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Synthesis and Biological Activities of 3-Aminomethyl-1,2-dihydronaphthalene Derivatives

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A series of 3-aminomethyl-1,2-dihydronaphthalene derivatives (**6**—**22**) was prepared from the corresponding 3,4-dihydro-1(2*H*)-naphthalenone derivatives (**24a**—**q**) in three steps, namely the Mannich reaction, reduction of the carbonyl group with sodium borohydride, and dehydration with ethanolic hydrogen chloride. Compounds **6**—**22** and several related analogs (**23**, **27**—**30**) were tested for vasodilating and antihypertensive activities. Potent cerebral vasodilating and antihypertensive activities were exhibited by 1-benzhydryl-4-(7-disubstituted amino-1,2-dihydro-3-naphthyl)methylpiperazines (**16**, **18** and **19**).

Keywords——dihydronaphthalene; piperazine; *N*-benzhydrylpiperazine; Mannich reaction; cerebral vasodilator; vasodilating activity; antihypertensive activity

3-(*N*-Substituted amino)methyl-1,2-dihydronaphthalenes (**1**) were first synthesized by Mannich in 1937.[1] Since then, relatively few papers have dealt with the synthesis or biological activity of these compounds.[2] Very recently CNS activity of compounds **4** and **5** was mentioned in a patent[3] and a report.[4] The structure of the 3-aminomethyl-1,2-dihydronaphthalene skeleton seemed to us to be of particular interest in view of its possible relationship with cardiovascular activity, because its partial structure Ph–C=C–C–N is involved in a cerebral vasodilator, cinnarizine (**2**), and there is a structural resemblance to piperoxan (**3**), an α-adrenergic blocker. This paper describes the synthesis of a variety of new 3-aminomethyl-1,2-dihydronaphthalene derivatives (**6**—**23**, Table I), as well as the vasodilating and hypotensive activities of the compounds.

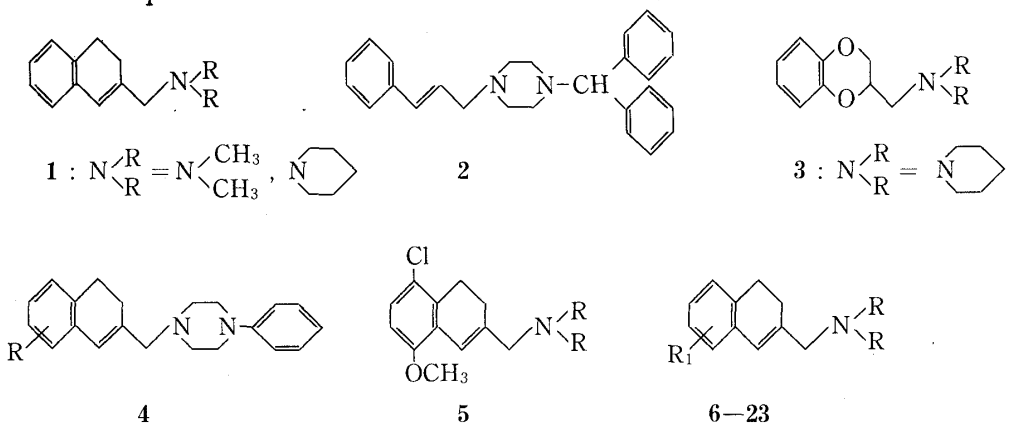
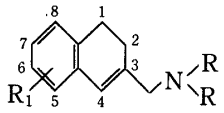


Chart 1

Chemistry

Most of the 3-aminomethyl-1,2-dihydronaphthalene derivatives (**6**—**22**) listed in Table I were prepared by the methods shown in Chart 2. Thus, 3,4-dihydro-1(2*H*)-naphthalenone derivatives (**24a**—**q**) having a variety of substituents on the benzene ring were subjected to the Mannich reaction with *N*,*N*-disubstituted amine hydrochloride and formaldehyde. The resulting Mannich bases (**25**) was reduced with sodium borohydride ($NaBH_4$) to give the

TABLE I. 3-Aminomethyl-1, 2-dihydronaphthalene Derivatives



Compd. No.	R_1	N^{R}_{R}	Yield (%) (Method)	Form	mp (°C) dec.	Formula	Analysis(%) Calcd (Found) C	H	N
6a	H	N-Ph	26 (I)	HCl	209—211	$C_{21}H_{24}N_2\cdot$ HCl	66.84 (66.41)	6.95 7.17	7.42 7.17)
6b	H	NCH$_2$Ph-3,4,5-(OCH$_3$)$_3$	62 (H)	HCl	215—225	$C_{25}H_{32}N_2O_3\cdot$ HCl·H$_2$O	60.11 (60.60)	7.27 7.08	5.61 5.69)
6c	H	NCH(Ph)$_2$	65 (F)	HCl	225—230	$C_{28}H_{30}N_2\cdot$ 2HCl	71.94 (72.03)	6.90 6.56	5.99 5.95)
7a	7-OCH$_3$	NCH$_2$COOC$_2$H$_5$	27 (H)	HCl	192—197	$C_{20}H_{28}N_2O_3\cdot$ 2HCl·H$_2$O	55.17 (55.44)	7.41 7.39	6.43 6.35)
7b	7-OCH$_3$	NCH$_2$CON	75 (J)	HCl	210—220	$C_{22}H_{31}N_3O_2\cdot$ 2HCl	59.72 (59.43)	7.52 7.54	9.50 9.35)
7c	7-OCH$_3$	N-Ph	24 (I)	HCl	205—210	$C_{22}H_{26}N_2O\cdot$ 2HCl	64.86 (64.99)	6.93 6.94	6.88 6.61)
7d	7-OCH$_3$	NCH$_2$Ph-3,4,5-(OCH$_3$)$_3$	74 (H)	HCl	218—231	$C_{26}H_{34}N_2O_4\cdot$ 2HCl	61.05 (60.59)	7.09 7.07	5.48 5.47)
7e	7-OCH$_3$	NCH(Ph)$_2$	68 (H)	HCl	224—228	$C_{29}H_{32}N_2O\cdot$ 2HCl	70.01 (69.99)	6.89 6.92	5.63 5.65)
7f	7-OCH$_3$	NCH(Ph)$_2$	34 (I)	HCl	145—150	$C_{30}H_{34}N_2O\cdot$ 2HCl·2H$_2$O·1/4Et$_2$O	65.77 (65.86)	7.57 7.40	4.95 4.95)
8a	7-OCH$_3$ 8-OCH$_3$	O	50 (H)	HCl	220—225	$C_{17}H_{23}NO_3\cdot$ HCl	62.66 (62.78)	7.42 7.42	4.30 4.12)
8b	7-OCH$_3$ 8-OCH$_3$	NCH$_2$COOC$_2$H$_5$	37 (I)	HCl	200—210	$C_{21}H_{30}N_2O_4\cdot$ 2HCl	56.37 (55.90)	7.21 7.29	6.26 6.51)
8c	7-OCH$_3$ 8-OCH$_3$	NCH$_2$CON	74 (J)	HCl	220—235	$C_{23}H_{33}N_3O_3\cdot$ 2HCl·H$_2$O	56.32 (56.33)	7.60 7.39	8.57 8.61)
8d	7-OCH$_3$ 8-OCH$_3$	N-Ph	13 (I)	HCl	235—245	$C_{23}H_{28}N_2O_2\cdot$ 2HCl	63.15 (63.16)	6.91 7.06	6.41 6.65)
8e	7-OCH$_3$ 8-OCH$_3$	NCH$_2$Ph-3,4,5-(OCH$_3$)$_3$	83 (H)	HCl	220—240	$C_{27}H_{36}N_2O_5\cdot$ 2HCl	59.88 (59.57)	7.07 7.12	5.17 5.01)
8f	7-OCH$_3$ 8-OCH$_3$	NCH(Ph)$_2$	91 (F)	HCl	230—240	$C_{30}H_{34}N_2O_2\cdot$ 2HCl	68.30 (68.16)	6.88 6.94	5.31 5.35)
9	6-OCH$_3$ 7-OCH$_3$	NCH(Ph)$_2$	95 (F)	HCl	230—243	$C_{30}H_{34}N_2O_2\cdot$ 2HCl	68.30 (68.15)	6.88 6.85	5.31 5.10)
10	5-OCH$_3$ 8-OCH$_3$	NCH(Ph)$_2$	27 (I)	Base	112—114	$C_{30}H_{34}N_2O_2\cdot$ H$_2$O	76.24 (75.85)	7.68 7.32	5.93 5.86)
11a	6-OCH$_3$ 7-NO$_2$	O	23 (I)	HCl	200—270	$C_{16}H_{20}N_2O_4\cdot$ HCl·1/2H$_2$O	54.93 (55.16)	6.34 6.31	8.01 7.89)
11b	6-OCH$_3$ 7-NO$_2$	NCH(Ph)$_2$	95 (F)	HCl	240—245	$C_{29}H_{31}N_3O_3\cdot$ 2HCl	64.20 (64.10)	6.13 6.13	7.75 7.82)
12a	7,8-OCH$_2$O-	O	61 (H)	HCl	237	$C_{16}H_{19}NO_3\cdot$ HCl	62.03 (61.93)	6.51 6.56	4.52 4.41)
12b	7,8-OCH$_2$O-	NCH(Ph)$_2$	64 (H)	HCl	234—235	$C_{29}H_{30}N_2O_2\cdot$ 2HCl·1/2H$_2$O	66.91 (67.00)	6.39 6.12	5.38 5.36)
13a	6,7-OCH$_2$O-	O	61 (H)	HCl	245—260	$C_{16}H_{19}NO_3\cdot$ HCl	62.03 (61.94)	6.51 6.60	4.52 4.47)
13b	6,7-OCH$_2$O-	NCH(Ph)$_2$	64 (H)	HCl	234—235	$C_{29}H_{30}N_2O_2\cdot$ 2HCl·1/2H$_2$O	66.91 (67.00)	6.39 6.12	5.38 5.36)
14	7-O(CH$_2$)$_3$CH$_3$ 8-O(CH$_2$)$_3$CH$_3$	O	29 (H)	HCl	196—201	$C_{23}H_{35}NO_2\cdot$ HCl	67.38 (67.35)	8.85 8.91	3.42 3.53)
15a	7-N O	O	79 (G)	HCl	198—200	$C_{19}H_{26}N_2O_2\cdot$ 2HCl·1/2H$_2$O	59.37 (59.22)	7.61 7.37	7.29 7.03)
15b	7-N O	N	35 (I)	HCl	206—210	$C_{20}H_{28}N_2O\cdot$ 2HCl	62.33 (61.87)	7.32 7.66	7.27 7.20)
15c	7-N O	N-CH$_2$Ph	88 (G)	HCl	212—214	$C_{27}H_{34}N_2O\cdot$ 2HCl	68.20 (68.29)	7.63 7.78	5.89 5.99)
15d	7-N O	N-CH$_3$	8.9 (H)	HCl	230—234	$C_{20}H_{29}N_3O\cdot$ 3HCl·1/2H$_2$O	53.87 (53.63)	7.46 7.41	9.43 9.35)
15e	7-N O	NCH$_2$COOC$_2$H$_5$	19 (I)	HCl	180—183	$C_{23}H_{33}N_3O_3\cdot$ 3HCl·1/2H$_2$O	53.33 (52.91)	7.20 7.06	8.11 7.95)
15f	7-N O	N-Ph	8 (I)	HCl	177—180	$C_{25}H_{31}N_3O\cdot$ 3HCl	60.18 (60.22)	6.87 7.15	8.42 8.26)

Compd. No.	R_1	$N\langle^{R}_{R}$	Yield (%) (Method)	Form	mp (°C) dec.	Formula	Analysis(%) Calcd (Found) C	H	N
15g	7-N O	N NCH$_2$Ph	49 (G)	HCl	219—223	$C_{26}H_{33}N_3O\cdot 3HCl$	60.88 (60.52	7.07 7.05	8.19 8.07)
15h	7-N O	N NCH(Ph)$_2$	40 (I)	HCl	193—197	$C_{32}H_{37}N_3O\cdot 3HCl\cdot H_2O$	63.31 (63.35	6.97 6.61	6.92 6.89)
15i	7-N O	N NCH(Ph)$_2$	47 (I)	HCl	173—176	$C_{33}H_{39}N_3O\cdot 3HCl\cdot 2H_2O\cdot AcOEt$	61.11 (60.63	7.07 7.00	5.78 6.04)
15j	7-N O	N	72 (G)	HCl	186—189	$C_{23}H_{26}N_2O\cdot 2HCl$	65.87 (65.49	6.73 6.67	6.68 6.56)
15k	7-N O	N	71 (G)	HCl	182—185	$C_{24}H_{28}N_2O_2\cdot 2HCl$	66.51 (66.10	6.98 6.98	6.46 6.41)
15l	7-N O	N, N, OCH$_3$, OCH$_3$	27 (I)	HCl	210—215	$C_{26}H_{32}N_2O_3\cdot 2HCl\cdot H_2O$	61.05 (61.02	6.70 6.93	5.48 5.46)
16	7-N	N NCH(Ph)$_2$	60 (I)	HCl	190—205	$C_{33}H_{39}N_3\cdot 3HCl\cdot H_2O$	65.50 (65.52	7.33 7.13	6.95 6.76)
17	7-N	N NCH(Ph)$_2$	14 (I)	HCl	187—190	$C_{34}H_{41}N_3\cdot 3HCl\cdot H_2O$	65.96 (65.59	7.49 7.25	6.79 6.39)
18	7-N(CH$_3$)$_2$	N NCH(Ph)$_2$	30 (I)	HCl	190—195	$C_{30}H_{35}N_3\cdot 3HCl\cdot 1/2H_2O$	64.80 (64.80	7.07 7.04	7.56 7.83)
19	7-N(C$_2$H$_5$)$_2$	N NCH(Ph)$_2$	24 (I)	HCl	195—220	$C_{32}H_{39}N_3\cdot 3HCl\cdot H_2O$	64.80 (64.81	7.48 7.21	7.09 6.96)
20	7-N(C$_4$H$_9$)$_2$	N NCH(Ph)$_2$	25 (I)	HCl	175—180	$C_{36}H_{47}N_3\cdot 3HCl$	68.50 (68.21	7.98 8.17	6.66 6.77)
22	7-NH$_2$	N NCH(Ph)$_2$	48 (I)	HCl	>160	$C_{28}H_{33}N_3\cdot 3HCl\cdot H_2O$	62.63 (62.00	6.76 6.65	7.83 7.71)
23a	7-NHCOCH$_3$	N NCH(Ph)$_2$	75 (K)	HCl	189—195	$C_{30}H_{33}N_3O\cdot 2HCl\cdot 3/2H_2O$	65.33 (65.21	6.94 6.57	7.62 7.46)
23b	7-NHCOC$_2$H$_5$	N NCH(Ph)$_2$	42 (K)	HCl	178—181	$C_{31}H_{35}N_3O\cdot 2HCl\cdot 2H_2O$	64.79 (64.36	7.19 6.78	7.31 7.25)
23c	7-NHCOC$_3$H$_7$	N NCH(Ph)$_2$	55 (K)	HCl	165—168	$C_{32}H_{37}N_3O\cdot 2HCl\cdot 2H_2O$	65.30 (64.87	7.36 6.95	7.14 6.90)
23d	7-NHSO$_2$CH$_3$	N NCH(Ph)$_2$	68 (L)	HCl	190—235	$C_{29}H_{33}N_3O_2S\cdot 2HCl\cdot H_2O$	60.21 (60.69	6.10 6.15	7.26 7.17)
21	6-N O	N NCH(Ph)$_2$	20 (H)	Maleate	195—197	$C_{32}H_{37}N_3O\cdot C_4H_4O_4$	72.58 (72.07	6.94 6.82	7.05 6.87)

corresponding alcohols (**26**) each as a mixture of two stereoisomers with respect to the aminomethyl group and the resulting hydroxyl group. Several pairs of isomers were separated by silica gel column chromatography, and the configuration of each was determined from the nuclear magnetic resonance (^{1}H-NMR) spectrum, in which the coupling constant (J) of C_1–H was 8—11 Hz for the *trans* and 0— 4Hz for the *cis* isomer. The alcohols (**26**) were dehydrated very smoothly to the desired dihydronaphthalene derivatives (**6**—**22**) by treatment with 20% ethanolic hydrogen chloride.

In the case of 6-acetamido-3,4-dihydro-1(2*H*)-naphthalenone (**24q**),[5] deacylation took place simultaneously with the dehydration to afford 1-benzhydryl-4-(7-amino-1,2-dihydro-3-naphthyl)methylpiperazine (**22**). By acylation with an anhydride or acyl chloride, , **22** was led to several 7-acylamino derivatives (**23a**—**d**). 1-Pyrrolidinylcarbonylmethylpiperazine derivatives, **7b** and **8c**, were prepared by the reaction of pyrrolidine with ethoxycarbonylmethylpiperazine derivatives, **7a** and **8b**, respectively.

Biological tests of the above dihydronaphthalene derivatives (**6**—**23**) in dogs revealed that a series of *N*-benzhydrylpiperazine derivatives elicit an increase in vertebral flow indicative of cerebral vasodilating action. Therefore, we undertook to synthesize some further 1-benzhydrylpiperazine derivatives having dihydrobenzocycloheptenylmethyl (**27**), tetrahydronaphthylmethyl (**28**), napthylmethyl (**29**) and dihydronaphthoyl (**30**) groups in place of the dihydro-

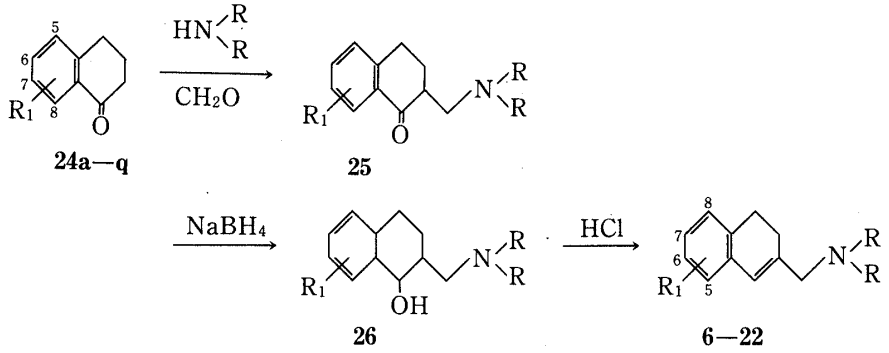


Chart 2

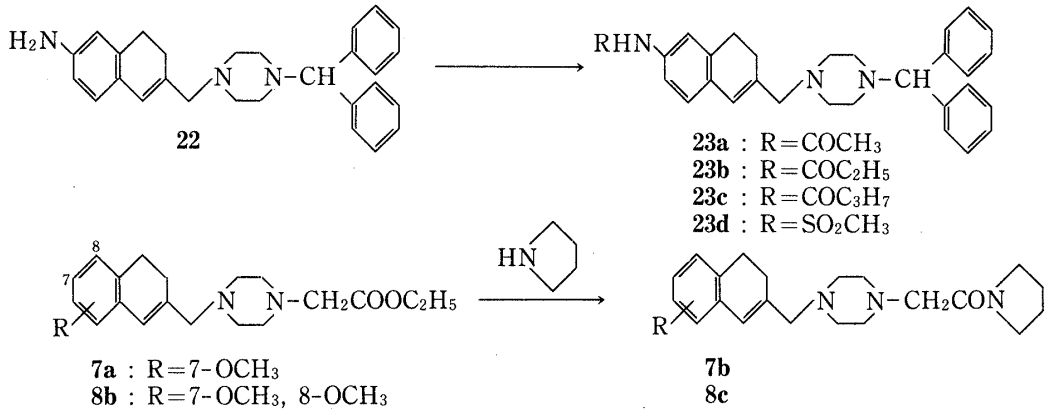
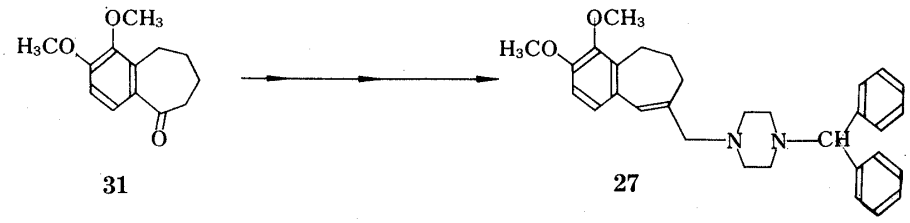


Chart 3



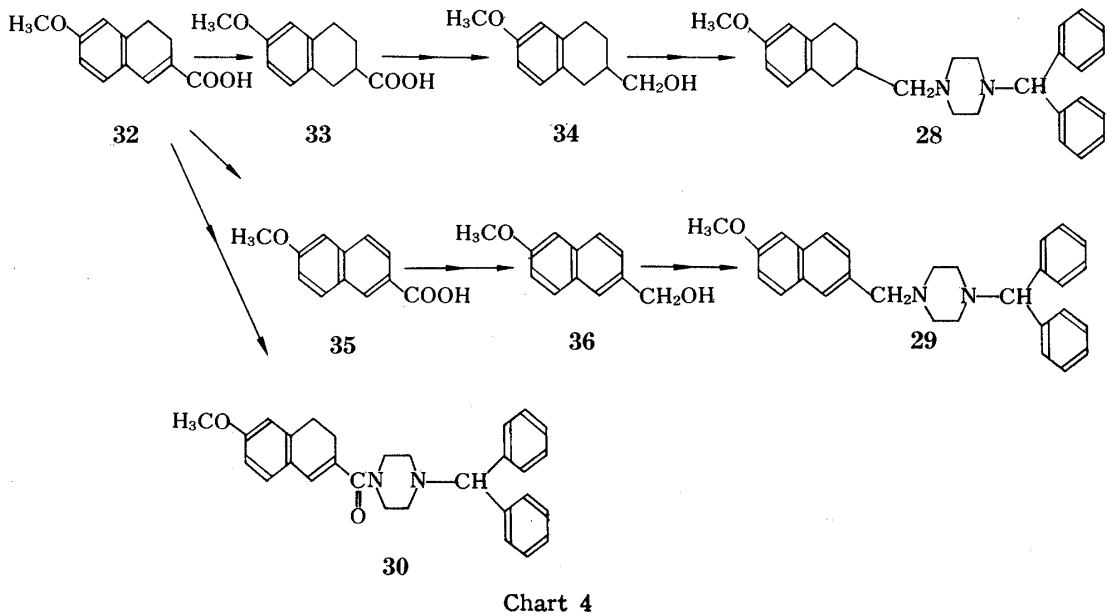


Chart 4

naphthylmethyl group. Thus, starting from 1,2-dimethoxy-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**31**),[6] 1-benzhydryl-4-(1,2-dimethoxy-8,9-dihydro-7*H*-benzocyclohepten-6-yl)methylpiperazine (**27**) was prepared by the same reaction sequence as that used for the dihydronaphthalene derivatives (**6**—**22**). On the other hand, 3,4-dihydro-6-methoxy-2-naphthoic acid (**32**)[7] was converted to 6-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid (**33**) by catalytic hydrogenation. Esterification of the carboxyl group of **33**, followed by reduction with lithium aluminum hydride ($LiAlH_4$), gave the alcohol (**34**). After chlorination of **34** with thionyl chloride, the resulting alkyl chloride was treated with 1-benzhydrylpiperazine to give 1-benzhydryl-4-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)methylpiperazine (**28**). By the same procedure, 6-methoxy-2-naphthoic acid (**35**), prepared by the dehydrogenation of **32** with sulfur, was converted to 1-benzhydryl-4-(6-methoxy-2-naphthyl)methylpiperazine (**29**). 1-Benzhydryl-4-(6-methoxy-3,4-dihydro-2-naphthoyl)piperazine (**30**) was prepared from **32** by chlorination with thionyl chloride followed by the reaction of the resulting acyl chloride with 1-benzhydrylpiperazine.

Biological Tests

The compounds listed above (**6**—**23** and **27**—**30**) were tested for vasodilating and antihypertensive activities. The results are summarized in Table II. Vasodilating activity was evaluated in terms of the change in blood flows in the vertebral (VBF) and femoral (FBF) arteries at 1, 5, and 20 min after intravenous administration of test compounds to dogs anesthe-

TABLE II. Biological Activities

Compd. No.	Dose (*i.v.*) mg/kg	Vasodilating activity (%) (Anesthetized dog) (min)												Antihypertensive activity mmHg		
		HR			SBP			VBF			FBF			Dose (*p.o.*)	(SHR)	
		1	5	20	1	5	20	1	5	20	1	5	20	mg/kg	1h	3h
6a	1	+15	+12	+1	−16	−1	−2	+37	−5	−7	+282	+26	+33	30	−19	−15
6b	1	+17	−1	−4	−12	−3	−3	+174	−3	+4	+163	+23	+60	30	+3	−2
7c	1	+10	+9	+13	−7	−2	0	+28	+6	+2	+89	+38	+38	30	−11	−15
7e	1	−1	+1	+2	−3	−2	−1	+59	+97	+38	+9	+19	+26	30	−8	−13
8c	1	+20	0	−6	−12	−5	−6	+101	−21	0	+49	+64	+67	30	+10	+6
8e	1	0	−3	−1	−12	−7	0	+56	+53	+31	+3	+9	+4	30	−7	−5
11b	2	+1	+2		+2	+4		+25	+22		+5	+6		30	+3	−2
12b	1	+2	+1	0	−4	+1	+5	+14	+52	+44	+27	−11	−12	—		
13a	1	+8	+2	+4	−28	−1	+2	+162	+31	+8	+296	+58	+18	30	−16	−3
13b	1	+4	+4	−1	−1	0	+3	+46	+51	+2	+19	+41	+18	30	0	−6
14	1	−2	−5	−5	+7	+6	+8	−8	−12	−17	+30	+23	+4	30	+3	+6
15f	1	+11	+10	+9	−17	−4	−4	+23	−13	−18	+473	+75	+85	30	−12	−4
15h	1	−4	−15	−16	−9	−13	−10	0	0	+10	−14	0	−14	30	−84[c]	−96[c]
15i	1	+8	+9	+10	−17	−10	−6	+148	+226	+126	0	+39	+44	30	−14	−6
15k	1	+28	+23	+22	−7	+4	−1	+83	+67	+28	+229	+486	+43	30	−27[a]	−23
16	1	0	−6	−10	−1	−8	−6	+14	+50	+54	−3	+50	+76	30	−44[b]	−58[b]
17	0.1	+2	+2	−1	0	0	+5	+1	+23	+84	−1	+2	+15	30	−12	−92[a]
18	1	+3	−3	+2	−8	−16	−10	+37	+77	+77	+3	+81	+94	30	−72[b]	−74[a]
19	0.1	+1	−1	−2	+1	+2	+2	+5	+21	+31	+10	−8	−6	10	−42[b]	−82[b]
23a	1	+9	0	+4	−16	−5	−5	+147	+25	+28	+156	+31	+95	30	−13	−29[b]
23c	1	+5	−1	0	−12	−11	−10	+47	+61	+58	+20	+10	+11	—		
27	1	+1	−2	−2	−5	−2	+2	+56	+51	+5	+1	+5	−5	—		
28	1	+9	+3	−3	+3	0	−2	+17	+6	−6	+11	−11	−11	30	−6	−13
29	—													30	−7	−5
30	—													30	−4	−3
Cinnarizine	1	+3	0		−10	−5		+35	+24	0	10	+1		—		
Hydralazine	0.5	0	+6	+4	−3	−7	−16	+4	+61	+89	+7	+8	+16	5	−41[b]	−38[b]
Prazocine	0.1	+16	+1	−2	−21	−9	−27	+8	−4	−8	+278	+222	+67	3	−33[a]	−35[a]
														30	−49[b]	−62[b]

a) $p<0.05$, *b*) $p<0.01$, *c*) $p<0.001$ in Student's *t*-test

tized with pentobarbital. Simultaneously, changes in beating rate (HR) and blood pressure (SBP) were also measured. Antihypertensive activity was tested in spontaneously hypertensive rats (SHR) and the activity was expressed in terms of the decrease ($-\Delta$mmHg) in blood pressure at 1 and 3 h after oral administration of the compounds.

Significant cerebral vasodilating activity was observed in nine compounds, **7e**, **8e**, **12b**, **15i**, **15k**, **16**, **17**, **18** and **23c**. Compounds **16**, **18** and **19** showed potent antihypertensive activity in SHR. Compound **15h** showed the most potent antihypertensive activity in SHR, but had no vasodilating action in anesthetized dogs.

Experimental

All melting points were determined on a Yanagimoto micro-melting point apparatus (a hot stage type) and are uncorrected. The infrared (IR) spectra were recorded with a Hitachi 215 spectrophotometer. The ^{1}H-NMR spectra were recorded with a Varian T-60, HA-100 or EM 390 spectrometer with tetramethylsilane (TMS) as an internal standard.

3,4-Dihydro-1(2*H*)-naphthalenone Derivatives (24a—q)——3,4-Dihydro-1(2*H*)-naphthalenone (**24a**) and 6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**24b**) were purchased from Aldrich Chemical Co.. 5,6-Dimethoxy-,[8] 6,7-dimethoxy-,[9] 5,8-dimethoxy,[10] 6-methoxy-5-nitro-,[11] 6,7-methylenedioxy-,[12] 6-morpholino-,[13] 6-(*N*,*N*-dimethylamino)-[14] and 6-acetamido-3,4-dihydro-1(2*H*)-naphthalenone[5] (**24c**, **24d**, **24e**, **24f**, **24h**, **24j**, **24m** and **24q**) were prepared according to the cited references. Compounds **24j** and **24m** were isolated by leading them to the crystalline hydrochlorides. **24j**·HCl, mp 118—121°C, *Anal.* Calcd for $C_{14}H_{17}NO_2$·HCl: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.32; H, 6.75; N, 5.31. **24m**·HCl, mp 136—140°C, *Anal.* Calcd for $C_{12}H_{15}NO$·HCl: C, 63.85; H, 7.15; N, 6.21. Found: C, 63.65; H, 7.07; N, 6.01.

5,6-Methylenedioxy-3,4-dihydro-1(2*H*)-naphthalenone (**24g**) was prepared from 5,6-dihydroxy-3,4-dihydro-1(2*H*)-naphthalenone[8b] in the manner described for the synthesis of the 6,7-methylenedioxy isomer (**24h**),[12] mp 140—142°C, *Anal.* Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.56; H, 5.30.

5,6-Dibutoxy-3,4-dihydro-1(2*H*)-naphthalenone (**24i**) was prepared by the reaction of 5,6-dihydroxy-3,4-dihydro-1(2*H*)-naphthalenone[8b] with butyl bromide.[11] IR ν_{max}^{neat} cm^{-1}: 1680 (C=O), ^{1}H-NMR ($CDCl_3$) δ: 0.8—1.2 (6H, m), 1.2—2.3 (10H, m), 2.5 (2H, t, J=6 Hz), 2.9 (2H, t, J=6 Hz), 3.8—4.2 (4H, m), 6.8 (1H, d, J=9 Hz), 7.8 (1H, d, J=9 Hz).

6-(*N*,*N*-Disubstituted amino)-3,4-dihydro-1(2*H*)-naphthalenones (**24k**, **24l**, **24n** and **24o**) were prepared by the reaction of 6-amino-3,4-dihydro-1(2*H*)-naphthalenone[5] with 1,5-dibromopentane, 1,6-dibromohexane, ethyl bromide and butyl bromide, respectively, under conditions similar to those used for the preparation of **24j**.[13]

6-Piperidino-3,4-dihydro-1(2*H*)-naphthalenone (**24k**·HCl), mp 200—205°C (in a sealed tube). *Anal.* Calcd for $C_{15}H_{19}NO$·HCl: C, 67.78; H, 7.59; N, 5.27. Found: C, 67.54; H, 7.56; N, 5.04.

6-(1-Perhydroazepinyl)-3,4-dihydro-1(2*H*)-naphthalenone (**24l**·HCl), mp 130—133°C. *Anal.* Calcd for $C_{16}H_{21}NO$·HCl: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.40; H, 7.64; N, 4.81.

6-(*N*,*N*-Diethylamino)-3,4-dihydro-1(2*H*)-naphthalenone (**24n**·HCl), mp 124—129°C. *Anal.* Calcd for $C_{14}H_{19}NO$·HCl: C, 66.25; H, 7.94; N, 5.52. Found: C, 66.28; H, 7.73; N, 5.46.

6-(*N*,*N*-Dibutylamino)-3,4-dihydro-1(2*H*)-naphthalenone (**24o**·HCl), mp 115—120°C. *Anal.* Calcd for $C_{18}H_{27}NO$·HCl: C, 69.76; H, 8.78; N, 4.52. Found: C, 69.90; H, 9.05; N, 4.45.

7-Morpholino-3,4-dihydro-1(2*H*)-naphthalenone (**24p**·HCl) was prepared from 7-amino-3,4-dihydro-1(2*H*)-naphthalenone[15] and bis(chloroethyl)ether in the manner described for the preparation of **24j**,[13] mp 230—233°C (dec.). *Anal.* Calcd for $C_{14}H_{17}NO_2$·HCl: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.74; H, 6.89; N, 5.11.

***N*,*N*-Disubstituted Amines**——Morpholine, piperidine, 4-benzylpiperidine, *N*-methylpiperazine, *N*-phenylpiperazine, *N*-benzylpiperazine and 1,2,3,4-tetrahydroisoquinoline were purchased from Aldrich Chemical Co. and Tokyo Kasei Kogyo Co., and were used after being derived to the crystalline hydrochlorides.

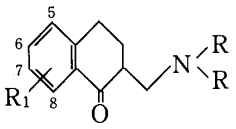
Ethyl *N*-piperazineacetate,[16] *N*-benzhydrylpiperazine,[17] *N*-benzhydrylhomopiperazine,[18] isoindoline,[19] and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[20] were prepared according to the cited references and isolated as the crystalline hydrochlorides. *N*-(3,4,5-Trimethoxybenzyl)piperazine[21] hydrochloride was synthesized in the manner described for the preparation of *N*-benzhydrylpiperazine.[17]

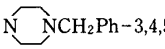
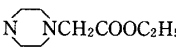
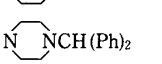
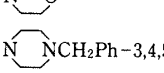
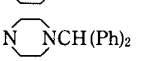
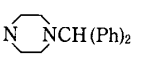
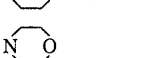
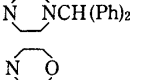
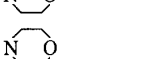
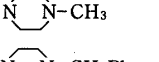
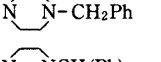
2-Aminomethyl-3,4-dihydro-1(2*H*)-naphthalenone Derivatives (25, Table III)——A) A mixture of a 3,4-dihydro-1(2*H*)-naphthalenone derivative (**24**, 4 g), an *N*,*N*-disubstituted amine hydrochloride (8 g), paraformaldehyde (4 g) and EtOH (50 ml) was refluxed for 7 h. After cooling, the reaction mixture was poured into water (500 ml) and extracted with ether (200 ml). The aqueous layer was made weakly basic with $NaHCO_3$ and extracted with $CHCl_3$ (20 ml×3). The extract was dried over Na_2SO_4 and concentrated *in vacuo* to give **25** as a viscous oil, which was led to the crystalline hydrochloride by treatment with 20% HCl–EtOH (5 ml). In the case of **25k**, colorless prisms of the free base were deposited from petroleum ether.

B) A mixture of **24** (3.5 g), an *N*,*N*-disubstituted amine hydrochloride (7 g), 37% formaldehyde (3.5 g) and EtOH (50 ml) was allowed to stand for 3—7 d at room temperature. Then, the mixture was poured into water (500 ml), made weakly basic with $NaHCO_3$, and extracted with $CHCl_3$ (50 ml × 3). The extract was dried over Na_2SO_4 and concentrated *in vacuo* to give a viscous oil, which was crystallized from MeOH to give **25** as colorless prisms. The free bases of **25a**, **25o** and **25p** were obtained as oily substances and were derived to the crystalline hydrochlorides by treatment with 20% HCl–EtOH (5 ml).

C) A mixture of **24** (2 g), an *N*,*N*-disubstituted amine hydrochloride (4 g), 37% formaldehyde (4 ml) and EtOH (50 ml) was allowed to stand at room temperature for 1 week. The deposited colorless crystals were collected by filtration to give **25**·HCl.

TABLE III. 2-Aminomethyl-3,4-dihydro-1(2*H*)-naphthalenone Derivatives



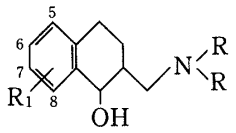
Compd. No.	R_1	$N\langle^{R}_{R}$	Yield(%) (Method)	Form	mp (°C) des.	Formula	Analysis(%) Calcd (Found) C	H	N
25a	H		57 (B)	HCl	163—166	$C_{25}H_{32}N_2O_4\cdot 2HCl\cdot H_2O$	58.25 (58.11)	7.04 (7.04)	5.44 (5.45)
25b	6-OCH_3		57 (A)	HCl	183—185	$C_{20}H_{28}N_2O_4\cdot 2HCl\cdot H_2O$	53.21 (53.55)	7.15 (6.96)	6.21 (6.26)
25c	6-OCH_3		47 (C)	HCl	163—165	$C_{26}H_{34}N_2O_5\cdot 2HCl\cdot H_2O$	57.24 (57.04)	7.02 (7.07)	5.14 (5.19)
25d	6-OCH_3		70 (B)	Base	158—160	$C_{29}H_{32}N_2O_2$	79.06 (78.71)	7.32 (7.31)	6.36 (6.21)
25e	5-OCH_3 6-OCH_3		53 (A)	HCl	183—185	$C_{17}H_{23}NO_4\cdot HCl$	59.73 (59.30)	7.08 (7.01)	4.10 (4.30)
25f	5-OCH_3 6-OCH_3		41 (C)	HCl	186—188	$C_{27}H_{36}N_2O_6\cdot 2HCl\cdot 5/2H_2O$	53.82 (53.77)	7.19 (7.02)	4.65 (4.50)
25g	5-OCH_3 6-OCH_3		44 (B)	Base	134—136	$C_{30}H_{34}N_2O_3$	76.56 (76.85)	7.28 (7.07)	5.95 (5.80)
25h	6-OCH_3 7-OCH_3		44 (B)	Base	142—144	$C_{30}H_{34}N_2O_3$	76.56 (76.62)	7.28 (7.41)	5.95 (6.11)
25i	5,6-OCH_2O-		88 (A)	HCl	199—202	$C_{16}H_{19}NO_4\cdot HCl$	58.98 (58.90)	6.19 (6.29)	4.30 (4.27)
25j	5,6-OCH_2O-		75 (B)	Base	160—161	$C_{29}H_{30}N_2O_3$	76.62 (76.39)	6.65 (6.48)	6.16 (6.00)
25k	6,7-OCH_2O-		59 (A)	Base	111—113	$C_{16}H_{30}NO_4$	66.42 (66.28)	6.62 (6.69)	4.84 (4.65)
25l	6,7-OCH_2O-		36 (B)	Base	143—146	$C_{29}H_{30}N_2O_3$	76.62 (76.95)	6.65 (6.40)	6.16 (5.93)
25m	5-$O(CH_2)_3CH_3$ 6-$O(CH_2)_3CH_3$		99 (A)	HCl	181—183	$C_{23}H_{35}NO_3\cdot HCl$	65.00 (65.03)	8.30 (8.59)	3.30 (3.34)
25n	6- 		62 (B)	Base	162—165	$C_{19}H_{26}N_2O_3$	69.06 (69.10)	7.93 (7.94)	8.48 (8.21)
25o	6- 		65 (B)	HCl	204—206	$C_{20}H_{29}N_3O_2\cdot 3HCl$	53.04 (59.34)	7.12 (7.47)	9.28 (9.64)
25p	6- 		51 (B)	HCl	215—220	$C_{26}H_{33}N_3O_2\cdot 3HCl$	59.03 (59.31)	6.86 (7.23)	7.94 (7.51)
25q	7- 		54 (B)	Base	159—161	$C_{32}H_{37}N_3O_2$	77.54 (77.47)	7.52 (7.42)	8.48 (8.34)

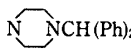
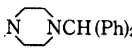
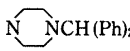
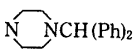
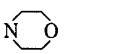
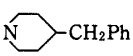
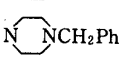
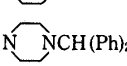
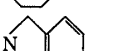
2-Aminomethyl-1,2,3,4-tetrahydronaphthalen-1-ol Derivatives (26, Table IV)——D) $NaBH_4$ (2.5 g) was added portionwise to a solution of the Mannich base (**25**, 3.5 g) in a mixture of MeOH (100 ml) and $CHCl_3$ (20 ml). After being stirred for 30 min at room temperature, the mixture was poured into water (500 ml), and extracted with $CHCl_3$ (50 ml × 2). The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The 6-morpholino derivatives (**26g** and **26i**) were obtained as colorless powders by triturating the residue with ether–petroleum ether. In the case of the dimethoxy derivatives (**25g, h**), the residue was chromatographed on silica gel using acetone–benzene (1: 9) as an eluent. Evaporation of the first fraction afforded *trans*-

26c, **e**, while the second fraction afforded *cis*-**26d**. These oily substances were led to the crystalline hydrogen fumarate derivatives by treatment with a saturated ethereal solution of fumaric acid.

E) Compound **24** was allowed to react with an *N*,*N*-disubstituted amine hydrochloride and formaldehyde according to method B. The resulting crude Mannich base (**25**) was reduced with $NaBH_4$ according to method D without purification, and the resultant alcohols (**26h**, **26l** and **26m**) were crystallized from ether. In the cases of **26a**, **26b**, **26f**, **26j** and **26k**, the stereoisomers were separated by silica gel column chromatography (acetone: benzene=1: 9). Compounds **26a** and **26b** were crystallized from ether as colorless prisms. Compounds **26f**, **26j** and **26k** were led to the crystalline hydrogen fumarate derivatives by treatment with a saturated ethereal solution of fumaric acid.

TABLE IV. 2-Aminomethyl-1,2,3,4-tetrahydronaphthalene-1-ol Derivatives



Compd. No.	R_1	$N\langle^{R}_{R}$	Yield (%) (Method)	Form (Config.)	mp (°C) dec.	Formula	Analysis (%) Calcd (Found) C	H	N	NMR C_1-H δ (J=Hz)
26a	H		15 (E)	Base (*trans*)	179—181	$C_{28}H_{32}N_2O$	81.51 (81.70	7.82 7.79	6.79 6.63)	4.60[a] (9)
26b	H		3.5 (E)	Base (*cis*)	150—152	$C_{28}H_{32}N_2O$	81.51 (81.61	7.82 8.03	6.79 6.68)	4.76[a] (4)
26c	5-OCH_3 6-OCH_3		32 (D)	Fumarate (*trans*)	195—200	$C_{30}H_{36}N_2O_3\cdot C_4H_4O_4$	69.37 (69.49	6.85 6.86	4.76 4.82)	4.26[b] (11)
26d	5-OCH_3 6-OCH_3		8.9 (D)	Fumarate (*cis*)	155—165	$C_{30}H_{36}N_2O_3\cdot C_4H_4O_4\cdot H_2O$	67.31 (67.67	6.98 6.59	4.62 4.41)	4.45[b] (2)
26e	6-OCH_3 7-OCH_3		36 (D)	Fumarate (*trans*)	164—167	$C_{30}H_{36}N_2O_3\cdot C_4H_4O_4$	69.37 (69.67	6.85 6.93	4.76 5.01)	—
26f	5-NO_2 6-OCH_3		13 (E)	Fumarate (*trans*)	215—220	$C_{29}H_{33}N_3O_4\cdot C_4H_4O_4$	65.66 (65.30	6.18 6.17	6.96 6.83)	4.54[a,c] (7)
26g	6- 		95 (D)	Base (Mixture)	155—165	$C_{19}H_{28}N_2O_3$	68.64 (68.46	8.49 8.49	8.43 8.02)	—
26h	6- 		32 (E)	Base (Mixture)	176—178	$C_{27}H_{36}N_2O_2$	77.10 (77.01	8.63 8.66	6.66 6.43)	—
26i	6- 		63 (D)	Base (Mixture)	157—160	$C_{26}H_{35}N_3O_2$	74.07 (73.94	8.37 8.34	9.97 9.70)	—
26j	6- 		11 (E)	Fumarate (*trans*)	184—187	$C_{32}H_{39}N_3O_2\cdot C_4H_4O_4$	70.45 (70.22	7.06 7.09	6.85 6.88)	4.28[b] (8)
26k	6- 		5.5 (E)	Fumarate (*cis*)	178—181	$C_{32}H_{39}N_3O_2\cdot C_4H_4O_4$	70.45 (70.20	7.06 7.04	6.85 6.65)	4.46[b] (0)
26l	6-		33 (E)	Base (Mixture)	174—177	$C_{23}H_{28}N_2O_2$	75.79 (75.90	7.74 7.83	7.69 7.49)	—
26m	6- 		34 (E)	Base (Mixture)	170—173	$C_{24}H_{30}N_2O_2$	76.15 (75.84	7.99 8.06	7.40 7.00)	—

a) In $CDCl_3$.
b) In -DMSO.
c) Free base.

3-Aminomethyl-1,2-dihydronaphthalene Derivatives (6—22, Table I)——F) A mixture of *trans*-**26** (free base or hydrogen fumarate, 0.8 g) and 20% HCl–EtOH (50 ml) was heated under reflux for 1—5 h, then cooled. Filtration of the deposited colorless crystals gave **6**—**22**·HCl.

G) The alcohol **26** (1 g, *cis* and *trans* mixture) was heated under reflux in 20% HCl–EtOH (50 ml). The resulting precipitates were collected by filtration to give **6**—**22**·HCl as colorless prisms.

H) Mannich base (**25**) was reduced with $NaBH_4$ according to method D. The resulting alcohol (**26**) was heated in 20% HCl–EtOH according to method F without purification. Filtration of the deposited crystals gave **6**—**22**·HCl.

I) Compound **24** was allowed to react successively with amine plus formaline, $NaBH_4$, and 20% HCl–EtOH according to methods B, D and F. The intermediates (**25** and **26**) of each reaction step were used for the next step without purification. In most cases, **6**—**22**·HCl was deposited as crystals from the reaction

mixture. When no precipitates were deposited in the reaction mixture, the product was purified by column chromatography on silica gel (acetone: benzene=1 : 4) to give pure **6**—**22** as an oil, which was led to the crystalline hydrochloride.

J) A mixture of ethyl 4-(1,2-dihydro-3-naphthyl)methyl-1-piperazine acetate derivative (**7a** or **8b**, 1 g) and pyrrolidine (10 ml) was heated under reflux for 3 h. The cooled reaction mixture was poured into water (100 ml) and extracted with $CHCl_3$ (20 ml×2). After evaporation of the extract, the residue was treated with 20% HCl–EtOH (2 ml) and diluted with AcOEt (50 ml) to deposit 1-(1,2-dihydro-3-naphthyl)-methyl-4-(1-pyrrolidinyl)carbonylmethylpiperazine derivative hydrochloride (**7b**·HCl or **8c**·HCl) as colorless crystals.

K) A mixture of a carboxylic acid anhydride (acetic, propionic or butyric anhydride, 8 ml) and a 7-amino derivative **22** (2 g) was heated at 80—90°C for 30 min. After cooling, the mixture was diluted with water (100 ml), neutralized with $NaHCO_3$, and extracted with $CHCl_3$ (50 ml×2). The extract was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using acetone–benzene (1: 4) as an eluent. The free bases of the 7-acylamino compounds (**23a**—**c**) were led to colorless prisms of the hydrochlorides by treatment with 20% HCl–EtOH (5 ml).

L) CH_3SO_2Cl (10 ml) was added dropwise to a mixture of **22** (1.5 g), Et_3N (20 ml), and AcOEt (100 ml) at room temperature. The mixture was stirred for 1 h, then the resulting solution was washed with water (30 ml×2) and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (acetone: benzene=1: 4). The free base of 1-benzhydryl-4-(7-methylsulfonylamino-1,2-dihydro-3-naphthyl)-methylpiperazine (**23d**) was treated with 20% HCl–EtOH (4 ml) to give the hydrochloride (1.1 g) as colorless prisms.

1-Benzhydryl-4-(3,4-dimethoxy-6,7-dihydro-5*H*-benzocyclohepten-8-yl)methylpiperazine (**27**)——The Mannich reaction of 1,2-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzocyclohepten-5-one[6] (**31**, 2 g) with 1-benzhydrylpiperazine was carried out under the same conditions as described for method B. The crude Mannich base was reduced to the alcohol and dehydrated according to methods D and F. The product **27** was purified by column chromatography (silica gel) using acetone–benzene (1: 4) as an eluent, and led to the crystalline hydrochloride by the addition of 20% HCl–EtOH (5 ml) to give 0.75 g of colorless prisms (overall yield, 15%), mp 205—210°C. *Anal.* Calcd for $C_{31}H_{36}N_2O_2 \cdot 2HCl$: C, 68.75; H, 7.07; N, 5.17. Found: C, 68.55; H, 7.09; N, 5.06.

1-Benzhydryl-4-(6-methoxy-1,2,3,4-tetrahydro-2-naphthyl)methylpiperazine (**28**)——7-Methoxy-1,2-dihydro-3-naphthoic acid[7] (**32**, 6.5 g) was dissolved in MeOH (200 ml) and hydrogenated over 10% Pd-C (1 g) under atmospheric pressure at room temperature until 1 equivalent of hydrogen had been consumed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was crystallized from dil. MeOH to give 6-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid (**33**, 6.5 g, 99%) as colorless plates, mp 154—155°C. *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 70.11; H, 6.93. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O).

A mixture of **33** (6.5 g) and 10% HCl–EtOH (150 ml) was heated under reflux for 6 h. Evaporation of the solvent gave ethyl 6-methoxy-1,2,3,4-tetrahydro-2-naphthoate (6.9 g, 93%) as a viscous oil. IR ν_{max}^{neat} cm^{-1}: 1730 (C=O).

$LiAlH_4$ (2 g) was added portionwise to a stirred solution of this ester (6.7 g) in ether (200 ml), and the mixture was stirred for 1 h at room temperature. Under ice cooling, water was added dropwise to the mixture to decompose excess $LiAlH_4$. Next, AcOEt (200 ml) was added and the precipitate was filtered off. The filtrate was dried over Na_2SO_4 and concentrated *in vacuo* to give 6-methoxy-1,2,3,4-tetrahydro-2-naphthyl-methyl alcohol (**34**, 4.2 g, 76%) as a colorless liquid. IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH).

A solution of $SOCl_2$ (2 ml) in benzene (20 ml) was added dropwise to a solution of the above compound (4 g) and *N*,*N*-diethylaniline (2 ml) in benzene (50 ml) at room temperature. The mixture was heated under reflux for 1 h, cooled, washed with water (20 ml×2) and 1 N HCl (20 ml), and concentrated to give a brown oil (2 g). A mixture of this compound with dimethylformamide (DMF) (30 ml), K_2CO_3 (5 g), KI (3 g), and 1-benzhydrylpiperazine (2.6 g) was heated at 100°C for 6 h and subsequently at 130°C for 3 h. After cooling, the mixture was poured into water (500 ml), and extracted with AcOEt (300 ml). The extract was washed with water (50 ml), dried over Na_2SO_4 and concentrated *in vacuo*. After addition of ether (50 ml) to the residue, the resulting precipitate was collected by filtration, dissolved again in AcOEt (100 ml), decolorized with activated carbon, and concentrated *in vacuo*. The residue was treated with 20% HCl–EtOH (10 ml) and diluted with ether (300 ml) to deposit **28**·HCl (1.8 g, 35%) as colorless needles, mp 215—220°C (dec.). *Anal.* Calcd for $C_{29}H_{34}N_2O \cdot 2HCl \cdot H_2O$: C, 67.30; H, 7.40; N, 5.41. Found: C, 67.04; H, 7.64; N, 5.03.

1-Benzhydryl-4-(6-methoxy-2-naphthyl)methylpiperazine (**29**)——A mixture of **32** (8 g) and sulfur (2 g) was heated at 220—230°C for 30 min. After cooling, the reaction mixture was diluted with acetone–AcOEt (1: 1, 500 ml). The resulting solution was washed with water (100 ml) and concentrated *in vacuo*. The residue was triturated with EtOH (100 ml) and the insoluble substance was removed by filtration. The filtrate was cooled to deposit 6-methoxy-2-naphthoic acid (**35**, 5.8 g, 73%) as colorless needles, mp 201—202°C. IR ν_{max}^{Nujol} cm^{-1}: 1680 (C=O). This acid (5.8 g) was heated in 10% HCl–EtOH (150 ml) for 6 h under reflux. Evaporation of the solvent gave ethyl 6-methoxy-2-naphthoate (6 g, 91%) as colorless plates, mp 96—97°C. IR ν_{max}^{Nujol} cm^{-1}: 1700 (C=O). This ester (6 g) was reduced with $LiAlH_4$ (2 g) in a manner similar to that

described for the preparation of **34**. 6-Methoxy-2-naphthylmethyl alcohol (**36**, 4.2 g, 86%) was obtained as colorless plates, mp 126—127°C. *Anal.* Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.86; H, 6.49. IR ν_{max}^{Nujol} cm^{-1}: 3200 (OH). Pyridine (0.5 ml) and $SOCl_2$ (2.5 ml) were added to a solution of this alcohol (2.5 g) in $CHCl_3$ (50 ml), and the resulting mixture was stirred for 30 min at room temperature. The mixture was washed with water (20 ml×2) and the $CHCl_3$ layer was concentrated *in vacuo* to give a colorless liquid, which was dissolved in acetone (50 ml). 1-Benzhydrylpiperazine (4 g) and K_2CO_3 (5 g) were added to the solution, and the resulting mixture was refluxed for 6 h. After cooling, the mixture was poured into water (500 ml). The resulting crystals were collected by filtration and recrystallized from AcOEt to give **29** as colorless crystals; **29** was led to the hydrochloride (colorless needles) by treatment with 20% HCl–EtOH (10 ml), mp 245—249°C (dec.). *Anal.* Calcd for $C_{29}H_{30}N_2O \cdot 2HCl$: C, 70.29; H, 6.51; N, 5.65. Found: C, 70.14; H, 6.64; N, 5.68.

1-Benzhydryl-4-(6-methoxy-3,4-dihydro-2-naphthoyl)piperazine (30)——A mixture of **32** (1 g), $SOCl_2$ (2 ml) and benzene (50 ml) was heated for 1 h under gentle reflux. Excess $SOCl_2$ was thoroughly evaporated off, and the residue was dissolved in dioxane (50 ml). 1-Benzhydrylpiperazine (1.5 g) and Et_3N (1 g) were added to the solution, and the mixture was stirred for 10 min at room temperature, poured into water (300 ml), extracted with AcOEt (100 ml×2), and evaporated to give crude **30**, which was purified by silica gel column chromatography (acetone: benzene=1: 4) and crystallized from 50% MeOH as colorless prisms, 1.6 g (79%), mp 163—165°C. *Anal.* Calcd for $C_{29}H_{30}N_2O_2$: C, 79.42; H, 6.90; N, 6.39. Found: C, 79.49; H, 6.69; N, 6.20.

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