Synthesis and Biological Activities of New 2-Substituted 1,4-Benzoxazine Derivatives

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A series of new 1,4-benzoxazine derivatives (XI, XII) possessing (4-phenyl-1-piperazinyl)alkyl moieties at the 2-position and related compounds (XIII) were synthesized and tested for calcium antagonistic, calmodulin antagonistic and antihypertensive activities. Various compounds had *in vitro* calmodulin antagonistic activity superior or comparable to that of trifluoperazine. Among these compounds, tetrahydronaphtho[2,3-*b*][1,4]oxazine derivatives such as 51, 53, 54, 58, 59, 60, 73 and 75 showed potent antihypertensive effects in spontaneously hypertensive rats. Optical isomers of 51 were also synthesized and evaluated biologically. No differences in biological activities were seen between the enantiomers.

Keywords 1,4-benzoxazine; piperazine; calmodulin antagonist; antihypertensive activity; intracellular calcium antagonist; spontaneously hypertensive rat

We reported earlier[1] that 2*H*-1,4-benzothiazin-3(4*H*)-one derivatives possessing a (4-phenyl-1-piperazinyl)propyl moiety at the 2-position had potent antihypertensive activity in spontaneously hypertensive rats (SHR). Although the mode of action of these compounds is not yet fully understood, their intracellular calcium antagonistic property could contribute to their antihypertensive effect.[1] These observations prompted us to synthesize their oxa-analogues, 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives (XI, XII and XIII), in order to explore the potential of intracellular calcium antagonists as a new type of antihypertensive agent.

A number of 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives have been synthesized so far and various pharmacological activities such as central nervous system (CNS) depressant,[2] analgesic,[3] α_2-antagonistic,[4] anthelmintic[5] and aldose reductase inhibitory[6] activity have been reported with this class of molecules. However, those bearing aminoalkyl groups at the 2-position have not yet been investigated as potential cardiovascular agents.[7] This paper describes the synthesis and pharmacological evaluation of 2-(4-phenyl-1-piperazinyl)alkyl-2*H*-1,4-benzoxazin-3(4*H*)-one derivatives.

Chemistry

The 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives (XI, XII and XIII) listed in Tables I—III were prepared according to the procedure shown in Chart 1. The key intermediates, 2-brmoalkyl-1,4-benzoxazin-3(4*H*)-ones (VIII) for the synthesis of XI and XIII were prepared *via* several routes. Reaction of 2-aminophenols (III), obtained from 2-nitrophenols (II) by hydrogenation, with dibromo esters (IV) gave VIII. Acylation of III with acyl chlorides (V) under Schotten–Baumann reaction conditions followed by cyclization in the presence of a base afforded VIII. The reductive cyclization of VI which was prepared by the alkylation of II with IV also yielded VIII. Compounds VIII thus obtained were converted to the desired compounds XI

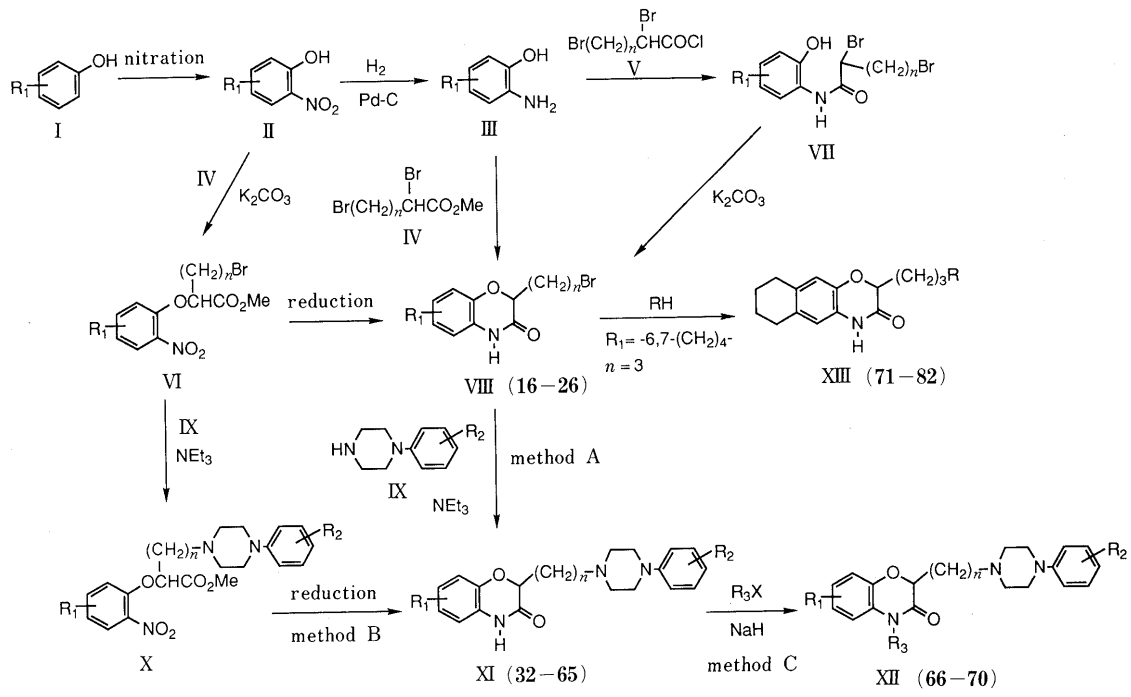


Chart 1

and XIII by reaction with phenylpiperazines (IX) (method A) and appropriate amines (RH), respectively. Compounds XI were alternatively synthesized from VI by first treating with IX to afford X and then reducing X followed by cyclization (method B). The alkylation of XI with alkyl halides (R_3X) in the presence of sodium hydride gave the *N*-alkyl compounds (XII) (method C).

Although the starting 2-nitrophenols (II) and 2-aminophenols (III) are mostly known compounds, commercially unavailable 2-nitrophenols (II) were synthesized by nitration of the phenols (I) using the method reported by Ouertani *et al.*[8] For instance, when 5,6,7,8-tetrahydro-2-naphthol (**1**) was treated with sodium nitrate in the presence of an excess amount of hydrogen chloride and a catalytic amount of $La(NO_3)_3$ in a two phase system of ether/water, the 3-nitrated compound (**2**) and the 1-nitrated compound (**3**) were obtained in a ratio of about 1 to 2 (Chart 2). Compounds **2** and **3** were then converted to the corresponding compounds **51** and **52** (Table I) by method A or B. However, this route was not satisfactory for the synthesis of **51** which is a potent antihypertensive agent (*vide post*), because the desired starting material (**2**) was the minor product and separation of **2** and **3** by column chromatography was rather laborious. Therefore, a more convenient route to **51** was investigated. Bromination of **1** with bromine proceeded selectively at the 1-position to give **4**. Then, **4** was nitrated with nitric acid followed by hydrogenation to give 3-amino-5,6,7,8-tetrahydro-2-naphthol[9] hydrobromide (**6**) which was identical with the one obtained from **2** by hydrogenation in the presence of hydrobromic acid. Compound **6** was converted to **51** following the general route, III→VII→VIII→XI.

Compound **53**, the oxa-analogue of 6,7-cyclopenteno-2-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-2*H*-1,4-benzothiazin-3(4*H*)-one, which was one of the most interesting compounds in the benzothiazine series,[1] was synthesized for comparison.

Nitration of 5-indanol (**7**) following the method of Ouertani *et al.*[8] affroded an inseparable mixture of **8** and **9** in a ratio of approximately 11 to 8 (Chart 3). This mixture was subjected to the reaction sequence, II→VI→VIII→XI or II→VI→X→XI, to yield **53** as crystals. Attempted isolation of **54**, a regioisomer of **53** which was expected to form from **9**, was unsuccesful. Compound **54** was therefore

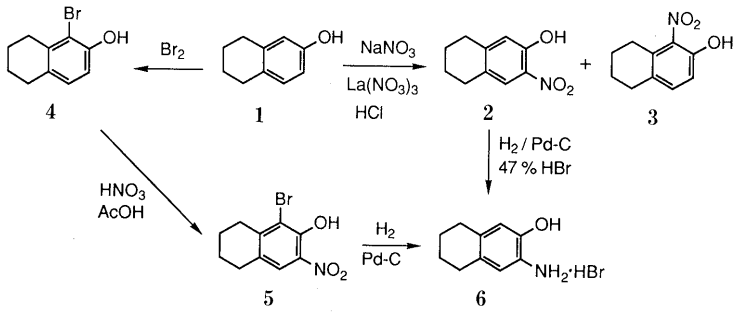


Chart 2

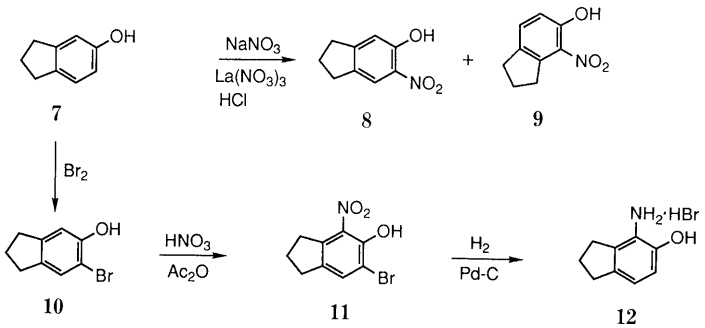


Chart 3

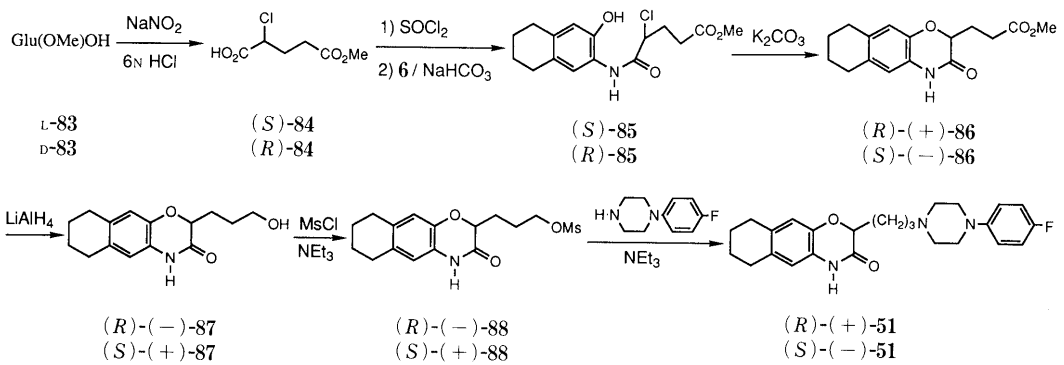


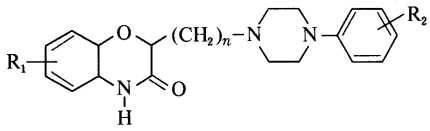
Chart 4

synthesized starting from **12** prepared as shown in Chart 3. Bromination of **7**, in contrast to the case of the tetrahydro-2-naphthol (**1**), gave the 6-bromo compound (**10**) as a single product in a high yield. Nitration of **10** followed by hydrogenation gave 4-amino-5-indanol hydrobromide (**12**).

As these 1,4-benzoxazin-3(4*H*)-one derivatives have an asymmetric carbon at the C-2 position of the oxazine ring, it is of interest to determine if there are differences in the biological activities of the optical isomers. Therefore, the enantiomers of compound **51** were synthesized as the representatives of this series.

Enantiomeric glutamic acid γ-methyl esters (**83**) were chosen as the chiral building blocks to prepare (*R*)- and (*S*)-**51** as shown in Chart 4. Treatment of L-glutamic acid γ-methyl ester (L-**83**) with sodium nitrite in the presence of 6 N HCl afforded the (*S*)-α-chlorocarboxylic acid [(*S*)-**84**]. This type of reaction is known to proceed while retaining

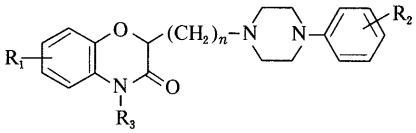
TABLE I. Physical and Biological Properties of 2-(4-Phenyl-1-piperazinyl)alkyl-2*H*-1,4-benzoxazin-3(4*H*)-ones (XI)[a]



Compd. No.	R_1	R_2	n	Method	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Ca^{2+} blocking activity[e] (% inhib. at 10^{-5} M) KCl (60 mM)	CaM antagonistic activity[e] IC_{50}[f] (M)
32	6-NO_2	4-F	3	A	80.6	153—154	EA–E	$C_{21}H_{23}FN_4O_4$	37	1.7×10^{-6}
33	6-Cl	4-F	3	A	72.1	189—190	EA–E	$C_{21}H_{23}ClFN_3O_2$	29	1.7×10^{-6}
34	6-Me	4-F	3	A	94.7	174—175	Et–EA	$C_{22}H_{26}FN_3O_2$	10	5.0×10^{-8}
35	6-Me	3-CF_3	3	A	70.0	144—145	EA–E	$C_{23}H_{26}F_3N_3O_2$	14	$>10^{-5}$
36	6-Me	4-F	2	A	80.4	199—200	EA–E	$C_{21}H_{24}FN_3O_2$	9	1.1×10^{-6}
37	H	4-F	3	A	36.1	142—143	EA–E	$C_{21}H_{24}FN_3O_2$	73	$>10^{-5}$
38	7-CO_2Et	4-F	3	A	34.8	147—148	EA–E	$C_{24}H_{28}FN_3O_4$	33	$>10^{-5}$
39	5-Me-8-iso-Pr	4-F	3	B	19.7	192—193	M–EA	$C_{25}H_{32}FN_3O_2$	−2	1.2×10^{-6}
40	6-iso-Pr-7-Me	4-F	3	B	16.3	174—175	Ch–EA	$C_{25}H_{32}FN_3O_2$	10	1.0×10^{-5}
41	6-CF_3	4-F	3	A	63.5	156—157	Ch–EA	$C_{22}H_{23}F_4N_3O_2$	36	5.6×10^{-6}
42	6-MeO	4-F	3	A	87.2	153—154	M	$C_{22}H_{26}FN_3O_3$	28	3.2×10^{-6}
43	7-MeO	4-F	2	B	17.7	146—147	Et	$C_{21}H_{24}FN_3O_3$	15	1.8×10^{-6}
44	6-iso-Pr-7-Me	4-F	9	B	11.1	108—109	IPE	$C_{31}H_{44}FN_3O_2$	4	$>10^{-5}$
45·2HCl	6-Ph	4-F	3	B	62.7[g,h]	202—204[i]	M–E	$C_{27}H_{28}FN_3O_2$ ·2HCl·1/2H_2O	18	$>10^{-5}$
46·2HCl	6-Cyclohexyl	4-F	3	B	28.7[g]	159—161[j]	M–E	$C_{27}H_{34}FN_3O_2$ ·2HCl	24	$>10^{-5}$
47	8-Cyclohexyl	4-F	3	B	20.2	171—173[k]	EA–E	$C_{27}H_{34}FN_3O_2$	6	$>10^{-5}$
48	6-NH_2	4-F	3	[l]	98.2	158—159	E	$C_{21}H_{25}FN_4O_2$	−2	$>10^{-5}$
49	6-$NHCONMe_2$	4-F	3	[l]	38.8	179—181	MC–EA	$C_{24}H_{30}FN_5O_3$	−1	$>10^{-5}$
50	6-NHCOMe	4-F	3	[l]	71.5	111—112	MC–EA	$C_{23}H_{27}FN_4O_3$ ·1/2H_2O	9	$>10^{-5}$
51	6,7-$(CH_2)_4$–	4-F	3	A B	59.3 43.1[n]	164—165[m]	Ch–EA	$C_{25}H_{30}FN_3O_2$	82	5.2×10^{-7}
52	5,6-$(CH_2)_4$–	4-F	3	B	19.3	176—177	AE	$C_{25}H_{30}FN_3O_2$	3	$>10^{-5}$
53	6,7-$(CH_2)_3$–	4-F	3	A B	90.9 35.4[n]	186—187	MC–EA	$C_{24}H_{28}FN_3O_2$	21	1.9×10^{-6}
54	5,6-$(CH_2)_3$–	4-F	3	A	76.7	171—172	Ch–EA	$C_{24}H_{28}FN_3O_2$	28	2.0×10^{-6}
55·2HCl	6,7-$(CH_2)_4$–	4-F	2	B	22.4[g,n]	232—234	M	$C_{24}H_{28}FN_3O_2$ ·2HCl	−2	$>10^{-5}$
56	6,7-$(CH_2)_4$–	4-F	4	B	31.5	160—161	Ch–EA	$C_{26}H_{32}FN_3O_2$	14	$>10^{-5}$
57	6,7-OCH_2O–	4-F	3	B	77.4[h]	194—195	EA–E	$C_{22}H_{24}FN_3O_4$	24	5.6×10^{-6}
58	6,7-$(CH_2)_4$–	3-F	3	A	54.1	158—159	Ch–EA	$C_{25}H_{30}FN_3O_2$	10	3.2×10^{-7}
59	6,7-$(CH_2)_4$–	H	3	A	53.9	178—179	Ch–EA	$C_{25}H_{31}N_3O_2$	12	1.0×10^{-6}
60·2HCl	6,7-$(CH_2)_4$–	2-MeO	3	A	90.0[g]	185—187[o]	Et	$C_{26}H_{33}N_3O_3$ ·2HCl	8	3.2×10^{-7}
61	6,7-$(CH_2)_4$–	3-CF_3	3	A	71.2	196—197	Ch–EA	$C_{26}H_{30}F_3N_3O_2$	−8	$>10^{-5}$
62	6,7-$(CH_2)_4$–	4-Me	3	A	31.9	180—181	Ch–EA	$C_{26}H_{33}N_3O_2$ ·1/2H_2O	−13	$>10^{-5}$
63	6,7-$(CH_2)_4$–	4-OH	3	A	64.8	217—218	Ch–M	$C_{25}H_{31}N_3O_3$ ·1/2HCl	26	1.3×10^{-6}
64	6,7-$(CH_2)_4$–	3-Cl-4-Me	3	A	45.7	174—175	Ch–EA	$C_{26}H_{32}ClN_3O_2$	10	7.3×10^{-6}
65	6,7-$(CH_2)_4$–	3,4-OCH_2O–	3	A	50.5	152—153	Ch–EA	$C_{26}H_{31}N_3O_4$	32	4.3×10^{-6}
Trifluoperazine										4.1×10^{-6}

a) Structures of all compounds were confirmed by IR and ^{1}H-NMR spectra. For typical examples, see Experimental. *b*) Yield from VIII (method A) and overall yield from II (method B) are shown. *c*) Solvents for recrystallization: A, acetone; Ch, chloroform; E, ethyl ether; EA, ethyl acetate; Et, ethanol; H, hexane; IPE, isopropyl ether; M, methanol; MC, methylene chloride. *d*) All compounds were analyzed for C, H and N and the analytical results were within ±0.4% of the calculated values for the formulae shown. *e*) For the biological methods, see ref. 1. *f*) IC_{50} values were determined by linear regression analysis; the correlation coefficient for each regression line was >0.95. *g*) Yield of free base. *h*) Yield from X. *i*) Free base: mp 173 °C (Ch–EA). *j*) Free base: mp 162—164 °C. *k*) 2HCl salt: mp 232—234 °C (M–E). *l*) For the method, see Experimental. *m*) 2HCl salt: mp 150–151 °C (M). *n*) Yield from VI. *o*) Free base: mp 146—147 °C (Ch–AE).

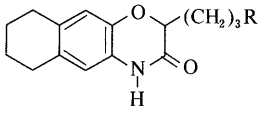
TABLE II. Physical and Biological Properties of 2-(4-Phenyl-1-piperazinyl)alkyl-2*H*-1,4-benzoxazin-3(4*H*)-ones (XII) Synthesized by Method C[a]

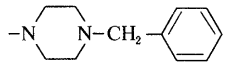
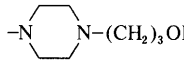
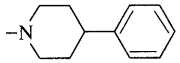
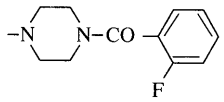
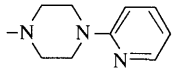
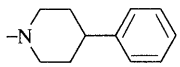
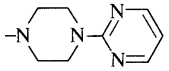
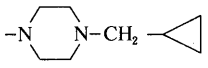
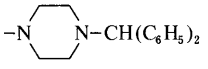
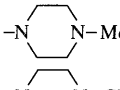
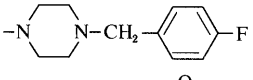
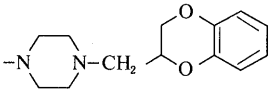


Compd. No.	R_1	R_2	R_3	n	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Ca^{2+} blocking activity[e] (% inhib. at 10^{-5} M) KCl (60 mM)	CaM antagonistic activity[e] IC_{50}[f] (M)
66	6-Me	4-F	CH_2CO_2Et	3	79.7	127	IPE	$C_{26}H_{32}FN_3O_4$	9	$>10^{-5}$
67·3HCl	6-Me	4-F	$CH_2CH_2NMe_2$	3	62.8	166—169	Et	$C_{26}H_{35}FN_4O_2 \cdot 3HCl \cdot H_2O$	13	$>10^{-5}$
68	6,7-$(CH_2)_4$–	4-F	Me	3	63.0	98—99	E	$C_{26}H_{32}FN_3O_2$	20	2.8×10^{-6}
69·2HCl	6,7-$(CH_2)_4$–	4-F	$CH_2CH_2NMe_2$	3	91.7	142—143	M	$C_{29}H_{39}FN_4O_2 \cdot 2HCl \cdot 1/2H_2O$	30	$>10^{-5}$
70 Trifluoerazine	6,7-$(CH_2)_4$–	4-F	CH_2CO_2Et	3	82.3	128—129	E	$C_{29}H_{36}FN_3O_4$	12	$>10^{-5}$ 4.1×10^{-6}

a—f) See footnotes *a—f*) in Table I.

TABLE III. Physical and Biological Properties of Compound XIII Synthesized by Method A[a]



Compd. No.	R	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Ca^{2+} blocking activity[e] (% inhib. at 10^{-5} M) KCl (60 mM)	CaM antagonistic activity[e] IC_{50}[f] (M)
71		63.0	141—142	Ch–EA	$C_{26}H_{33}N_3O_2$	42	5.2×10^{-6}
72·2HCl		78.3	235—239	M	$C_{22}H_{33}N_3O_3 \cdot 2HCl$	4	$>10^{-5}$
73		56.9	169—170	Ch–EA	$C_{26}H_{30}N_2O_2$	18	6.8×10^{-6}
74		60.4	144—145	Ch–EA	$C_{26}H_{30}FN_3O_3$	16	$>10^{-5}$
75		71.8	150—151	EA	$C_{24}H_{30}N_4O_2$	23	1.5×10^{-6}
76		37.1	154—155	E	$C_{26}H_{32}N_2O_2$	10	$>10^{-5}$
77		74.3	181—182	EA–E	$C_{23}H_{29}N_5O_2$	21	1.0×10^{-5}
78		43.5	107—108	EA–E	$C_{23}H_{33}N_3O_2$	15	$>10^{-5}$
79		76.3	173—174	Ch–EA	$C_{32}H_{37}N_3O_2$	33	$>10^{-5}$
80		46.7	118—119	EA–E	$C_{20}H_{29}N_3O_2$	19	$>10^{-5}$
81·2HCl		87.0	229—230	Et	$C_{26}H_{32}FN_3O_2 \cdot 2HCl \cdot 1/2H_2O$	43	$>10^{-5}$
82 Trifluoperazine		44.2	154—157	EA	$C_{28}H_{35}N_3O_4$	22	4.2×10^{-6} 4.1×10^{-6}

a—f) See footnotes *a—f*) in Table I.

its configuration.[10] Then, (*S*)-**84** was allowed to react with the aminophenol (**6**) *via* the acid chloride and the subsequent cyclization of the resulting acylamide derivative (*S*)-**85** with potassium carbonate gave (*R*)-**86**. This reaction is assumed to proceed *via* an *SN*2 mechanism and thus the configuration is inverted. By the same procedure, (*S*)-**86** was obtained starting from D-glutamic acid γ-methyl ester (D-**83**). The enantiomeric esters, (*R*)-(+)- and (*S*)-(−)-**86**, were reduced with $LiAlH_4$ to the alcohols (*R*)-(−)- and (*S*)-(+)-**87**, which were then mesylated to give (*R*)-(−)- and (*S*)-(+)-**88**, respectively. The reaction of (*R*)-(−)- and (*S*)-(+)-**88** with 1-(4-fluorophenyl)piperazine gave (*R*)-(+)-**51**, mp 155.5—156 °C, $[\alpha]_D^{26}$ +19.9° ($c=0.7$, $CHCl_3$), and (*S*)-(−)-**51**, mp 156—156.5 °C, $[\alpha]_D^{26}$ −19.9° ($c=1.2$, $CHCl_3$), respectively. The optical purities of the enantiomeric **51** were satisfactory as estimated by their nuclear magnetic resonance (^{1}H-NMR, 400 MHz) spectra in the presence of a chiral shift reagent, tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato], europium(III) [Eu(hfc)$_3$] in $CDCl_3$. Each methine proton at C-2 and the NH proton of (±)-**51** was observed as a pair at δ 6.29 and 6.36 and at δ 8.55 and 8.76, respectively. However, these protons of each isomer appeared as single peaks at the expected positions, the higher chemical shifts being attributed to the (*S*)-isomer.

Results and Discussion

The calcium channel blocking and calmodulin antagonistic activity of the new 2*H*-1,4-benzoxazin-3(4*H*)-one derivatives (XI, XII and XIII) are shown in Tables I—III.

As expected from the results[1] obtained with the 1,4-benzothiazin-3(4*H*)-one series, these compounds showed very weak calcium channel blocking effects, while some of them showed potent calmodulin antagonistic activity superior or comparable to that of a phenothiazine derivative, trifluoperazine.[1] Of the compounds with a 3-(4-fluorophenyl-1-piperazinyl)propyl moiety, those bearing an ethoxycarbonyl (**38**), an amino (**48**), or an acylamino (**49**, **50**) group as the R_1 substituent did not show calmodulin antagonistic activity. The compounds having bulky substituents, such as phenyl (**45**) and cyclohexyl (**46**, **47**) as R_1, as well as the unsubstituted compound (**37**) were not calmodulin antagonists. As to the length of the alkylene at the C-2 position, the trimethylene group ($n=3$) seems to be better than others (**34** *vs.* **36**, **40** *vs.* **44**, **51** *vs.* **55** and **56**). In general, compounds with a fused ring at the 5,6- or 6,7-positions of the benzoxazine ring in combination with a 2-methoxyphenyl or 4-fluorophenyl group as an *N*-substituent of the piperazine ring tend to show potent calmodulin antagonistic activity as seen with compounds **51**, **53**, **54** and **60**. Compound **52** with a 5,6-fused six-membered ring was the only exception. In other cases, compounds having a 3-fluoro (**58**), no substituent (**59**), 4-hydroxy (**63**), 3-chloro-4-methyl (**64**) or 3,4-methylenedioxy (**65**) substituent on the benzene ring of the phenylpiperazine moiety also showed potent calmodulin antagonistic activity. Substitution of the nitrogen at the 4-position resulted in a decrease in activity (Table II). Among the other analogues of XI listed in Table III, compound **75** with a 4-(2-pyridyl)-1-piperazinyl group in the side chain retained considerably potent calmodulin antagonistic activity, but introduction of other functional groups generally decreased the activity as compared to that of the corresponding piperazine derivative (**59**).

Several compounds which showed potent calmodulin antagonistic activity were subsequently examined for antihypertensive activity in conscious SHR by the method described in the previous paper,[1] and the results are shown in Table IV. Compounds **51**, **53**, **54**, **58**, **59**, **60**, **73** and **75** having a cycloalkylene ring fused at 5,6- or 6,7-positions of the benzoxazine are particularly interesting, as they showed potent antihypertensive activity in accordance with

TABLE IV. Antihypertensive Effects of 2*H*-1,4-benzoxazin-3(4*H*)-ones in SHR

Compd. No.	Antihypertensive activity[a]	
	Dose (mg/kg *p.o.*)	Maximum change (mmHg)
32	60	43.3
33	30	9.7
34	60	45.0
36	60	39.7
39	60	27.3
41	3	12.0
51	3	30.0
53	3	29.3
54	3	19.7
57	3	26.7
58	3	59.3
59	3	43.3
60	3	49.7
63	3	2.7
65	3	16.3
71	10	11.8
73	3	53.8
75	3	43.0
77	3	19.0

a) See footnote *e*) in Table I. The change in blood pressure is an average of the values from 3 animals.

TABLE V. Antiarrhythmic Activity of **51**

Compd. No.	Dose (mg/kg, *p.o.*)	VT (%)	VF (%)	Mortality (%)
Control	—	100 (16)	100 (16)	38 (16)
51	3	42[a] (12)	25[a] (12)	0[a] (12)

The percentage incidence of reperfusion-induced VT, VF and mortality in control animals and animals pretreated with **51**. The number of animals used in each group is shown in parentheses. *a*) Denotes significant difference ($p<0.05$) from the control group.

TABLE VI. Pharmacological Effects of Compounds (±)-, (*R*)-(+)- and (*S*)-(−)-**51**

Compd. No.	Calmodulin antagonistic activity[a] IC_{50}[b] (M)	Inhibitory effect (%) on caffein-induced contraction[c] (10^{-6} M)	Antihypertensive activity[d] maximum change in systolic blood pressure (3 mg/kg, *p.o.*)
(±)-**51**	5.2×10^{-7}	43± 7 (3)	30
(*R*)-(+)-**51**	5.0×10^{-7}	43±14 (3)	30
(*S*)-(−)-**51**	7.4×10^{-7}	44± 8 (3)	28

a, b) See footnotes *e*) and *f*) in Table I. *c*) For the biological methods, see ref. 1. Values represent mean±S.E. The average control contractile response of the rabbit aortic strips was 1.94±0.26 g (mean±S.E. $n=8$). The number of experiments is shown in parentheses. *d*) See footnote *a*) in Table IV.

their potent calmodulin antagonistic property. Moreover, the antiarrhythmic activity of **51** was evaluated in the anesthetized rat by Winslow's method,[11] and the results are shown in Table V.

Compound **51** antagonized the development of ventricular fibrillation (VF) and ventricular tachycardia (VT), and also reduced the mortality resulting from 5 min of occlusion followed by reperfusion. Compound **51** also inhibited the caffeine induced contraction of rabbit aorta in a calcium-free buffer (Table VI), suggesting that this compound blocks intracellular calcium movement rather than the influx of calcium into the cell. Therefore, intracellular calcium antagonism including calmodulin antagonistic activity may play a major role in the antihypertensive and antiarrhythmic effects[12] of these 1,4-benzoxazines.

The relationship between the absolute configuration of **51** and its biological activities was also examined. However, in contrast to our expectations, there were almost no differences in activity of the racemate and the two enantiomers, as evidenced by the three parameters shown in Table VI: calmodulin antagonism, inhibitory effect on the caffeine induced contraction of rabbit aorta and antihypertensive effect in SHR.

Experimental

Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Hitachi IR-260-10 spectrophotometer. ^{1}H-NMR spectra were recorded on a Varian EM-390 (90 MHz) spectrometer in the solvent indicated. Chemical shifts are given in ppm relative to Me_4Si as the internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Column chromatography was performed on E. Merck 70—230 mesh silica gel. Evaporation was carried out *in vacuo* on a rotary evaporator.

Synthesis of 2-Nitrophenols (II) Most 2-nitrophenols which are not commercially available were synthesized following the procedure of Ouertani *et al.*[8] A typical example is given to illustrate the general procedure.

5,6,7,8-Tetrahydro-3-nitro-2-naphthol (2)[13] and 5,6,7,8-Tetrahydro-1-nitro-2-naphthol (3) A solution of 5,6,7,8-tetrahydro-2-naphthol (**1**, 29.6 g, 0.20 mol) in Et_2O (600 ml) was added to a stirred mixture of $NaNO_3$ (17.0 g, 0.20 mol), $La(NO_3)_3 \cdot 6H_2O$ (0.87 g, 2.0 mmol) and 6 N HCl (320 ml). The mixture was stirred for 20 h at room temperature (the color of Et_2O layer changed to dark red), diluted with water, and the organic layer was separated. The aqueous layer was extracted with Et_2O, and the combined organics were washed with saturated aqueous NaCl, dried ($MgSO_4$) and concentrated. The oil obtained was purified by column chromatography on silica gel. The first eluate with hexane–AcOEt (9:1, v/v) gave **2** which was triturated with *n*-pentane, filtered and recrystallized from aqueous MeOH to give yellow prisms (9.52 g, 24.6%), mp 89.5—90 °C (lit.[13] mp 89—90 °C). IR (Nujol): 3170, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.64—1.97 (4H, m), 2.59—2.90 (4H, m), 6.80 (1H, s), 7.75 (1H, s), 10.32 (1H, s). The second eluate with hexane–AcOEt (9:1, v/v) gave **3** as a reddish oil (17.72 g, 45.9%). IR (Nujol): 3420, 1605 cm^{-1}. NMR ($CDCl_3$) δ: 1.58—1.92 (4H, m), 2.57—3.08 (4H, m), 6.87 and 7.17 (2H, each d, J=9 Hz).

1-Bromo-5,6,7,8-tetrahydro-2-naphthol (4)[14] A solution of Br_2 (10.8 ml, 0.21 mol) in CCl_4 (100 ml) was added dropwise to a stirred and ice-cooled solution of **1** (29.6 g, 0.20 mol) in CCl_4 (200 ml). After the addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried ($MgSO_4$) and concentrated. The residual oil was distilled to yield **4** (43.7 g, 96.2%), bp 115—117 °C (0.15 mmHg), mp 52—53 °C (lit.[14] bp 160 °C (13 mmHg), mp 74 °C). IR (Nujol): 3520 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53—1.99 (4H, m), 2.49—2.90 (4H, m), 5.43 (1H, s). *Anal.* Calcd for $C_{10}H_{11}BrO$: C, 52.89; H, 4.88. Found: C, 52.88; H, 4.85.

1-Bromo-5,6,7,8-tetrahydro-3-nitro-2-naphthol (5)[13] Fumic HNO_3 (d=1.52, 1.87 ml, 45.1 mmol) was added to a stirred solution of **4** (9.77 g, 43.0 mmol) in AcOH (80 ml) at 0 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 1 h, diluted with water and extracted with CH_2Cl_2. The extract was washed with water, dried ($MgSO_4$) and concentrated to give a solid. Recrystallization from AcOEt afforded **5** as yellow prisms (6.52 g, 55.7%), mp 133—133.5 °C (lit.[13] mp 129.5—130 °C). IR (Nujol): 3200 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.62—2.02 (4H, m), 2.48—2.93 (4H, m), 7.77 (1H, s), 10.04 (1H, s). *Anal.* Calcd for $C_{10}H_{10}BrNO_3$: C, 44.14; H, 3.70; N, 5.15. Found: C, 44.11; H, 3.68; N, 5.18.

Nitration of 5-Indanol (7) A solution of **7** (5.40 g, 40.2 mmol) in Et_2O (120 ml) was treated with a mixture of $NaNO_3$ (3.42 g, 40.2 mmol), $La(NO_3)_3 \cdot 6H_2O$ (174 mg, 0.40 mmol) and 6 N HCl (64 ml) in the same manner as described for **1**. Purification by column chromatography on silica gel (200 g) with hexane–AcOEt (9:1, v/v) gave 4.85 g (67.3%) of a solid mixture of 6-nitro- and 4-nitro-5-indanols (**8** and **9**) which could not be separated by column chromatography or thin-layer chromatography (TLC). The approximate ratio (**8**:**9**=11:8) was determined from the ^{1}H-NMR integrals for the OH singlet for each regioisomer. IR (Nujol): 3220, 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) data for the aromatic protons and OH group of **8** and **9** are as follows: **8**, δ: 6.91 (1H, s, C_4-H), 7.83 (1H, s, C_7-H), 10.67 (1H, s, OH); **9**, δ: 6.88 (1H, d, J=9 Hz, C_6-H), 7.33 (1H, d, J=9 Hz, C_7-H), 10.58 (1H, s, OH). *Anal.* Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.24; H, 5.04; N, 7.79.

6-Bromo-5-indanol (10) Compound **10** was prepared in the same manner as described for the synthesis of **4**. Yield: 84.1%, bp 87—88 °C (0.4 mmHg). This oil crystallized on standing, mp 38—39 °C. IR ($CHCl_3$): 3525 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.27 (2H, m), 2.82 (2H×2, t, J=7.2 Hz), 5.33 (1H, s, OH), 6.88 (1H, s), 7.27 (1H, s). *Anal.* Calcd for C_9H_9BrO: C, 50.73; H, 4.26. Found: C, 50.72; H, 4.07.

6-Bromo-4-nitro-5-indanol (11) Compound **11** was prepared in the same manner as described for the synthesis of **5**. Yield: 52.6%, mp 104 °C (iso-Pr_2O). IR ($CHCl_3$): 3150 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.12 (2H, m), 2.88 (2H, t, J=7.2 Hz), 3.30 (2H, t, J=7.2 Hz), 7.63 (1H, s), 11.13 (1H, s, OH). *Anal.* Calcd for $C_9H_8BrNO_3$: C, 41.89; H, 3.12; N, 5.43. Found: C, 41.94; H, 3.10; N, 5.42.

Synthesis of 2-Aminophenols (III) Typical examples are given to illustrate the general procedure.

3-Amino-5,6,7,8-tetrahydro-2-naphthol[9] Hydrobromide (6) From **2**: A mixture of **2** (8.55 g, 44.3 mmol) and 47% HBr (6.2 ml) in MeOH (300 ml) was hydrogenated in the presence of 10% Pd–C (50% wet, 1.08 g). After the usual workup, the residual oil was crystallized from AcOEt to give **6** (10.5 g, 97.0%), mp 236—238 °C (dec.). IR (Nujol): 3250, 1630 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.50—1.85 (4H, m), 2.39—2.77 (4H, m), 6.72 (1H, s), 6.99 (1H, s), 9.54 (2H, br), 10.15 (1H, br s). *Anal.* Calcd for $C_{10}H_{13}NO \cdot HBr$: C, 49.20; H, 5.78, N, 5.74. Found: C, 48.95; H, 5.75; N, 5.83.

From **5**: A solution of **5** (2.00 g, 7.35 mmol) in MeOH (20 ml)–tetrahydrofuran (THF, 20 ml) was hydrogenated in the presence of 5% Pd–C (50% wet, 0.50 g). After the usual workup, the residual oil was crystallized from Et_2O to give **6** (1.72 g, 95.8%), mp 235—236 °C (dec.). This sample was identical with **6** obtained from **2**.

4-Amino-5-indanol Hydrobromide (12) Hydrogenation of **11** in the same manner as described for the synthesis of **6** gave **12**. Yield 98.7%, mp 262—264 °C (dec.). IR (Nujol): 3240, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.03 (2H, t, J=7.2 Hz), 2.80 (2H, t, J=7.2 Hz), 2.91 (2H, t, J=7.2 Hz), 6.81 (1H, d, J=8.2 Hz), 7.06 (1H, d, J=8.2 Hz), 9.61 (2H, br), 10.35 (1H, br s). *Anal.* Calcd for $C_9H_{11}NO \cdot HBr$: C, 46.98; H, 5.26; N, 6.09. Found: C, 46.80; H, 5.22; N, 6.13.

Synthesis of VI Typical examples are given to illustrate the general procedure.

Methyl 4-Bromo-2-(5,6,7,8-tetrahydro-3-nitro-2-naphthyloxy)butyrate (13) A mixture of **2** (2.62 g, 13.6 mmol), methyl 2,4-dibromobutylate (3.70 g, 14.2 mmol), K_2CO_3 (2.25 g, 16.3 mmol) and dimethylformamide (DMF, 30 ml) was stirred at room temperature for 5 h. The reaction mixture was worked up to yield the residue which was chromatographed on silica gel with hexane–AcOEt (4:1, v/v) followed by crystallization from Et_2O to give **13** as light yellow crystals (3.34 g, 66.2%), mp 99—100 °C. IR ($CHCl_3$): 1740, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63—1.92 (4H, m), 2.35—2.85 (6H, m), 3.57—3.71 (2H, m), 3.77 (3H, s), 4.92 and 4.97 (1H each, d, J=5 Hz), 6.63 (1H, s), 7.59 (1H, s). *Anal.* Calcd for $C_{15}H_{18}BrNO_5$: C, 48.40; H, 4.87; N, 3.76. Found: C, 48.44; H, 4.90; N, 3.77.

Methyl 5-Bromo-2-(5,6,7,8-tetrahydro-3-nitro-2-naphthyloxy)valerate (14) A mixture of **2** (8.0 g, 41.4 mmol), methyl 2,5-dibromovalerate (11.5 g, 42.0 mmol), K_2CO_3 (6.0 g, 43.4 mmol) and DMF (100 ml) was stirred at room temperature for 8 h. The reaction mixture was diluted with

water and extracted with Et_3O. The extract was washed with water, dried ($MgSO_4$) and concentrated. The oil obtained was purified by column chromatography on silica gel with hexane–AcOEt (4 : 1, v/v) to afford **14** as a solid (15.7 g, 98.2%). An analytical sample was obtained by recrystallization from iso-Pr_2O as pale yellow prisms, mp 73—74 °C. IR (Nujol): 1745, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.69—1.87 (4H, m), 2.08—2.30 (4H, m), 2.60—2.90 (4H, m), 3.40—3.58 (2H, m), 3.76 (3H, s), 4.63—4.82 (1H, m), 6.57 (1H, s), 7.58 (1H, s). *Anal.* Calcd for $C_{16}H_{20}BrNO_5$: C, 49.76; H, 5.22; N, 3.63. Found: C, 49.63; H, 5.26; N, 3.55.

Other compounds (VI) were isolated as oils after column chromatography on silica gel. Therefore, these VI were used for the subsequent reaction without further purification.

Synthesis of 2,5-Dibromo-*N*-(2-hydroxyphenyl)valeramide (VII) A typical example is given to illustrate the general procedure.

2,5-Dibromo-*N*-(2-hydroxy-4,5,6,7-tetrahydronaphthyl)valeramide (15) A solution of 2,5-dibromovaleryl chloride[15] (1.94 g, 7.0 mmol) in AcOEt (6 ml) was added dropwise to a vigorously stirred mixture of **6** (1.70 g, 7.0 mmol), $NaHCO_3$ (1.46 g, 17.4 mmol), AcOEt (15 ml) and water (10 ml) with ice-cooling. After being stirred for 30 min, the reaction mixture was diluted with water and the organic layer was separated. The aqueous layer was extracted with AcOEt. The combined organic layers were washed with water, dried ($MgSO_4$) and concentrated to give **15** as crystals (2.80 g), which was used for the next reaction without further purification. An analytical sample was obtained by recrystallization from AcOEt as colorless crystals, mp 148—149 °C. IR (Nujol): 3350, 3160, 1645 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.58—2.33 (8H, m), 2.43—2.80 (4H, m), 3.51 (2H, t, J=6 Hz), 4.88 (1H, t, J=7 Hz), 6.53 (1H, s), 7.53 (1H, s), 9.28 (1H, s, OH; disappeared on treatment with D_2O), 9.36 (1H, s, NH). *Anal.* Calcd for $C_{15}H_{19}Br_2NO_2$: C, 44.47; H, 4.73; N, 3.46. Found C, 44.34; H, 4.69; N, 3.43.

Other compounds (VII) were prepared similarly and used for the subsequent reaction without further purification.

Synthesis of 2-(2-, 3- or 4-Bromoalkyl)-2*H*-1,4-benzoxazin-3(4*H*)-ones (VIII) Typical examples are given to illustrate the general procedure.

2-(3-Bromopropyl)-6-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one (16) From III: A mixture of 2-amino-4-methylphenol (1.23 g, 10 mmol), methyl 2,5-dibromovalerate (2.74 g, 10 mmol), K_2CO_3 (1.38 g, 10 mmol) and acetone (30 ml) was refluxed with stirring for 5 h. The reaction mixture was diluted with water and extracted with AcOEt. The extract was worked up and the residue was chromatographed on silica gel with hexane–AcOEt (4 : 1, v/v). The product was crystallized from iso-Pr_2O to give **16** (0.88 g, 31.0%), mp 157—158 °C. IR (Nujol): 3200, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.87—2.23 (4H, m), 2.28 (3H, s), 3.30—3.54 (2H, m), 4.53 (1H, t, J=6 Hz), 6.59—6.92 (3H, s), 9.14 (1H, br s, NH). *Anal.* Calcd for $C_{12}H_{14}BrNO_2$: C, 50.72; H, 4.97; N, 4.93. Found: C, 50.75; H, 4.88; N, 4.75.

2-(3-Bromopropyl)-6,7,8,9-tetrahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-3(4*H*)-one (17) From VI: A solution **14** (9.50 g, 24.6 mmol) in EtOH (200 ml) was hydrogenated in the presence of 5% Pd–C (50% wet, 1.0 g). The catalyst was filtered off and the filtrate was concentrated. The residual solid was triturated with Et_2O, collected by filtration and recrystallized from AcOEt to give **17** as prisms (6.47 g, 81.1%), mp 139—140 °C. IR ($CHCl_3$): 3390, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.67—1.89 (4H, m), 2.00—2.29 (4H, m), 2.53—2.80 (4H, m), 3.32—3.56 (2H, m), 4.40—4.59 (1H, m), 6.50 (1H, s), 6.63 (1H, s), 9.23 (1H, s). *Anal.* Calcd for $C_{15}H_{18}BrNO_2$: C, 55.57; H, 5.60; N, 4.32. Found: C, 55.58; H, 5.41; N, 4.29.

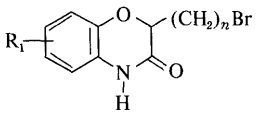
From VII: A mixture of **15** (3.1 g, 12.7 mmol), K_2CO_3 (1.8 g, 13.0 mmol) and DMF (20 ml) was stirred at room temperature for 1.5 h and diluted with water. The precipitate was collected by filtration, washed with water and dried. Recrystallization from AcOEt gave **17** (1.63 g, 72.0%), mp 139—140 °C. This compound was identical with **17** obtained from **14**. *Anal.* Calcd for $C_{15}H_{18}BrNO_2$: C, 55.57; H, 5.60; N, 4.32. Found: C, 55.60; H, 5.76; N, 4.36.

2-(3-Bromopropyl)-6,7-cyclopenteno-2*H*-1,4-benzoxazin-3(4*H*)-one (18) (i) A mixture of 3.85 g (21.5 mmol) of the isomeric mixture of **8** and **9**, methyl 2,5-dibromovalerate (5.90 g, 21.5 mmol), K_2CO_3 (3.00 g, 21.7 mmol) and DMF (30 ml) was stirred at room temperature for 4 h. The mixture was diluted with water and extracted with Et_2O. The extract was washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The residual oil was purified by column chromatography on silica gel (150 g) with hexane–AcOEt (9 : 1, v/v) to give 4.93 g (61.6%) of an oily mixture of methyl 5-bromo-2-(4,5-cyclopenteno-2-nitrophenoxy)valerate (**27**) and methyl 5-bromo-2-(3,4-cyclopenteno-2-nitrophenoxy)valerate (**28**) in a ratio of approximately 1 : 1 (determined from the ^{1}H-NMR integrals of aromatic protons for each regioisomer) which could not be separated by column chromatography or TLC. IR (neat): 1745, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10—2.30 (6H, m), 2.78—3.14 (4H, m), 3.37—3.58 (2H, m), 3.74 (1.5H × 2, s), 4.61—4.80 (0.5H × 2, m), 6.68 (0.5H, d, J=9 Hz), 6.73 (0.5H, s), 7.22 (0.5H, d, J=9 Hz), 7.66 (0.5H, s).

(ii) The isomeric mixture of **27** and **28** (1.90 g, 5.10 mmol) prepared in (i) in EtOH (30 ml) was hydrogenated in the presence of 10% Pd–C (50% wet, 0.32 g). The catalyst was filtered off and the filtrate was concentrated. The residue was chromatographed on silica gel (100 g) with hexane–AcOEt (2 : 1, v/v) and **18** (0.38 g, 25.3%), mp 154—155 °C, was obtained as colorless plates when crystallized from Et_2O. IR ($CHCl_3$): 3410, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.85—2.28 (6H, m), 2.68—2.98 (4H, m), 3.35—3.55 (2H, m), 4.50 (1H, t, J=6 Hz), 6.67 (1H, s), 6.78 (1H, s), 9.23 (1H, br s). *Anal.* Calcd for $C_{14}H_{16}BrNO_2$: C, 54.21; H, 5.20; N, 4.52. Found: C, 54.38; H, 5.18; N, 4.66.

2-(3-Bromopropyl)-5,6-cyclopenteno-2*H*-1,4-benzoxazin-3(4*H*)-one (19) (i) 2,5-Dibromovaleryl chloride (1.84 g, 6.6 mmol) in AcOEt (7 ml) was added dropwise to a stirred and ice-cooled mixture of **12** (1.25 g, 5.4 mmol), $NaHCO_3$ (1.06 g, 12.6 mmol), AcOEt (10 ml) and water (7 ml). After being stirred at 0 °C for 30 min, the organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organics were washed with saturated NaCl, dried ($MgSO_4$) and concentrated to yield 2,5-dibromo-1-(2-hydroxy-5,6-cyclopentenophenyl)valeramide as an oil. This was used for the subsequent reaction without further purification.

TABLE VII. 2-Bromoalkyl-2*H*-1,4-benzoxazin-3(4*H*)-ones (VIII)



Compd. No.	R_1	n	Starting material	Yield (%)	mp (°C)	Recrystn. solvent[a]	Formula[b]
16	6-Me	3	III	31.0	157—158	IPE	$C_{12}H_{14}BrNO_2$
17	6,7-$(CH_2)_4$–	3	VI	81.1	139—140	EA	$C_{15}H_{18}BrNO_2$
			VII	72.0			
18	6,7-$(CH_2)_3$–	3	VI	15.6[c]	154—155	E	$C_{14}H_{16}BrNO_2$
19	5,6-$(CH_2)_3$–	3	VII	60.0[d]	155—156	EA	$C_{14}H_{16}BrNO_2$
20	6-NO_2	3	III	27.0	150—151	E	$C_{11}H_{11}BrNO_4$
21	6-Cl	3	III	30.2	157—158	E	$C_{11}H_{11}BrClNO_2$
22	6-Me	2	III	9.6	183—184	IPE	$C_{11}H_{12}BrNO_2$
23	H	3	VI	60.6[e]	90— 92	E	$C_{11}H_{12}BrNO_2$
24	7-CO_2Et	3	VI	78.4[e]	118—119	E	$C_{14}H_{16}BrNO_4$
25	6-CF_3	3	VII	35.6[f]	123—124	IPE	$C_{12}H_{11}BrF_3NO_2$
26	6-MeO	3	VII	62.5[e]	102—103	E	$C_{12}H_{14}BrNO_3$

a, b) See footnotes *c*) and *d*) in Table I. *c*) Overall yield from a mixture of **8** and **9**. *d*) Overall yield from **12**. *e*) Overall yield from II. *f*) Overall yield from III.

(ii) A mixture of the amide obtained in (i), K_2CO_3 (0.91 g, 6.6 mmol) and DMF (15 ml) was stirred at room temperature for 4 h. Water was added and the mixture was extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$) and concentrated. The residue was recrystallized from AcOEt to give **19** (1.01 g, 60.0%), mp 155—156 °C as colorless crystals. IR ($CHCl_3$): 3400, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.92—2.35 (6H, m), 2.71—3.00 (4H, m), 3.37—3.59 (2H, m), 4.51 (1H, t, J=6 Hz), 6.74 (1H, d, J=9 Hz), 6.84 (1H, d, J=9 Hz), 8.42 (1H, br). *Anal.* Calcd for $C_{14}H_{16}BrNO_2$: C, 54.21; H, 5.20; N, 4.52. Found: C, 54.05; H, 5.16; N, 4.51.

Other compounds (**20**—**26**) listed in Table VII were prepared similarly from III, VI or VII.

Synthesis of X Typical examples are given to illustrate the general procedure.

Methyl 5-[4-(4-Fluorophenyl)-1-piperazinyl]-2-(2-nitro-4-phenylphenoxy)valerate (29) A mixture of methyl 5-bromo-2-(2-nitro-4-phenylphenoxy)valerate (3.51 g, 8.6 mmol), 1-(4-fluorophenyl)piperazine (1.98 g, 11.0 mmol), NEt_3 (1.40 ml, 10.0 mmol) and DMF (20 ml) was stirred at 80 °C for 2 h. Water was added and the mixture was extracted with AcOEt. The extract was washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (100 g) with hexane–AcOEt (2 : 3, v/v) as eluant to yield **29**. Recrystallization from Et_2O gave yellow crystals (2.00 g, 35.8%), mp 126—127 °C. IR (Nujol): 1740, 1625 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.28 (4H, m), 2.63 (2H, t, J=6 Hz), 2.51—2.69 (4H, m), 2.92—3.17 (4H, m), 3.75 (3H, s), 4.89 (1H, t, J=6 Hz), 6.68—7.75 (11H, m), 8.04 (1H, d, J=2.4 Hz). *Anal.* Calcd for $C_{28}H_{30}FN_3O_5$: C, 66.26; H, 5.96; N, 8.28. Found: C, 66.17; H, 5.91; 8.19.

Methyl 5-[4-(4-Fluorophenyl)-1-piperazinyl]-2-(4,5-methylenedioxy-2-nitrophenoxy)valerate (30) A mixture of methyl 5-bromo-2-(4,5-methylenedioxy-2-nitrophenoxy)valerate (0.30 g, 0.8 mmol), 1-(4-fluorophenyl)piperazine (0.23 g, 1.3 mmol), NEt_3 (0.14 ml, 1.3 mmol) and DMF (10 ml) was stirred at 80 °C for 2 h. The mixture was worked up in the same manner as described for **29** to give **30** (0.27 g, 71.2%), mp 98—99 °C (iso-Pr_2O). IR (Nujol): 1735, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.57—2.23 (4H, m), 2.44 (2H, t, J=6 Hz), 2.48—2.67 (4H, m), 2.95—3.17 (4H, m), 3.75 (3H, s), 4.76 (1H, t, J=6 Hz), 6.00 (2H, s), 6.47 (1H, s), 6.70—7.06 (4H, m), 7.40 (1H, s). *Anal.* Calcd for $C_{23}H_{26}FN_3O_7$: C, 58.10; H, 5.51; N, 8.81. Found: C, 58.05; H, 5.41; N, 8.81.

Other compounds (X) prepared similarly were isolated as oils after column chromatography on silica gel. Therefore these X were used for the subsequent reaction without further purification.

Synthesis of 2-(4-Phenyl-1-piperazinyl)alkyl-2*H*-1,4-benzoxazin-3(4*H*)-ones (XI, Table I and Related Compounds XIII, Table III) Typical examples are given to illustrate the general procedure.

2-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]-6,7,8,9-tetrahydro-2*H*-naphtho[2,3-*b*][1,4]oxazin-3(4*H*)-one (51) Method A: A stirred mixture of **17** (3.1 g, 9.6 mmol), 1-(4-fluorophenyl)piperazine (2.3 g, 13 mmol), NEt_3 (1.5 ml, 11 mmol) and DMF (100 ml) was heated at 80 °C for 1.5 h. The reaction mixture was poured into ice-water and extracted with AcOEt. The organic extract was washed with water, dried ($MgSO_4$) and concentrated. The residue was recrystallized from $CHCl_3$–AcOEt to give **51** as colorless crystals (2.4 g, 59.3%), mp 164—165 °C. IR ($CHCl_3$): 3410, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55—2.11 (8H, m), 2.43 (2H, t, J=6.0 Hz), 2.48—2.81 (8H, m), 3.02—3.18 (4H, m), 4.53 (1H, t, J=6.0 Hz), 6.47 (1H, s), 6.63 (1H, s), 6.70—7.12 (4H, m), 8.79 (1H, br s). *Anal.* Calcd for $C_{25}H_{30}FN_3O_2$: C, 70.90; H, 7.14; N, 9.92. Found: C, 70.72; H, 7.02; N, 9.88.

Dihydrochloride: A solution of **51** in a small amount of $CHCl_3$–MeOH (1 : 2, v/v) was treated with 20% methanolic hydrogen chloride and concentrated. The crystals obtained were recrystallized from MeOH to give **51**·2HCl as colorless crystals, mp 150—151 °C. IR (Nujol): 3450, 1685 cm^{-1}. NMR (DMSO-d_6) δ: 1.55—2.18 (8H, m), 2.43—2.75 (6H, m), 2.93—3.83 (8H, m), 4.38—4.57 (1H, m), 6.40—7.19 (6H, m), 10.55 (1H, s). *Anal.* Calcd for $C_{25}H_{30}FN_3O_2 \cdot 2HCl$: C, 60.48; H, 6.50; N, 8.46. Found: C, 60.35; H, 6.65; N, 8.42.

Method B: (i) A stirred mixture of **14** (5.00 g, 13.0 mmol), 1-(4-fluorophenyl)piperazine (2.45 g, 13.6 mmol), DMF (40 ml) and NEt_3 (1.99 g, 19.7 mmol) was heated at 80 °C for 2 h. The reaction mixture was diluted with water and extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel with hexane–AcOEt (1 : 1, v/v) to give methyl 5-[4-(4-fluorophenyl)-1-piperazinyl]-2-(5,6,7,8-tetrahydro-3-nitro-2-naphthyloxy)valerate (**31**) as an oil (4.51 g, 71.8%). IR (neat): 1755, 1620 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.57—2.22 (8H, m), 2.35—2.82 (10H, m), 2.95—3.15 (4H, m), 3.73 (3H, s), 4.80 (1H, t, J=5.7 Hz), 6.55 (1H, s), 6.69—7.05 (4H, m), 7.58 (1H, s).

(ii) Iron powder (1.90 g, 34.0 mmol) was added in a small portion to a stirred solution of **31** (4.10 g, 8.4 mmol) in AcOH (15 ml)–H_2O (2.5 ml). The mixture was stirred at room temperature for 30 min and at 80 °C for an additional 15 min. The insoluble material was filtered off and the filtrate was concentrated, neutralized with aqueous Na_2CO_3 and extracted with $CHCl_3$. The extract was washed with water, dried ($MgSO_4$) and concentrated to afford a solid which was recrystallized from $CHCl_3$–AcOEt to give **51** (1.54 g, 43.1%), mp 164—165 °C. The IR and ^{1}H-NMR spectra of this sample were identical with those of **51** obtained by method A.

6,7-Cyclopenteno-2-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-2*H*-1,4-benzoxazin-3(4*H*)-one (53) Method B: (i) A solution of 2.40 g (6.45 mmol) of the isomeric mixture of **27** and **28** (see preparation of **18**), 1-(4-fluorophenyl)piperazine (1.28 g, 7.10 mmol) and NEt_3 (0.9 ml, 6.5 mmol) in DMF (20 ml) was stirred at 80 °C for 2.5 h. The mixture was diluted with water and extracted with Et_2O. The extract was washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (100 g) with Hexane–AcOEt (2 : 3, v/v) to give 2.80 g of an oil.

(ii) A solution of the oil obtained in (i) in AcOH (10 ml)–H_2O (2 ml) was treated with iron powder (1.26 g, 22.6 mmol) and worked up as described for **51**. The residue was chromatographed on silica gel (120 g) using hexane–AcOEt (2 : 3, v/v) as eluant and recrystallized from CH_2Cl_2–AcOEt to give **53** as colorless crystals (0.86 g, 35.4%), mp 186—187 °C. IR ($CHCl_3$): 3400, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.58—2.24 (6H, m), 2.43 (2H, t, J=6.0 Hz), 2.48—2.67 (4H, m), 2.69—2.93 (4H, m), 3.0—3.18 (4H, m), 4.53 (1H, t, J=6.0 Hz), 6.64 (1H, s), 6.72—7.08 (5H, m), 8.84 (1H, br s). *Anal.* Calcd for $C_{24}H_{28}FN_3O_2$: C, 70.39; H, 6.89; N, 10.26. Found: C, 70.37; H, 6.66; N, 10.37.

Other compounds (XI) listed in Table I were prepared similarly. Compounds XIII in Table III were prepared substantially by applying method A.

6-Amino-2-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-2*H*-1,4-benzoxazin-3(4*H*)-one (48) A solution of **32** (2.03 g, 4.90 mmol) in MeOH (80 ml)–THF (20 ml) was hydrogenated in the presence of 10% Pd–C (50% wet, 0.6 g). The catalyst was filtered off and the filtrate was concentrated. The residue was crystallized from Et_2O to give **48** (1.85 g, 98.2%) as a crystalline solid, mp 158—159 °C. IR (Nujol): 3440 and 3350, 3230, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.47—2.09 (4H, m), 2.32—2.70 (6H, m), 2.89—3.21 (4H, m), 3.49 (2H, br s), 4.50 (1H, t, J=6.0 Hz), 6.12—6.38 (2H, m), 6.70—7.07 (5H, m), 8.49 (1H, br s). *Anal.* Calcd for $C_{21}H_{25}FN_4O_2$: C, 65.61; H, 6.55; N, 14.57. Found: C, 65.16; H, 6.46; N, 14.33.

2-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]-6-(3,3-dimethylureido)-2*H*-1,4-benzoxazin-3(4*H*)-one (49) Dimethylcarbamyl chloride (0.13 ml, 1.41 mmol) was added to a stirred and ice-cooled solution of **48** (0.50 g, 1.30 mmol) in pyridine (10 ml). The reaction mixture was stirred at 0 °C for 2 h and at room temperature for an additional 4 h, diluted with water and extracted with EtOAc. The extract was washed with saturated NaCl, dried ($MgSO_4$) and concentrated to give **49** (0.29 g, 48.9%). Recrystallization from CH_2Cl_2–AcOEt gave pale yellow crystals (0.23 g, 38.8%), mp 179—181 °C. IR ($CHCl_3$): 3475, 3400, 1670. ^{1}H-NMR ($CDCl_3$) δ: 1.56—2.10 (4H, m), 2.33—3.33 (10H, m), 3.00 (6H, s), 4.47 (1H, t, J=6.0 Hz), 6.38 (1H, s), 6.50—7.33 (7H, m), 8.98 (1H, s). *Anal.* Calcd for $C_{23}H_{30}FN_5O_3$: C, 63.28; H, 6.64; N, 15.37. Found: C, 62.92; H, 6.46; N, 15.09.

6-Acetamido-2-[3-[4-(4-fluorophenyl)-1-piperazinyl]propyl]-2*H*-1,4-benzoxazin-3(4*H*)-one (50) Acetic anhydride (0.18 ml) was added to a stirred solution of **48** (0.50 g, 1.30 mmol) in pyridine (5 ml). The reaction mixture was stirred at room temperature for 4 h and poured into ice-water. The resulting crystals were collected by filtration and dried to give **50** (0.46 g, 83.0%). Recrystallization from CH_2Cl_2–AcOEt afforded colorless prisms (0.40 g, 71.5%), mp 111—112 °C. IR (Nujol): 1675 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.49—1.89 (4H, m), 1.98 (3H, s), 2.25—2.63 (6H, m), 2.92—3.13 (4H, m), 4.39—4.58 (1H, m), 6.75—7.40 (8H, m), 9.77 (1H, br s). *Anal.* Calcd for $C_{23}H_{27}FN_4O_3 \cdot 1/2H_2O$: C, 63.43; H, 6.48; N, 12.86. Found: C, 63.57; H, 6.44; N, 12.74.

Synthesis of XII A typical example is given to illustrate the general procedure.

2-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]-6,7,8,9-tetrahydro-4-methyl-2*H*-naphtho[2,3-*b*][1,4]oxazin-3(4*H*)-one (68) Method C: A solution of **51** (0.42 g, 1.0 mmol) in DMF (6 ml) was added dropwise to a stirred and ice-cooled mixture of NaH (60% dispersion in oil, 60 mg, 1.5 mmol) and DMF (4 ml). After stirring for 10 min, methyl iodide (0.10 ml, 1.6 mmol) was added dropwise and the whole mixture was stirred

for an additional 30 min at 0 °C. The reaction mixture was diluted with water and extracted with Et_2O. The organic layer was washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (70 g) with AcOEt–hexane (3 : 2, v/v) as eluant to give **68** as an oil (0.41 g, 93.6%), which was crystallized from Et_2O to afford colorless crystals (0.28 g, 63.0%), mp 98—99 °C. IR (Nujol): 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53—2.07 (8H, m), 2.41 (2H, t, J=6.0 Hz), 2.52—2.87 (8H, m), 2.93—3.17 (4H, m), 3.28 (3H, s), 4.50 (1H, t, J=6.0 Hz), 6.60 (1H, s), 6.68 (1H, s), 6.74—7.07 (4H, m). *Anal.* Calcd for $C_{26}H_{32}FN_3O_2$: C, 71.37; H, 7.37; N, 9.60. Found: C, 71.30; H, 7.33; N, 9.65.

Other compounds (XII) listed in Table II were prepared similarly.

(*R*)-(+)-Methyl 3-(3,4,6,7,8,9-Hexahydro-3-oxo-2*H*-naphtho[2,3-*b*]-[1,4]oxazin-2-yl)propionate [(*R*)-(+)-86] (i) A solution of $NaNO_2$ (3.80 g, 55.1 mmol) in water (30 ml) was added dropwise to a stirred and ice-cooled solution of L-glutamic acid γ-methyl ester (L-**83**, 8.06 g, 50.0 mmol) and 6 N HCl (28 ml) at such a rate that the reaction temperature did not exceed 0 °C. The resulting mixture was stirred at 0 °C for 1 h and then extracted with Et_2O. The extract was washed with saturated NaCl, dried ($MgSO_4$) and concentrated to yield the crude (*S*)-2-chloroglutaric acid γ-methyl ester [(*S*)-**84**, 2.69 g, 29.8%] as a colorless oil. This was used for the next reaction without further purification. IR ($CHCl_3$): 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.07—2.70 (4H, m), 3.67 (3H, s), 4.46 (1H, dd, J=5.4, 7.5 Hz), 8.90 (1H, br s).

(ii) A mixture of (*S*)-**84** (0.89 g, 4.9 mmol) and $SOCl_2$ (0.54 ml, 7.4 mmol) was refluxed with stirring for 1 h. The mixture was concentrated to yield the corresponding acid chloride which was used for the next reaction without purification.

(iii) A solution of the acid chloride obtained above in AcOEt (8 ml) was added to a stirred and ice-cooled mixture of **6** (0.80 g, 3.3 mmol), $NaHCO_3$ (0.50 g, 6.0 mmol), AcOEt (8 ml) and water (5 ml). After being stirred at 0 °C for 1 h, the mixture was taken up with AcOEt. The AcOEt layer was washed with saturated NaCl, dried ($MgSO_4$) and concentrated to give (*S*)-methyl 4-chloro-4-(4,5,6,7-tetrahydro-2-hydroxynaphthylcarbamoyl)-butyrate [(*S*)-**85**] as an oil.

(iv) A mixture of (*S*)-**85** obtained in (iii), K_2CO_3 (0.68 g, 4.9 mmol) and DMF (10 ml) was stirred at room temperature for 1 h. Water was added and the resulting precipitate was collected by filtration to give (*R*)-**86**. Recrystallization from CH_2Cl_2–AcOEt gave colorless crystals (0.31 g, 21.7% based on **6**), mp 137—138 °C. $[\alpha]_D^{26}$ +10.3° (c=0.5, $CHCl_3$). IR ($CHCl_3$): 3400, 1720, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.93 (4H, m), 2.00—2.87 (8H, m), 3.69 (3H, s), 4.54 (1H, dd, J=5.4, 7.5 Hz), 6.48 (1H, s), 6.63 (1H, s), 8.99 (1H, br). *Anal.* Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.25; H, 6.67; N, 4.95.

(*R*)-(−)-6,7,8,9-Tetrahydro-2-(3-hydroxypropyl)-2*H*-naphtho[2,3-*b*]-[1,4]oxazin-3(4*H*)-one [(*R*)-(−)-87] (*R*)-(+)-**86** (2.16 g, 74.7 mmol) in anhydrous THF (10 ml) was added dropwise to a stirred and ice-cooled suspension of $LiAlH_4$ (0.43 g, 11.3 mmol) in anhydrous THF (20 ml). The mixture was stirred at 0 °C for 1.5 h and neutralized with 6 N HCl. The insoluble material was removed by filtration and washed with AcOEt. The combined filtrate and the washings were partitioned between water and AcOEt. The organic layer was separated, washed with water, dried ($MgSO_4$) and concentrated to yield the crude alcohol (*R*)-**87** (1.84 g, 94.3%). Recrystallization from AcOEt gave colorless crystals, mp 141—141.5 °C $[\alpha]_D^{26}$ −3.1° (c=0.3, $CHCl_3$). IR ($CHCl_3$): 3410, 1685 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.58—2.18 (8H, m), 2.44—2.81 (4H, m), 3.53—3.88 (2H, m), 4.55 (1H, t, J=5.7 Hz), 6.51 (1H, s), 6.67 (1H, s), 8.98 (1H, br s). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.02; H, 7.35; N, 5.55.

(*R*)-(−)-6,7,8,9-Tetrahydro-2-(3-methanesulfonyloxypropyl)-2*H*-naphtho-[2,3-*b*][1,4]oxazin-3(4*H*)-one [(*R*)-(−)-88] NEt_3 (0.85 ml, 6.1 mmol) and then methanesulfonyl chloride (0.62 ml, 8.0 mmol) were added dropwise to a solution of (*R*)-(−)-**87** (1.0 g, 3.8 mmol) in CH_2Cl_2 (40 ml) with ice-cooling. The mixture was stirred at 0 °C for 1.5 h and then water was added. The organic layer was washed with water, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (60 g) using hexane–AcOEt (1 : 2, v/v) as eluant and recrystallized from MeOH–AcOEt to yield (*R*)-(−)-**88** as colorless needles (1.01 g, 77.8%), mp 154—155 °C, $[\alpha]_D^{26}$ −9.3° (c=0.3, $CHCl_3$). IR ($CHCl_3$): 3390, 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55—2.25 (8H, m), 2.53—2.82 (4H, m), 2.98 (3H, s), 4.21—4.38 (2H, m), 4.42—4.63 (1H, m), 6.50 (1H, s), 6.64 (1H, s), 8.96 (1H, br s). *Anal.* Calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.70; H, 6.20; N, 4.24.

(*R*)-(+)-2-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]-6,7,8,9-tetrahydro-2*H*-naphtho[2,3-*b*][1,4]oxazine-3-(4*H*)-one [(*R*)-(+)-51] A mixture of (*R*)-(−)-**88** (0.44 g, 1.3 mmol), 1-(4-fluorophenyl)piperazine (0.35 g, 1.9 mmol), NEt_3 (0.18 ml, 1.3 mmol) and DMF (8 ml) was stirred at 70 °C for 2.5 h. The mixture was concentrated and the residue was subjected to column chromatography on silica gel (60 g). Elution with hexane–AcOEt (1 : 3, v/v) afforded (*R*)-(+)-**51** which was recrystallized twice from MeOH to give colorless needles (0.37 g, 66.5%), mp 153—154 °C, $[\alpha]_D^{26}$ +19.9° (c=0.7, $CHCl_3$). IR ($CHCl_3$): 3415, 1685, 1505 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.59—2.10 (8H, m), 2.32—2.82 (10H, m), 2.98—3.20 (4H, m), 4.54 (1H, t, J=6.0 Hz), 6.47 (1H, s), 6.65 (1H, s), 6.71—7.10 (4H, m), 8.83 (1H, br s). *Anal.* Calcd for $C_{25}H_{30}FN_3O_2$: C, 70.90; H, 7.14; N, 9.92. Found: C, 70.60; H, 7.14; N, 9.89.

The following compounds were prepared starting from D-glutamic acid γ-methyl ester (D-**83**) by the same procedure described for the synthesis of (*R*)-(+)-**51**.

(*S*)-(−)-Methyl 3-(3,4,6,7,8,9-Hexahydro-3-oxo-2*H*-naphtho[2,3-*b*]-[1,4]oxazin-2-yl)propionate [(*S*)-(−)-86] Starting from D-glutamic acid γ-methyl ester (D-**83**), (*S*)-(−)-**86** was obtained *via* (*R*)-**85** in 36.0% yield (based on **6**), mp 138—138.5 °C (AcOEt–Et_2O), $[\alpha]_D^{26}$ −7.8° (c=0.3, $CHCl_3$). IR ($CHCl_3$): 3395, 1720, 1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.57—1.93 (4H, m), 2.00—2.82 (8H, m), 3.67 (3H, s), 4.54 (1H, dd, J=5.4, 7.5 Hz), 6.50 (1H, s), 6.63 (1H, s), 9.23 (1H, br s). *Anal.* Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.01; H, 6.45; N, 4.94.

(*S*)-(+)-6,7,8,9-Tetrahydro-2-(3-hydroxypropyl)-2*H*-naphtho[2,3-*b*]-[1,4]oxazin-3(4*H*)-one [(*S*)-(+)-87] Yield 98.7%, mp 139—140 °C (AcOEt). $[\alpha]_D^{26}$ +1.4° (c=0.5, $CHCl_3$). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.76; H, 7.37; N, 5.41.

(*S*)-(+)-6,7,8,9-Tetrahydro-2-(3-methanesulfonyloxypropyl)-2*H*-naphtho[2,3-*b*][1,4]oxazin-3(4*H*)-one [(*S*)-(+)-88] Yield 79.7%, mp 153—154 °C (MeOH). $[\alpha]_D^{26}$ +4.8° (c=0.8, $CHCl_3$). *Anal.* Calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.59; H, 6.20; N, 4.14.

(*S*)-(−)-2-[3-[4-(4-Fluorophenyl)-1-piperazinyl]propyl]-6,7,8,9-tetrahydro-2*H*-naphto[2,3-*b*][1,4]oxazin-3(4*H*)-one [(*S*)-(−)-51] Yield 59.6%, mp 156—156.5 °C (MeOH). $[\alpha]_D^{26}$ −19.9° (c=1.2, $CHCl_3$). *Anal.* Calcd for $C_{25}H_{30}FN_3O_2$: C, 70.90; H, 7.14; N, 9.92. Found: C, 70.80; H, 7.10; N, 9.88.

Pharmacological Methods Calcium channel blocking, antihypertensive and calmodulin antagonistic activities and inhibitory effects of caffeine-induced contraction of rabbit aorta were assayed using the methods described earlier.[1]

Antiarrhythmic Activity[11] Male Sprague-Dawley rats (9 weeks old) were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and artificially ventilated with room air (stroke volume, 6 ml; 60 strokes/min). The electrocardiogram (Lead II) was recorded from subcutaneous steel needle electrodes. A left thoracotomy was performed, the heart was exteriorized and a 6/0 silk suture placed under the main left coronary artery. The heart was repositioned in the thoracic cavity and the ligature loosely tied around a fine piece of polyethylene tubing. A stabilization period of 15 min was allowed. Drugs or vehicle (distilled water, 10 ml/kg) were orally given 1 h before tightening the ligature. Five minutes later the ligature was released by sliding a scalpel blade over the polyethylene tubing. The incidence of VF, VT and electrical deaths (mortality) were noted.

References and Notes

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