[Chem. Pharm. Bull. 33(3)1129—1139(1985)]

Spiropiperidines. I. Synthesis of 1′-Substituted Spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one Derivatives and Evaluation of Their Antihypertensive Activity

HARUKI TAKAI,*[,a] HIROYUKI OBASE,[a] MASAYUKI TERANISHI,[a] AKIRA KARASAWA,[b] KAZUHIRO KUBO,[b] KATSUICHI SHUTO,[b] YUTAKA KASUYA,[c] MAKIKO HASHIKAMI,[c] NAOKO KARASHIMA,[c] and KOKI SHIGENOBU[c]

Tokyo Research Laboratory,[a] Kyowa Hakko Kogyo Co., Ltd., Asahimachi 3–6–6, Machidashi, Tokyo 194, Japan, Pharmaceutical Research Laboratories,[b] Fuji, Kyowa Hakko Kogyo Co., Ltd., Shimotogari 1188, Nagaizumi-cho, Shizuoka 411, Japan and Faculty of Pharmaceutical Sciences, University of Tokyo,[c] Bunkyo-ku, Tokyo 113, Japan

(Received June 8, 1984)

General synthetic methods for the preparation of 4-(2-aminophenyl)-4-hydroxypiperidine derivatives have been developed. The application use of these derivatives in the synthesis of 1′-substituted spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one derivatives is described, and the antihypertensive activity of the products is also reported.

Keywords——antihypertensive activity; spiro ring; piperidine; alpha receptor blocking; oxazine

Previous reports[1] on piperidine derivatives with a quinazolinone ring or a related heterocyclic ring at the 4-position led us to consider the possibility of developing a useful antihypertensive agent through further modification of this series. In the process of this investigation, we were interested in the effect of the stereochemical relationship between the piperidine ring and the heterocyclic ring on the antihypertensive activity. Several reports have appeared on antihypertensive piperidine derivatives with a heterocyclic ring in the spiro form.[2] Accordingly, we selected the spiro compound A (Chart 1) for further modification.

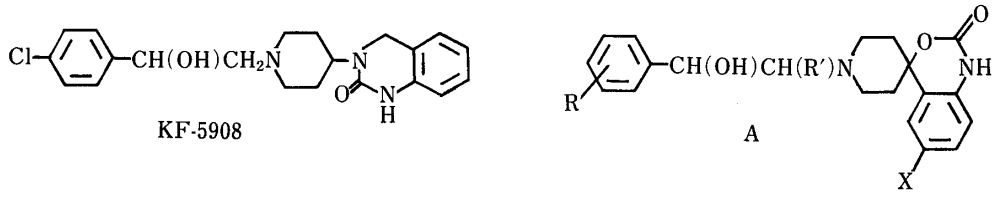


Chart 1

The choice of A was also based on the similarity to KF 5908,[1] which was previously reported to exhibit interesting antihypertensive activity. In this paper, the synthesis and biological activity of these spiro compounds are described. Recently, methods of *ortho* functionalization of aromatic amines *via ortho* lithiation of *N*-pivaloylanilines or *N*-*tert*-butoxycarbonylanilines were reported.[3] In the light of these results, we first attempted to prepare 4-(2-aminophenyl)-4-hydroxypiperidine derivatives which could be used to synthesize the desired spiro piperidine derivatives. The first synthetic approach made use of the method of Fuhrer.[3a] Reaction of the dilithium derivative of *N*-pivaloyl-4-chloroaniline (**1**) in tetrahydrofuran (THF)–hexane

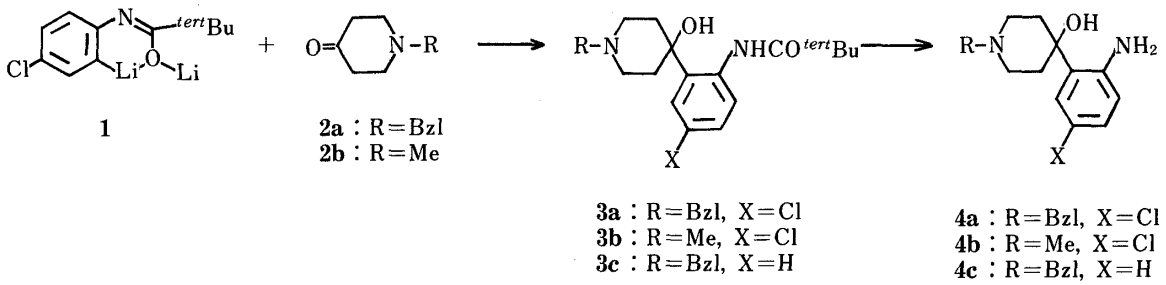


Chart 2

(3 : 1) with piperidones (**2a**, **b**) at 0 °C gave the expected piperidinols (**3a**, **b**) in 38.5% and 40.0% yields, respectively with some recovery of the starting piperidones (**2a**, **b**) as well as *N*-pivaloyl-4-chloroaniline, probably as a result of the competing enolization of **2a** and **2b** by the dilithium salt. In the separation of **3a** and **3b** from recovered *N*-pivaloyl-4-chloroaniline, **3b** was easily isolated by extraction with dil. HCl, but **3a** could not be isolated in a similar manner because it was only slightly soluble in dil. HCl. Compound **3a** was isolated by column chromatography on silica gel with ethyl acetate (AcOEt)–hexane (1 : 4, v/v), followed with AcOEt. This method of isolation sometimes encountered the difficulty that crystals of *N*-pivaloyl-4-chloroaniline separated out and could not be removed from **3a**. This problem was resolved by chromatography of the mixture of *N*-pivaloyl-4-chloroaniline and **3a**, after the addition of acetic acid (AcOH) to convert **3a** to the AcOH salt, on silica gel with $CHCl_3$, followed by MeOH. However, we needed a simpler method for the preparation of **3a** on a large scale. Furthermore, the reaction conditions were examined and it was found that after the reaction of the dilithium derivative of 0.35 M *N*-pivaloyl-4-chloroaniline in THF–hexane (1 : 1) with 1-benzyl-4-piperidone (**2a**), washing of the reaction mixture with H_2O caused almost pure crystals of **3a** to separate from the reaction solution. Subsequent acid hydrolysis of **3a** and **3b** in 2 or 3 N H_2SO_4 under reflux for 16—54 h led to the desired **4a** and **4b** in 62.4% and 66.7% yields, respectively (Chart 2). 5′-Unsubstituted piperidinol **4c** was obtained in 40.8% yield by acid hydrolysis, after dechlorination of **3b** by catalytic hydrogenation under alkaline conditions.

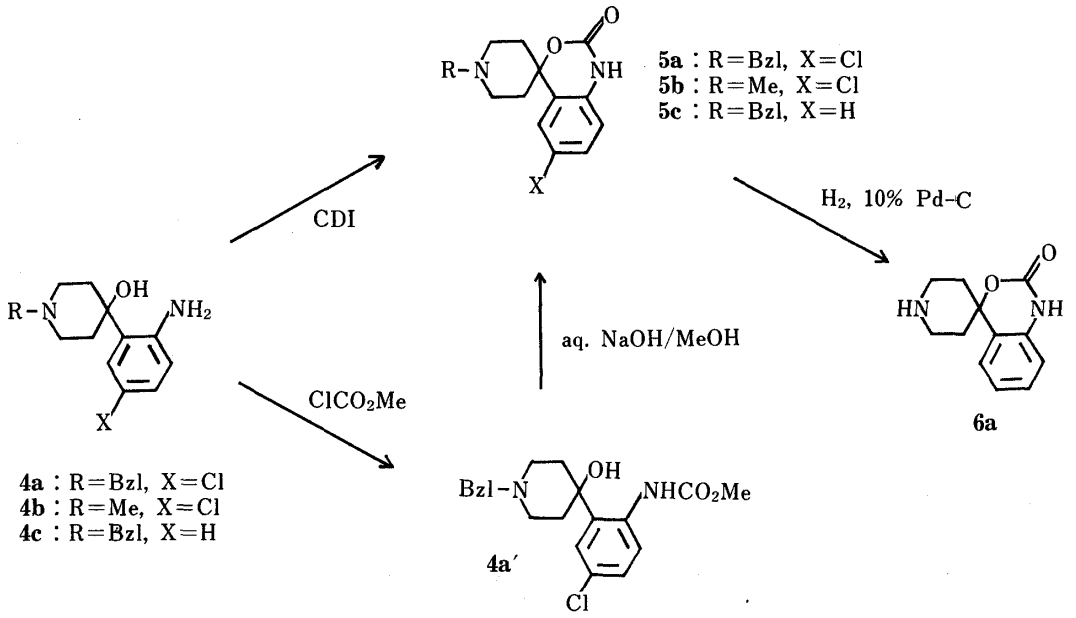


Chart 3

The piperidinols (**4a**—**c**) were converted to benzoxazines (**5a**—**c**) by treatment wih 1,1′-carbonyldiimidazole (CDI) in 94.5%, 66.7%, and 60.7% yields, respectively. Compound **5a** was also obtained in 89.1% yield *via* **4a′** by treatment of **4a** with methyl chloroformate (1.4 eq) in pyridine at 0 °C, followed by treatment with 2 N NaOH in MeOH at room temperature. Subsequent catalytic hydrogenation over 10% Pd–C at 40 °C gave **6a**[4] in 85.5% yield. These results are shown in Chart 3.

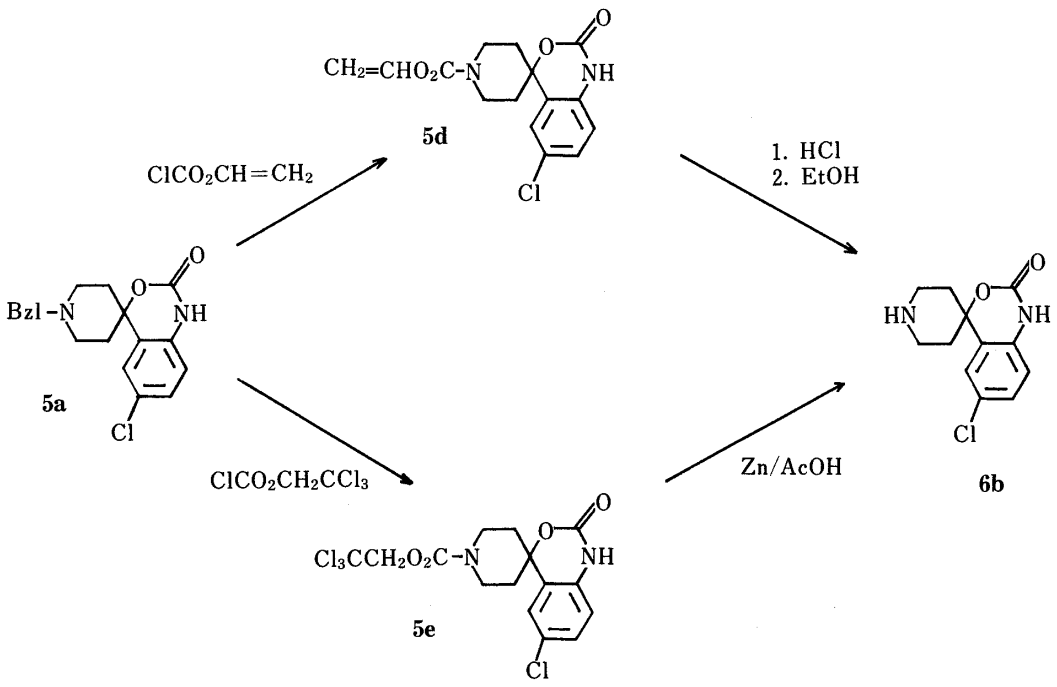
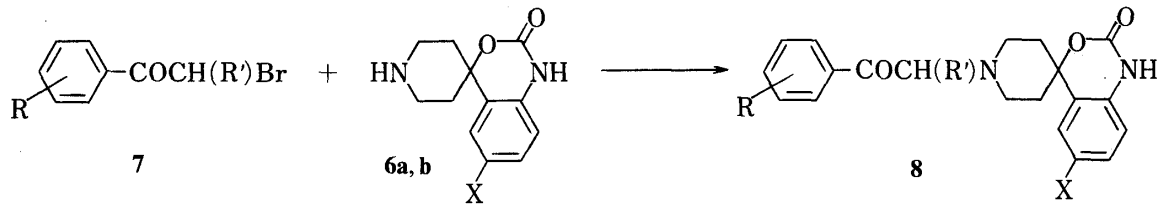


Chart 4

The 6-chloro compound (**6b**) was obtained in 72.5% yield *via* **5d** from **5a** according to Olofson *et al.* by using vinyl chloroformate.[5] Compound **6b** was also obtained in 26.5% yield *via* **5e** from **5a** by using 2,2,2-trichloroethyl chloroformate (Chart 4). The spiro compounds (**6a, b**) thus obtained were used to prepare the 1-benzoylalkylpiperidine derivatives (**8**) listed in Table I by using triethylamine (TEA) as a base in ethanol. The benzyl alcohol derivatives (**9a**—**i**) listed in Table II were prepared by reduction of the corresponding 1-benzoylmethyl derivatives (**8a**—**i**) with $NaBH_4$. Reduction of 1-(1-benzoylethyl) derivatives (**8j**—**l**) with $NaBH_4$ gave diastereomixtures of the corresponding benzyl alcohol derivatives (**10j**—**l** and **11j**—**l**). These diastereomixtures were separated by column chromatography on silica gel with AcOEt. Analysis of the proton nuclear magnetic resonance (^{1}H-NMR) spectra of the benzyl alcohol derivatives (**10j**—**l** and **11j**—**l**) in chloroform-*d* medium permitted assignment of the configurations. The coupling constants of the benzylic proton (C-3″ methine proton) of each compound (Table III) were 10 Hz for **10j**—**l** and 4.5, 3.5, and 3.5 Hz, respectively, for **11j**—**l**. These are comparable with the values of 8.3 and 4.0 Hz for pseudoephedrine (*threo*) and ephedrine (*erythro*).[6] Similar values have been found for other epimeric amino alcohols.[7] The virtual identity of the coupling constants of these compounds supported the assignment of *threo* configuration to **10j**—**l** and *erythro* to **11j**—**l**. The ^{1}H-NMR spectra of the diastereomixtures indicated that the formation of *threo* isomers (**10j**—**l**) was predominant over that of *erythro* isomers (**11j**—**l**), based on the doublet peak due to the C-3″ methine proton of each compound, as shown in Table III. Further, the carbon-13 nuclear magnetic resonance (^{13}C-NMR) signals of these compounds were assigned as shown in Table IV.

Reduction of these compounds (**8j**—**l**) was also attempted by catalytic hydrogenation

TABLE I.

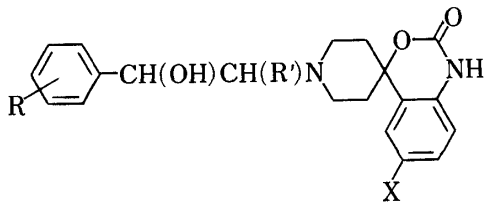


7 6a, b 8

Compd. No.	R	R′	X	Yield (%)	Recrystn. solvent[a]	mp (°C)	Formula[b]
8a	3,4-DiCH_3O	H	H	93.2	$CHCl_3$–EtOH	185.0—186.0	$C_{22}H_{24}N_2O_5$
8c	4-Cl	H	H	83.0		Crude crystals	
8d	H	H	H	86.3	$CHCl_3$	183.5—185.0	$C_{20}H_{20}N_2O_3$
8e	3-OH, 4-CH_3O	H	H	70.0		Crude crystals	
8f	3-OH, 4-CO_2CH_3	H	H	88.4		Crude crystals	
8g	3,4-DiCH_3O	H	Cl	89.8	DMF–MeOH	200.0—204.0	$C_{22}H_{23}ClN_2O_5$
8h	4-Cl	H	Cl	85.5	DMF–EtOH	209.0—212.2	$C_{20}H_{18}Cl_2N_2O_3$
8i	H	H	Cl	90.6	EtOH	175.5—177.8	$C_{20}H_{19}ClN_2O_3$
8j	3,4-DiCH_3O	CH_3	H	63.3	EtOH	184.0—185.8	$C_{23}H_{26}N_2O_5$
8k	3,4,5-TriCH_3O	CH_3	H	88.3	EtOH	176.0—177.9	$C_{24}H_{28}N_2O_6$
8l	3,4,6-TriCH_3O	CH_3	H	70.9	EtOH	178.0—179.0	$C_{24}H_{28}N_2O_6$
8m	4-$C_6H_5CH_2O$	CH_3	H	71.2	EtOH	194.0—197.0	$C_{28}H_{28}N_2O_4$

a) EtOH, ethanol; MeOH, methanol. *b*) Compounds for which the formula is given were analyzed for C, H, and N, and analytical values were within ±0.3% of the calculated values for these formulas.

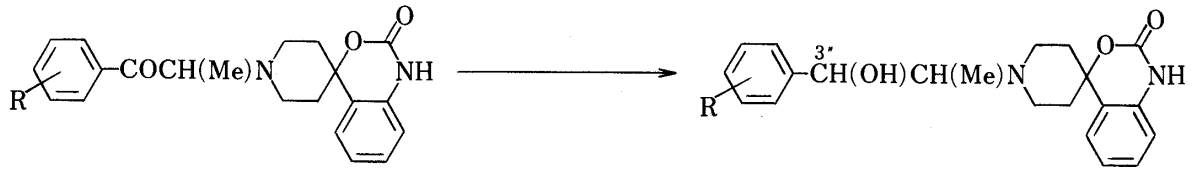
TABLE II.



Compd.	R	R′	X	Config.	Yield (%)	Recrystn. solvent	mp (°C)	Formula[c]
9a	3,4-DiCH_3O	H	H	—	91.9	DMF–MeOH	212.5—213.5	$C_{22}H_{26}N_2O_5$
9b	3,4,5-TriCH_3O	H	H	—	44.7[a]	EtOH	224.5—226.0	$C_{23}H_{28}N_2O_6$
9c	4-Cl	H	H	—	72.7	DMF–EtOH	217.8—219.2	$C_{20}H_{21}ClN_2O_3$
9d	H	H	H	—	97.7	DMF–MeOH	242.5—243.5	$C_{20}H_{22}N_2O_3$
9e	3-OH, 4-CH_3O	H	H	—	59.3	DMF–EtOH	230.5—234.2	$C_{21}H_{24}N_2O_5$
9f	3-OH, 4-CO_2CH_3	H	H	—	77.2	MeOH	204.0—205.0	$C_{22}H_{24}N_2O_6 \cdot 0.5H_2O$
9g	3,4-DiCH_3O	H	Cl	—	83.6	DMF–MeOH	207.5—208.5	$C_{22}H_{25}ClN_2O_5$
9h	4-Cl	H	Cl	—	88.6	DMF–EtOH	238.2—240.0	$C_{20}H_{20}Cl_2N_2O_3$
9i	H	H	Cl	—	89.4	DMF–EtOH	244.8—247.0	$C_{20}H_{21}ClN_2O_3$
10j	3,4-DiCH_3O	CH_3	H	*threo*	[b]	EtOH	151.5—153.2	$C_{23}H_{28}N_2O_5$
11j	3,4-DiCH_3O	CH_3	H	*erythro*	[b]	EtOH	200.0—202.8	$C_{23}H_{28}N_2O_5$
10k	3,4,5-TriCH_3O	CH_3	H	*threo*	[b]	EtOH	241.2—243.0	$C_{24}H_{30}N_2O_6$
11k	3,4,5-TriCH_3O	CH_3	H	*erythro*	[b]	EtOH	169.0—170.5	$C_{24}H_{30}N_2O_6 \cdot 0.5H_2O$
10l	3,4,6-TriCH_3O	CH_3	H	*threo*	[b]	EtOH	209.6—210.2	$C_{24}H_{30}N_2O_6$
11l	3,4,6-TriCH_3O	CH_3	H	*erythro*	[b]	EtOH	210.9—212.0	$C_{24}H_{30}N_2O_6$
10m	4-$C_6H_5CH_2O$	CH_3	H	*threo*	56.4	EtOH	253.0—254.2	$C_{28}H_{30}N_2O_4$

a) Yield from **6a**. This reaction was carried out *in situ* without isolation of the intermediate **8** obtained from 3,4,5-trimethoxy-ω-bromoacetophenone and **6a**. *b*) See Table III. *c*) All compounds were analyzed for C, H, and N, and analytical values were within ±0.3% of the calculated values for these formulas.

TABLE III.

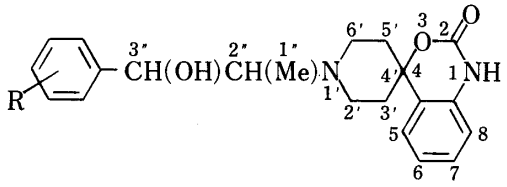


8j—l **10j—l + 11j—l** (*threo*) (*erythro*)

Compd.	R	Method	Yield (%) 10	Yield (%) 11	Ratio (^{1}H-NMR) 10 : 11	^{1}H-NMR signal of C-3″ proton (ppm) 10	11
j	3,4-DiCH_3O	A	65.3	15.7	4.6 : 1	4.24	4.87
		B	0	66.3		(d, J=10 Hz)	(d, J=4.5 Hz)
		C	88.8	0		$CDCl_3$	$CDCl_3$
k	3,4,5-TriCH_3O	A	35.4	16.9	4.5 : 1	4.22	4.88
		B	0	90.5		(d, J=10 Hz)	(d, J=3.5 Hz)
		C	73.5	0		$CDCl_3$	$CDCl_3$
l	3,4,6-TriCH_3O	A	60.0	23.2	2 : 1	4.84	5.22
		B	0	0		(d, J=10 Hz)	(d, J=3.5 Hz)
		C	63.2	0		$CDCl_3$	$CDCl_3$

A, $NaBH_4$; B, Pd–C; C, L-Selectride.

TABLE IV.



9a: R=3,4-diCH_3O; C-4″,5″
10j, 11j: R=3,4-diCH_3O; C-4″,5″
10k, 11k: R=3,4,5-triCH_3O; C-4″,5″,6″
10l, 11l: R=3,4,6-triCH_3O; C-4″,5″,6″

Compd.	C-2′,6′	C-3′,5′	C-4(4′)	C-1″	C-2″	C-3″	C-4″,5″,6″	Solvent
9a	47.906 49.125	34.992	80.377	—	66.548	69.959	55.948 55.765	DMSO-d_6
10j	39.232 46.860	35.041 35.407	80.366	8.480	65.599	73.372	55.413 55.462	DMSO-d_6
11j	43.326 45.032	35.285 35.504	80.293	9.064	65.306	72.495	55.413 55.510	DMSO-d_6
10k	46.847	35.059 35.455	80.353	8.650	65.549	73.773	55.772 59.914	DMSO-d_6
11k	43.405 44.928	35.363 35.577	80.322	9.198	65.214	72.799	55.772 59.945	DMSO-d_6
10l	39.184 47.761	36.406 35.870	81.804	8.236	66.257	67.158	56.144 56.534	$CDCl_3$
11l	44.349 46.360	36.003	81.754	10.569	62.656	67.621	56.015 56.229 56.655	$CDCl_3$

over 10% Pd–C in the presence of 1 eq of HCl in aq. EtOH at 40 °C. Compounds **8j—k** were converted to the *erythro* isomers (**11j—k**) without formation of the *threo* isomers (**10j—k**) as by-products. However, an attempt to convert **8l** to **11l** failed, and the starting material was recovered. *threo* Isomers (**10j—l**) were also obtained by selective reduction of compounds **8j—l** with L-selectride in dry THF at room temperature. In this process, the formation of *erythro*

isomers (**11j**—**l**) was not detected. The results of these reactions are summarized in Table III.

Biological Results

The compounds listed in Table II were examined for hypotensive activities. Blood pressure was measured in unanesthetized spontaneously hypertensive rats (SHR) and in anesthetized normotensive rats. SHR utilized were male Okamoto strain rats whose systolic pressure was higher than 180 mmHg at the 18th week after birth. Systolic blood pressure was measured with a plethysmograph after preheating the tail at 37 °C for 15 min.[8] Test compounds were suspended in 0.3% (w/v) carboxymethylcellulose (CMC) aqueous solution at a concentration of 1, 2.5, or 3 mg/ml and orally administered to the rats at a dose of 1 ml/100 g body weight. Hypotensive activities were also examined in anesthetized normotensive rats. Male Wistar strain rats weighing 250—320 g were anesthetized with urethane (600 mg/kg, *i.p.*) and alpha-chloralose (60 mg/kg, *i.p.*). Arterial blood pressure was measured from the left common carotid artery by means of a pressure transducer. Heart rate was also measured with a cardiotachometer triggered by pressure pulses. Test compounds were dissolved or suspended at a concentration of 3 mg/ml in 0.3% (w/v) CMC saline to which a minimum quantity of Tween 80 was, if necessary, added and intraperitoneally administered to the rats at a dose of 1 ml/100 g body weight.

All of the compounds tested produced relatively strong hypotension in unanesthetized SHR. Maximum decreases in blood pressure produced by the present compounds are shown in Table V; the maximum decrease was usually achieved 1.5—3.0 h after oral administration. Among the compounds tested in the present study, **9a**, **9b**, **10j**, **10l** were the most potent, followed by **9h**, **9i**, **11j**, **10k** and **11l**. Compounds **9c** and **9d** showed moderate activities, while **9e**, **9f**, **9g**, **11k** and **10m** were rather weakly hypotensive.

TABLE V. Changes in Blood Pressure of Unanesthetized SHR

Compd. No.	Dose (mg/kg *p.o.*)	Initial level[a] (mmHg)	Maximum level[a] (mmHg)	Maximum change (Δ mmHg)	Time[b] (h)
9a	10	220.0± 9.4 (4)	185.0± 3.5	−35.0	1.5
	30	210.0± 7.0 (4)	115.0±10.8	−95.0	5
9b	10	214.4± 6.5 (8)	170.6± 4.4	−43.8	1.5
	30	208.8± 5.7 (4)	132.5± 8.4	−76.3	1.5
9c	30	198.7± 5.9 (4)	155.0±11.0	−43.7	3
9d	30	210.0±14.5 (4)	163.7±10.9	−46.3	3
9e	30	205.0±12.5 (4)	182.5± 8.0	−22.5	1.5
9f	25	190.0± 4.7 (3)	190.0±12.5	0	
9g	30	205.0± 5.5 (4)	177.5± 8.9	−27.5	5
9h	30	207.5± 4.1 (3)	140.2±12.2	−67.3	3
9i	30	192.5± 9.6 (4)	126.2± 2.4	−66.3	1.5
10j	10	212.5± 6.8 (8)	165.0± 6.2	−47.5	1.5
	30	205.0± 6.4 (4)	121.3± 2.7	−83.7	1.5
11j	30	203.8± 2.1 (4)	148.8± 2.7	−55.0	1.5
10k	10	230.0± 7.4 (4)	196.3±13.4	−33.7	1.5
	30	195.0± 8.9 (4)	133.8±10.7	−61.2	1.5
11k	30	181.3± 3.7 (4)	167.5± 8.4	−13.8	1.5
10l	10	214.4± 6.4 (8)	158.1± 4.0	−56.3	1.5
	30	207.5±14.5 (4)	125.0± 7.4	−82.5	1.5
11l	10	228.8± 7.2 (4)	207.5± 5.2	−21.3	1.5
	30	192.5± 6.6 (4)	128.8± 9.7	−63.7	1.5
10m	25	190.0± 8.5 (3)	151.7±21.1	−38.3	1.5

a) Each number represents the mean±standard error, with the number of experiments in parentheses. *b*) The time until the maximum change was recorded after dosing.

The most potent compounds, **9a**, **9b**, **10j**, **10l**, and some of the other compounds were tested for hypotensive activities in anesthetized normotensive rats. The results are shown in Table VI. It is clear that the results with normotensive rats were broadly the same as those with SHR. Compounds **9a**, **9b**, **10j** and **10l** were again the most potent; however, compounds **11j** and **10k** showed about equipotent hypotensive activities. The hypotensions produced by these compounds were relatively long-lasting. Compounds **9f** and **10m** were less potent. Compounds **9c** and **9d**, whose hypotensive potencies were low in SHR, showed quite strong hypotensive activities in anesthetized normotensive rats. The reason for this discrepancy is unclear at present; many factors might be involved, *i.e.*, differences in the route of administration, influence of anesthesia, *etc.* All of the compounds tested except for **9d** produced a decrease in heart rate, as shown in Table VII. However, no definite correlation was observed between the decreases in blood pressure and heart rate.

It is difficult to discuss the structure–activity relationship on the basis of the present results obtained from only a limited number of experiments. When comparing the potencies of *threo* and *erythro* isomers of particular compounds, the *threo* isomers tended to show higher hypotensive activities in SHR. However, although only data on **10j** and **11j** were available, the *erythro* isomer was rather more potent in normotensive rats. In our previous

TABLE VI. Changes in Blood Pressure of Anesthetized Normotensive Rats[a]

Compd. No.	No. of animals	Initial level	Changes in blood pressure (mmHg)					
			10	30	60	120	180	240 (min)
9a	6	119±5	−21±5	−28±5	−38± 5	−29±6	−30± 6	−40± 7
9b	4	127±4	−15±4	−24±2	−30± 3	−30±2	−28± 2	−27± 5
9c	3	108±8	−23±5	−30±9	−24± 5	−28±6	−8±10	−5±14
9d	5	115±8	−15±4	−23±3	−29±10	−28±8	−35± 6	−22± 9
9f	3	119±6	−11±9	−16±7	−13±10	−11±9	−15± 8	−6± 7
10j	3	102±3	−23±4	−26±6	−29± 8	−26±5	−24± 3	−23± 3
11j	5	120±5	−35±4	−37±4	−35± 6	−22±8	−23± 5	−20± 5
10k	4	128±6	−34±5	−38±5	−37± 3	−44±3	−43± 4	−36± 6
10l	4	126±3	−40±5	−35±7	−31± 9	−27±6	−29± 2	−25± 7
10m	4	123±7	−7±6	−10±7	−20± 7	−22±3	−17± 3	−28± 2

a) Each number represents the mean ± standard error. Each compound was administered intraperitoneally at a dose of 30 mg/kg.

TABLE VII. Changes in Heart Rate of Anesthetized Normotensive Rats[a]

Compd. No.	No. of animals	Initial level	Changes in heart rate (beats/min)					
			10	30	60	120	180	240 (min)
9a	6	375±12	−11± 9	−18±14	−28±13	−42±16	−50±13	−61±19
9b	4	353± 9	−15±10	−30±10	−59±10	−100±12	−98±12	−71±11
9c	3	380±42	−38±14	−37±26	−43±29	−48±31	−43±28	+27±47
9d	5	359±29	+4± 5	+4± 9	+1±14	+7±26	−17±13	−12±19
9f	3	461±26	−13±27	−39±18	−18±28	−23±35	−48±41	−32±49
10j	3	345±16	−16± 9	−38± 4	−75± 5	−90± 9	−109±19	−122±16
11j	5	380±36	−64±40	−87±37	−79±37	−47±36	−69±40	−74±41
10k	4	427±17	−12±12	−17±13	−22±18	−56± 9	−61± 2	−45± 8
10l	4	385±20	−43±27	−24±18	−5± 7	+6± 7	−5±21	+1±25
10m	4	450± 9	−4±11	−2±13	−26±22	−24±37	+53±28	−49±11

a) Each number represents the mean ± standard error. Each compound was administered intraperitoneally at a dose of 30 mg/kg.

study with some benzimidazolinone derivatives, no significant difference was found between the pharmacological activities of the *threo* and *erythro* isomers.[9]

In conclusion, most of the compounds synthesized in the present study showed strong hypotensive activities both in SHR and in normotensive rats. Moreover, among these compounds, several were found to produce a very large and long-lasting decrease in blood pressure.

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were measured on a Shimadzu IR-27G spectrometer. ^{1}H-NMR spectra were measured on a Varian T-60 spectrometer, a Varian EM 390 spectrometer, and a JEOL JNM-PS-100 spectrometer with tetramethylsilane (TMS) as an internal standard. ^{13}C-NMR spectra were obtained at 25.1 MHz on a JEOL JNM-FX-100 spectrometer, operating in the Fourier-transform mode with TMS as an internal standard.

1-Benzyl-4-hydroxy-4-(2-pivaloylamino-5-chlorophenyl)piperidine (3a)——Method A: A 15% solution of *n*-butyllithium in hexane (240 ml, 374.4 mmol) was added in a dropwise manner to a solution of 1-pivaloylamino-4-chlorobenzene (31.8 g, 150.2 mmol) in dry THF (750 ml, N_2 atmosphere) at -5 to 0 °C over 35 min, and the solution was maintained at 0 °C for 2 h. A solution of 1-benzyl-4-piperidone (**2a**) (30 g, 158.5 mmol) in dry THF (45 ml) was added in portions to the above solution of the dianion (**1**) at 0 to 3 °C over 1 h with stirring. The reaction mixture was stirred for 3 h at 0 °C and then overnight at room temperature. This solution was partitioned between THF and water. The organic layer was washed with saturated NaCl solution, dried over sodium sulfate, and evaporated *in vacuo*. The product was isolated by one of the following procedures. (1): The residue was chromatographed on silica gel (AcOEt : hexane = 1 : 4, followed with AcOEt) to give **3a** (23.1 g, 38.5%) as crystals. Recrystallization from AcOEt–hexane afforded an analytical sample, mp 202.0—202.7 °C. *Anal.* Calcd for $C_{23}H_{29}ClN_2O_2$: C, 68.90; H, 7.29; N, 6.99. Found: C, 68.85, H, 7.38; N, 7.08. IR (KBr): 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (9H, s, $C(CH_3)_3$), 1.7—2.9 (8H, m, piperidine ring H), 3.4 (1H, br s, OH), 3.50 (2H, s, $-CH_2Ar$), 7.0—7.3 (7H, m, aromatic H), 8.07 (1H, d, aromatic H), 10.1 (1H, br s, NH). (2): The residue was triturated with *n*-hexane and collected by filtration to give a crystalline mixture (31.9 g) of **3a** and 1-pivaloylamino-4-chlorobenzene. The mixture was dissolved in $CHCl_3$ and the solution was evaporated after addition of AcOH (4.67 g, 77.8 mmol) to give a residue which was chromatographed on silica gel with $CHCl_3$, followed with MeOH. The eluent was worked up in the usual manner to give **3a** (17.5 g, 29.1%) as the free base.

Method B: A 15% solution of *n*-butyllithium in hexane (2.88 l, 4.49 mol) was added in a dropwise manner to a solution of 1-pivaloylamino-4-chlorobenzene (444 g, 2.10 mol) in dry THF (31, N_2 atmosphere) maintained at -30 °C over 1 h, and the mixture was maintained at -5 °C for 2 h. A solution of 1-benzyl-4-piperidone (420 g, 2.22 mol) was added in portions to the above solution of the dianion at -5 °C over 1 h 20 min with stirring. The reaction mixture was stirred overnight at -5 °C. This solution was successively washed with H_2O (2 l) and sat. aq. NaCl (2 l × 4). Precipitated crystals were collected by filtration and washed with H_2O (1 l) to give almost pure crystals of **3a** (382.1 g, 45.4%).

1-Methyl-4-hydroxy-4-(2-pivaloylamino-5-chlorophenyl)piperidine (3b)——A 15% solution of *n*-butyllithium in hexane (16 ml, 25.0 mmol) was added in a dropwise manner to a solution of 1-pivaloylamino-4-chlorobenzene (2.12 g, 10.0 mmol) in dry THF (60 ml, N_2 atmosphere) at -5 to 0 °C over 15 min, and the mixture was maintained at 0 °C for 2 h. A solution of 1-methyl-4-piperidone (1.13 g, 10 mmol) in dry THF (3 ml) was added to the above solution of the dianion at 0 °C over 1 h with stirring. The reaction mixture was stirred for 2 h at 0 °C and then overnight at room temperature. This solution was poured into ice water, made acidic with conc. HCl and extracted with AcOEt. The extract was shaken with 1 N HCl. This water layer was made basic and extracted with AcOEt. The organic layer was washed with H_2O and concentrated to give **3b** (1.3 g, 40.0%) as crystals. Recrystallization from MeOH afforded an analytical sample, mp 246.0—247.5 °C. *Anal.* Calcd for $C_{17}H_{25}ClN_2O_2$: C, 62.86; H, 7.76; N, 8.62. Found: C, 62.65; H, 7.89; N, 8.50. IR (KBr): 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (9H, s, $-CO(CH_3)_3$), 1.86—2.1 (4H, m, piperidine H), 2.25 (3H, s, $>NCH_3$), 2.4—2.8 (4H, m, piperidine H), 3.52 (1H, br s, OH), 7.1—7.3 (2H, m, aromatic H), 8.25 (1H, d, J = 8 Hz, aromatic H), 10.1 (1H, br s, NH).

1-Benzyl-4-hydroxy-4-(2-amino-5-chlorophenyl)piperidine (4a)——A solution of **3a** (700 g, 1.75 mmol) in 3 N H_2SO_4 (5.8 l) was stirred under reflux for 16 h and then ice water (1 l) was added. The solution was made basic with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evaporated to give a crude crystalline residue. This residue was triturated with AcOEt–hexane (2 : 3, v/v), and collected by filtration to give **4a** (346.0 g, 62.4%). Recrystallization from AcOEt–hexane afforded an analytical sample, mp 100.0—101.0 °C. *Anal.* Calcd for $C_{18}H_{21}ClN_2O$: C, 68.24; H, 6.68; N, 8.84. Found: C, 68.41; H, 6.96; N, 8.57. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.9 (8H, m, piperidine ring H), 3.3—3.65 (3H, m, OH and $-CH_2Ar$ (s at 3.49)) 4.53 (2H, br s, NH_2), 6.40 (1H, d, J = 9 Hz, aromatic H), 6.8—7.4 (7H, m, aromatic H).

1-Methyl-4-hydroxy-4-(2-amino-5-chlorophenyl)piperidine (4b)——A solution of **3b** (9.9 g, 30.5 mmol) in 2 N H_2SO_4 (150 ml) was stirred under reflux for 54 h. The solution was adjusted to pH 10 with aq. NaOH and extracted with AcOEt. The organic layer was washed with saturated NaCl solution and concentrated to give a crystalline residue, which was triturated with *n*-hexane and collected to yield **4b** (4.9 g, 66.7%). Recrystallization from AcOEt gave an analytical sample, mp 199.5—200.5 °C. *Anal.* Calcd for $C_{12}H_{17}ClN_2O$: C, 59.62; H, 7.09; N, 11.59. Found: C, 59.76; H, 7.21; N, 11.38. ^{1}H-NMR (DMSO-d_6) δ: 1.5—2.8 (11H, m, piperidine ring H and $>NCH_3$ (s at 2.17)), 5.12 (1H, br s, OH), 5.47 (2H, br s, NH_2), 6.62 (1H, d, J=9 Hz, aromatic H), 6.85—7.10 (2H, m, aromatic H).

1-Benzyl-4-hydroxy-4-(2-aminophenyl)piperidine (4c)——A mixture of **3a** (50 g, 125 mmol), NaOH (10 g, 250 mmol), and 10% Pd–C (5 g) in EtOH (1 l) was stirred at room temperature under a hydrogen atmosphere for 7 d to achieve selectively reductive dehalogenation. Then, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was dissolved in 2 N H_2SO_4 (750 ml) and the solution was refluxed for 44 h. The reaction mixture was made basic with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried and concentrated *in vacuo* to give an oily residue, which was crystallized from AcOEt–hexane to afford **4c** (14.4 g, 40.8%). Recrystallization from AcOEt–hexane gave an analytical sample, mp 121.0—122.5 °C. *Anal.* Calcd for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.60; H, 7.95; N, 9.97. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.9 (9H, m, piperidine H and OH), 3.55 (2H, s, CH_2Ar), 4.6 (2H, br s, NH_2), 4.53—7.4 (9H, m, aromatic H).

1′-Benzyl-6-chlorospiro[4*H*-3,1-benzoxazine-4,4′-piperidin]2(1*H*)-one (5a)——Method A: A suspension of **4a** (31.6 g, 100 mmol) in acetonitrile (220 ml) was treated with CDI [20 g (123 mmol), followed by further addition of 10 g (62 mmol) after 4 h] and the mixture was stirred at room temperature overnight. Precipitated crystals were collected by filtration, washed successively with CH_3CN, H_2O, and MeOH, and dried to give **5a** (32.4 g, 94.5%). Recrystallization from DMF–MeOH gave an analytical sample, mp 271.1—273.0 °C. *Anal.* Calcd for $C_{19}H_{19}ClN_2O_2$: C, 66.57; H, 5.59; N, 8.17. Found: C, 66.41; H, 5.48; N, 8.13. IR (KBr): 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.22 (4H, m, piperidine H), 2.41—2.96 (4H, m, piperidine H), 3.60 (2H, s, $-CH_2Ar$), 6.77 [1H, q, J=8 Hz, J'=1 Hz, aromatic H), 6.86—7.40 (7H, m, aromatic H), 8.47 (1H, br s, NH).

Method B: Methyl chloroformate (12.1 g, 128.0 mmol) was added dropwise to a stirred solution of **4a** (29 g, 91.6 mmol) in pyridine (140 ml) at 0 °C over 30 min and the mixture was stirred at room temperature for 1 h, then concentrated *in vacuo*. The residue was dissolved in MeOH (200 ml), treated with 2 N NaOH (92 ml), and stirred at room temperature for 2 h. Precipitated crystals were collected by filtration, washed successively with H_2O and MeOH, and dried to give white crystals (28.0 g, 89.1%) of **5a**.

6-Chloro-1′-methylspiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (5b)——This compound was prepared in 66.7% yield (as the HCl salt) from **4b** as described for **5a** by method A. Recrystallization from MeOH afforded an analytical sample, mp >300 °C. *Anal.* Calcd for $C_{13}H_{15}ClN_2O_2 \cdot HCl$: C, 51.50; H, 5.32; N, 9.24. Found: C, 51.28; H, 5.41; N, 9.06. IR (KBr): 1710 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.85 (3H, s, $>NCH_3$), 6.95—7.44 (3H, m, aromatic H), 10.59 (1H, s, NH), 11.26 (1H, br s, $>NCH_3 \cdot HCl$).

1′-Benzylspiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (5c)——This compound was prepared in 60.7% yield from **4c** as described for **5a** by method A. mp 210.5—212.0 °C. *Anal.* Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.98; H, 6.59; N, 9.08. IR (KBr): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.18 (4H, m, piperidine H), 2.41—2.92 (4H, m, piperidine H), 3.60 (2H, s, $-CH_2Ar$), 6.8—7.39 (9H, m, aromatic H), 9.05 (1H, br s, NH).

Spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (6a)——A mixture of **5a** (5.49 g, 16.0 mmol), 1 N HCl (16 ml), and 10% Pd–C (1.6 g) in H_2O (48 ml) and MeOH (96 ml) was stirred at 40 °C under a hydrogen atmosphere for 20 h. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to leave a crystalline residue, which was triturated with MeOH and collected by filtration to give **6a** (3.48 g, 85.5%) as the HCl salt. Recrystallization from MeOH afforded an analytical sample, mp >300 °C. *Anal.* Calcd for $C_{12}H_{14}N_2O_2 \cdot HCl$: C, 56.59; H, 5.94; N, 11.00. Found: C, 56.40; H, 5.85; N, 10.83. IR (KBr): 1710 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.93—7.39 (4H, m, aromatic H), 9.40 (2H, br s, $NH \cdot HCl$), 10.41 (1H, s, $-CONHAr$).

6-Chlorospiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (6b)——Method A: Vinyl chloroformate (1.43 g, 13.4 mmol) in ether (6 ml) was added to a solution of **5a** (2.74 g, 8.0 mmol) in 1,2-dichloroethane (30 ml). The mixture was stirred at room temperature for 1 h and then under reflux for 5 h. The reaction mixture was, after removal of the starting material as the HCl salt by filtration, concentrated *in vacuo* to give a crystalline residue, which was triturated with pet. ether (20 ml) and collected by filtration to afford crude crystals (2.2 g, 85.4%) of **5d**. Recrystallization from EtOH gave an analytical sample of **5d**, mp 217.0—219.8 °C. *Anal.* Calcd for $C_{15}H_{15}ClN_2O_4$: C, 55.82; H, 4.68; N, 8.68. Found: C, 55.90; H, 4.94; N, 8.48. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.3 (4H, m, piperidine H), 3.2—3.7 (2H, m, piperidine H), 4.1—4.4 (2H, m, piperidine H), 4.49 (1H, q, J=6 Hz, J'=1.5 Hz, $-OCH=CH-$), 4.82 (1H, J''=14 Hz, J'=1.5 Hz, $-OCH=CH-$), 6.83—7.36 (4H, m, aromatic H and $-OCH=CH_2$), 9.53 (1H, s, NH). A solution of **5d** (2.0 g, 6.20 mmol) in CH_2Cl_2 (40 ml) was mixed with 3.52 N HCl/AcOEt (20 ml) and stirred at room temperature for 1.5 h. The mixture was evaporated and the residue was dissolved in EtOH (50 ml). This solution was stirred at 50 °C for 1 h. The solution was concentrated to give a crystalline residue, which was triturated with EtOH and collected by filtration to afford **6b** (1.52 g, 84.9%) as the HCl salt. Recrystallization from EtOH gave an analytical sample, mp >300 °C. *Anal.* Calcd for $C_{12}H_{13}ClN_2O_2 \cdot HCl$: C, 49.85; H, 4.88; N, 9.69. Found: C, 49.81; H, 4.83; N, 9.42. IR

(KBr): 1720 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 6.98 (1H, d, J=8 Hz, aromatic H), 7.25 (1H, d, J'=2 Hz, aromatic H), 7.38 (1H, q, J=8 Hz, J'=2 Hz, aromatic H), 9.29 (2H, br s, >NH·HCl), 10.58 (1H, s, CONHAr).

Method B: A mixture of **5a** (10 g, 29.2 mmol) and 2,2,2-trichloroethyl chloroformate (15.5 g, 73 mmol) in 1,2-dichloroethane (100 ml) was stirred under reflux for 4 h. The reaction mixture was, after removal of the starting material as the HCl salt by filtration, concentrated *in vacuo* to give a crystalline residue, which was triturated with hexane (50 ml) and collected by filtration to afford crude crystals (5.79 g, 61.5%) of **5e**. Recrystallization from EtOH gave an analytical sample of **5e**, mp 256.0—257.5 °C. *Anal.* Calcd for $C_{15}H_{14}Cl_4N_2O_4$: C, 42.09; H, 3.30; N, 6.54. Found: C, 42.39; H, 3.28; N, 6.48. IR (KBr): 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.3 (4H, m, piperidine H), 3.2—3.8 (2H, m, piperidine H), 4.1—4.4 (2H, m, piperidine H), 4.80 (2H, s, $-OCH_2CCl_3$), 6.75—7.3 (3H, m, aromatic H), 9.30 (1H, s, NH). Zinc powder (3.9 g, 60 mmol) was added to a solution of **5e** (5.14 g, 15 mmol) in AcOH (50 ml) and the mixture was stirred at room temperature for 25 h. Then, the reaction mixture was filtered and the filtrate was diluted with H_2O. The solution was made basic with aq. NaOH and extracted with $CHCl_3$. The extract was washed with H_2O, dried, and evaporated *in vacuo* to give an amorphous residue, which was crystallized to afford **6b** (1.87 g, 43.1%) as the HCl salt from MeOH–AcOEt.

1′-(3,4-Dimethoxybenzoylmethyl)spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (8a)——A mixture of ω-bromo-3,4-dimethoxyacetophenone (2.59 g, 10 mmol), **6a** (2.55 g, 10 mmol as the HCl salt), and TEA (2.8 ml, 20 mmol) in EtOH (50 ml) was stirred at room temperature overnight. Precipitated crystals were collected by filtration, washed successively with EtOH, H_2O, and EtOH, and dried to give **8a** (3.70 g, 93.2%). Recrystallization from $CHCl_3$–EtOH afforded an analytical sample, mp 185.0—186.0 °C. *Anal.* Calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07. Found: C, 66.54; H, 6.05; N, 7.04. IR (KBr): 1680, 1725 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75—3.11 (8H, m, piperidine H), 3.92, 3.95, and 3.96 (8H, each s, $-CH_2CO$ and 2 × CH_3O), 6.83—7.72 (7H, m, aromatic H), 8.62 (1H, s, CONH).

Substituted 1′-Benzoylmethylspiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones (8c—f and 8j—m) (Table I)——These compounds were prepared in the manner described for **8a** except for the use of the appropriate substituted ω-bromoacetophenone.

1′-(4-Chlorobenzoylmethyl)-6-chlorospiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (8h)——A mixture of ω-bromo-4-chloroacetophenone (467 mg, 2.0 mmol), **6b** (578 mg, 2.0 mmol, as the HCl salt), and TEA (0.56 ml, 4.0 mmol) in EtOH (10 ml) was stirred at room temperature overnight. Precipitated crystals were collected by filtration, washed successively with MeOH and H_2O, and dried to give **8h** (692 mg, 85.5%). Recrystallization from DMF–EtOH afforded an analytical sample, mp 209.0—212.2 °C. *Anal.* Calcd for $C_{20}H_{18}Cl_2N_2O_3$: C, 59.27; H, 4.48; N, 6.91. Found: C, 58.99; H, 4.62; N, 7.10. IR (KBr): 1678, 1718 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.90 (2H, s, $COCH_2Ar$), 10.27 (1H, br s, NH).

Substituted 1′-Benzoylmethyl-6-chlorospiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones (8g and 8i)——These compounds were prepared in the manner described for **8h** except for the use of the appropriately substitute ω-bromoacetophenones.

1′-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (9a)——$NaBH_4$ (400 mg, 10.6 mmol) was added in one portion to a suspension of **8a** (1.09 g, 2.84 mmol) in EtOH (50 ml) at room temperature. The resulting mixture was stirred, with further addition of $NaBH_4$ (100 mg, 2.6 mmol) after 1 d, for 2 d at room temperature. The precipitated crystals were collected by filtration, successively washed with MeOH and H_2O, and dried to give 910 mg of crystals. On the other hand, the ethanol solution obtained as the filtrate was concentrated *in vacuo*, and the resulting residue was mixed with H_2O (10 ml). The deposited crystals were collected by filtration, washed with H_2O and dried to give 97 mg of crystals. These products were combined to give **9a** (1.01 g, 91.9%). Recrystallization from DMF–MeOH gave an analytical sample, mp 212.5—213.5 °C. *Anal.* Calcd for $C_{22}H_{26}N_2O_5$: C, 66.32; H, 6.58; N, 7.03. Found: C, 66.44; H, 6.61; N, 7.05. IR (KBr): 1715 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.86 and 3.90 (6H, each s, 2 × CH_3O), 4.60—4.86 (1H, m, $-CH(OH)-$), 8.85 (1H, br s, NH).

1′-[2-(3,4,5-Trimethoxyphenyl)-2-hydroxyethyl]spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (9b)——A mixture of ω-bromo-3,4,5-trimethoxyacetophenone (867 mg, 3 mmol), **6a** (764 mg, 3 mmol as the HCl salt), and TEA (0.84 ml, 6 mmol) in EtOH (20 ml) was stirred at room temperature overnight. Then, $NaBH_4$ (1 g, 26.4 mmol) was added to the stirred solution and the reaction mixture was further stirred at room temperature overnight. The deposited crystals were collected by filtration, and washed successively with MeOH and H_2O to give 482 mg of crystals. On the other hand, the filtrate was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$. The solution was washed with H_2O and concentrated *in vacuo*. The resulting oily residue was chromatographed on silica gel with AcOEt to give 93 mg of the desired compound as crystals. These products were combined to give **9b** (575 mg, 44.7%). Recrystallization from EtOH provided an analytical sample, mp 224.5—226.0 °C. *Anal.* Calcd for $C_{23}H_{28}N_2O_6$: C, 64.47; H, 6.59; N, 6.54. Found: C, 64.23; H, 6.58; N, 6.67. IR (KBr): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.0—2.3 (4H, m, piperidine H), 2.43—3.2 (6H, m, piperidine H, $CH(OH)CH_2$), 3.83 and 3.86 (9H, each s, 3 × CH_3O), 4.56—4.8 (1H, m, $-CH(OH)-$), 6.60 (2H, s, aromatic H), 6.73—7.36 (4H, m, aromatic H), 8.83 (1H, br s, NH).

Preparation of 1′-(2-Aryl-2-hydroxyethyl)spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-ones (9c—i)——These compounds were prepared from the corresponding amino ketones (**8c—i**) in the manner described for **9a**.

Preparation of 1'-(2-Aryl-2-hydroxy-1-methylethyl)spiro[4*H*-3,1-benzoxazine-4,4'-piperidin]-2(1*H*)-ones (10j—l and 11j—l) by Reduction of 8j—l (Table III)——General Procedures: Method A: $NaBH_4$ (945.8 mg, 25 mmol) was added to a stirred solution of the starting material (2.5 mmol) in EtOH (30 ml) at room temperature. The solution was stirred for 12 h at room temperature, concentrated *in vacuo*, and mixed with H_2O. The aqueous suspension was extracted with $CHCl_3$. The extract was washed with H_2O, dried, and concentrated *in vacuo*. The residue was worked up in the usual manner to give an amorphous powder, which was chromatographed on silica gel with AcOEt.

Method B: A mixture of the starting material (3 mmol), 1 N HCl (3 ml), and 10% Pd–C (200 mg) in H_2O (7.5 ml) and MeOH (15 ml) was stirred at 40 °C under a hydrogen atmosphere for 26 h. The catalyst was filtered off. The products were isolated by one of the following procedures. (1): The filtrate was made basic with aq. NaOH, diluted with H_2O, and extracted with $CHCl_3$ to give a product, which was recrystallized from EtOH. (2): The filtrate was treated with 3 M NaOH solution and concentrated *in vacuo* to give a crystalline residue, which was triturated with H_2O and collected by filtration. The product was recrystallized from EtOH.

Method C: A stirred solution of the starting material (3 mmol) in dry THF (60 ml) was treated with 1 M L-selectride/THF (9 ml) and the mixture was stirred for 1 h at room temperature. The reaction mixture, after addition of H_2O (2 ml), was concentrated *in vacuo* and the residue was taken up with H_2O. Precipitated crystals were collected by filtration and recrystallized from EtOH to yield a product.

Acknowledgement We are grateful to Mrs. Mayumi Yosida for measuring the ^{13}C-NMR spectra and to Mrs. Kazuko Yamaguchi for the elemental analyses. We are also grateful to Miss Keiko Kuwahara for her technical assistance.

References and Notes

1) *a*) H. Takai, H. Obase, M. Teranishi, K. Kubo, K. Shuto, and N. Nakamizo, Abstracts of Papers, the 102nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1982, p. 383; *b*) H. Takai, H. Obase, N. Nakamizo, M. Teranishi, K. Kubo, K. Shuto, Y. Kasuya, K. Shigenobu, M. Hashikami, and N. Karashima, *Chem. Pharm. Bull.*, **33**, 1116 (1985); *c*) H. Takai, H. Obase, N. Nakamizo, M. Teranishi, K. Kubo, K. Shuto, and T. Hashimoto, *ibid.*, **33**, 1104 (1985).
2) *a*) J. Maillard, P. Delaunary, M. Langlois, and T. Vo Van, *Bull. Soc. Chim. Fr.*, **1970**, 1389; *b*) J. Maillard, M. Langlois, P. Delaunay, T. Vo Van, J. Chenu, R. Morin, M. Benharkate, C. Manuel, and F. Motosso, *J. Med. Chem.*, **15**, 1123 (1972); *c*) J. Maillard, M. Langnois, P. Delaunay, T. Vo Van, G. Garcia, R. Morin, P. Eskenazi, M. Benharkate, C. Manuel, and F. Motosso, *Eur. J. Med. Chem.*, **7**, 458 (1972); *d*) J. Maillard, M. Langlois, T. Vo Van, P. Delaunay, R. Morin, M. Benharkate, C. Manuel, and F. Motosso, *ibid.*, **8**, 393 (1973); *e*) J. Maillard, M. Langnois, T. Vo Van, R. Morin, M. Benharkate, and P. Ple, *ibid.*, **9**, 128 (1974); *f*) S. S. Klioze and W. J. Novick, Jr., *J. Med. Chem.*, **21**, 400 (1978). Further papers have appeared since the completion of this part of our work; *g*) J. M. Caroon, R. D. Clark, A. F. Kluge, J. T. Nelson, A. M. Strosberg, S. H. Unger, A. D. Michel, and R. L. Whiting, *J. Med. Chem.*, **24**, 1320 (1981); *h*) R. D. Clark, J. M. Caroon, A. F. Kluge, D. B. Repke, A. P. Roszkowski, A. M. Strosberg, S. Baker, S. M. Bitter, and M. D. Okada, *ibid.*, **26**, 657 (1983).
3) *a*) W. Fuhrer and H. W. Gschwend, *J. Org. Chem.*, **44**, 1133 (1979); *b*) J. M. Muchowski and M. C. Venuti, *ibid.*, **45**, 4798 (1980).
4) The method for obtaining **6a** was unknown at the beginning of our investigation, but has since been described by Clark *et al.* in reference 2*h*.
5) R. A. Olofson, R. C. Schnur, L. Bunes, and J. P. Pepe, *Tetrahedron Lett.*, **1977**, 1567.
6) G. G. Lyle and L. K. Keefer, *J. Org. Chem.*, **31**, 3921 (1966).
7) *a*) G. G. Lyle and M. L. Durand, *J. Org. Chem.*, **32**, 3295 (1967); *b*) M. E. Munk, M. K. Meilahn, and P. Franklin, *ibid.*, **33**, 3480 (1968).
8) T. Sakamoto, K. Shiono, T. Watanabe, and H. Sokabe, *J. Pharmacobio-Dyn.*, **3**, 1 (1980).
9) Y. Kasuya, K. Shigenobu, M. Hashikami, N. Karashima, H. Obase, H. Takai, M. Teranishi, A. Karasawa, and K. Kubo, *J. Med. Chem.*, **26**, 208 (1983).