary analytical data are given in Table II.

Biological Testing Method——The cerebral blood flow-increasing activity was measured by using the amount of vertebral blood flow as an index.[10] Mongrel dogs of either sex (body weight 11 to 18 kg) were anesthetized with sodium pentobarbital (30 mg/kg, by intravenous injection) and artificially ventilated. The right vertebral artery was isolated from the surrounding tissues and a flow probe was attached to it and led to an electromagnetic flow meter (MVF-2100, Nihon Koden Co., Ltd.). The blood flow was periodically measured.

Each of the test compounds was dissolved in a 2% tartaric acid solution containing 20% dimethylacetamide, and administered to the right femoral vein at a dose of 1 mg/kg. The potency was expressed in terms of the ratio of the maximum change of blood flow induced by the test compound to that induced by papaverine.

References and Notes

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