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Synthesis of 1′-Substituted 2-Amino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] Derivatives

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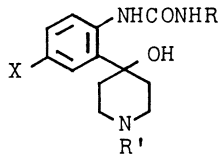
In the cyclization reaction of 4-hydroxy-4-[2-(*N*-substituted carbamoyl)aminophenyl]piperidine derivatives (**3**) by treatment with acid, 2-amino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] derivatives (**4**) were obtained. One of the products, 2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (**4g**), was converted to 1-(2-hydroxy-2-phenethyl)-2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] derivatives (**12**), which are our target compounds for pharmacological screening tests on antihypertensive activity. However, these compounds did not show any remarkable antihypertensive activity.

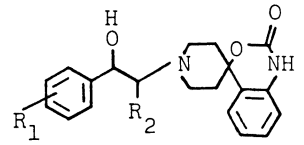
Keywords——benzoxazine; cyclization; piperidine; quinazoline; reductive cleavage; spiro compound; urea

Recently, we have described the synthesis and pharmacological evaluation of 1′-substituted spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one derivatives (**1**), a new class of antihypertensive agents.[1] As an extension of our investigation, we were interested in the preparation of 1′-substituted 2-amino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] derivatives (**4**) and 1-substituted spiro[piperidine-4,4′(3′*H*)-quinazolin]-2′(1′*H*)-one derivatives (**5**). In this paper, we wish to describe the cyclization reaction of 4′-hydroxy-4-[2-(*N*-substituted carbamoyl)aminophenyl]piperidine derivatives (**3**). Although the cyclization reaction of 2-ureidobenzyl alcohol derivatives with acid has already been reported by Soderbaum and Widman,[2,3] no application of this reaction to the preparation of spiro compounds has been reported so far. Therefore, we attempted the cyclization of **3** by treatment with acid, expecting the formation of **4** or **5**. The starting materials **3** were obtained by the reaction of **2**[1] with an appropriate isocyanate in ethyl acetate (AcOEt). The results are summarized in Table I. First, we attempted the cyclization of **3** with trifluoroacetic acid (TFA) at room temperature or at 65 °C overnight, but the desired reaction did not take place. However, heating a solution of **3** in 12 N hydrochloric acid or conc. sulfuric acid at 65—80 °C gave **4**. These results and analytical data for **4** are summarized in Table II. The structure of the product **4e** was determined by direct comparison of the spectroscopic data with those of a sample prepared by an alternative route, as shown in Chart 2. Thus, methylthiourea (**6**), which was obtained by the reaction of **2e** with methyl thioisocyanate, was treated with methyl iodide, followed by treatment with aqueous NaOH to give **4e** in 45.0% yield. The spectroscopic data of this compound were in accord with those of **4e** obtained by the above method shown in Chart 1. The selectivity of substitution reactions of ambident nucleophiles was described by Gould,[4] as follows. In an *S*N1 reaction, the incoming nucleophile attacks the carbonium-ion intermediate largely because of the gain in electrostatic stability resulting from the neutralization of charge. It will be advantageous for the carbonium ion to approach the anion near the spot where the latter has its highest concentration of negative charge. Since excess negative charge is greatest on the most electronegative atom, the new bond should form at this atom. This may also be the case in our reaction.

TABLE I. Analytical Data for the Ureas (**3**)



Compd. No.	R	R′	X	Yield (%)	Recrystn. solvent	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
3a	CH_3	Bzl	H	44.7	AcOEt	172—173	$C_{20}H_{25}N_3O_2$	70.77 (70.99)	7.42 (7.60)	12.38 (12.30)
3b	CH_3	CH_3	Cl	84.5	AcOEt	161—163	$C_{14}H_{20}ClN_3O_2 \cdot 5H_2O$	54.81 (54.74)	6.90 (6.73)	13.70 (13.53)
3c	C_2H_5	CH_3	Cl	83.5	AcOEt	177—179	$C_{15}H_{22}ClN_3O_2$	57.78 (57.86)	7.11 (7.29)	13.48 (13.24)
3d	C_6H_5	CH_3	Cl	90.3	AcOEt–MeOH	179—181	$C_{19}H_{22}ClN_3O_2$	63.42 (63.51)	6.16 (6.14)	11.68 (11.64)
3e	CH_3	Bzl	Cl	66.1	AcOEt–hexane	117—119	$C_{20}H_{24}ClN_3O_2 \cdot 0.5H_2O$	62.74 (62.91)	6.58 (6.83)	10.97 (11.05)
3f	4-Cl-C_6H_4	CH_3	Cl	91.3	Crude crystals					



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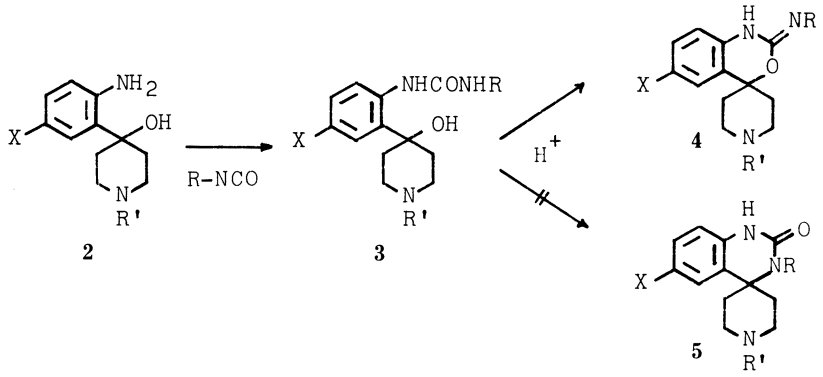
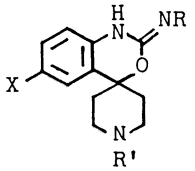


Chart 1

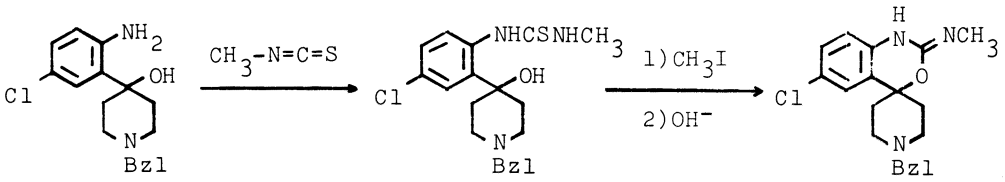
The product **4f** was found to be unstable under the conditions of recrystallization. Therefore, the thermolysis of these compounds **4b—d**, and **4f** (as HCl salt) in aqueous EtOH ($EtOH : H_2O = 10 : 1$, v/v) under reflux was investigated further. Compounds **4d** and **4f** afforded the same product **7**, but **4b** and **4c** were stable on prolonged heating. This suggested that the instability of the amino group at the 2-position of **4** is due to the phenyl group on the nitrogen atom. The product **7** was identified as 6-chloro-1′-methyl-spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one, which has been reported previously[1] (Chart 3). Next, for the modification of the 1′-position of the piperidine ring, we tried to prepare the 1′-unsubstituted

TABLE II. Analytical Data for the Benzoxazines (**4**)



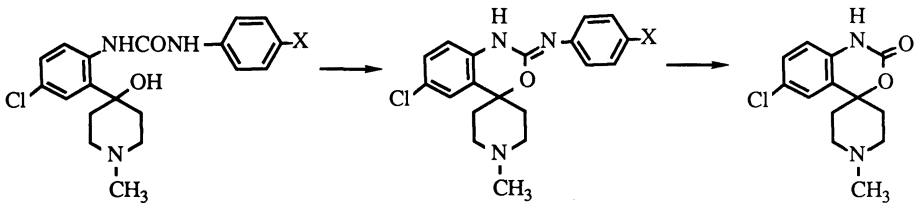
Compd. No.	R	R′	X	Form	Yield (%)	Recrystn. solvent	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
4a	CH_3	Bzl	H	Base	63.3	AcOEt–hexane	172—173	$C_{20}H_{23}N_3O$	74.74 (74.60)	7.21 (7.32)	13.07 (13.04)
4b	CH_3	CH_3	Cl	2 HCl	72.6	MeOH	248—252	$C_{14}H_{18}ClN_3O \cdot 2HCl$	47.68 (47.63)	5.72 (5.74)	11.91 (11.69)
4c	C_2H_5	CH_3	Cl	2 HCl	47.8	AcOEt–MeOH	176—178	$C_{15}H_{20}ClN_3O \cdot 2HCl \cdot 0.5H_2O$	47.95 (48.13)	6.17 (6.03)	11.18 (11.06)
4d	C_6H_5	CH_3	Cl	Base	86.3	MeOH	172—175	$C_{19}H_{20}ClN_3O$	66.76 (66.54)	5.90 (5.89)	12.29 (12.30)
4e	CH_3	Bzl	Cl	Base	45.9[a] 45.0[b]	AcOEt–hexane	146—147	$C_{20}H_{22}ClN_3O$	67.50 (67.74)	6.23 (6.29)	11.81 (11.70)
4f	4-Cl-C_6H_4	CH_3	Cl	Base	80.9	Crude crystals					
4g	CH_3	H	H	Base	55.6[c] 63.2[d]	EtOH	184—185	$C_{13}H_{17}N_3O$	67.51 (67.74)	7.41 (7.56)	18.17 (17.94)

a) Method A. *b*) Method B. *c*) Method C. *d*) Method D (see experimental section).



2e **6** **4e**

Chart 2



3d : X=H
3f : X=Cl

4d : X=H
4f : X=Cl

7

Chart 3

compound **4g**. Thus, the elimination of the benzyl group from **4a** was attempted. Debenzylation of **4a** by catalytic hydrogenation over 10% Pd–C at 40 °C for 4.5 h in the presence of 1 eq of HCl in 60% aqueous MeOH gave **8**, which was, without purification, converted to **9** by treatment with 3,4-dimethoxy-α-bromoacetophenone **10a** and triethylamine (TEA), followed by treatment with $NaBH_4$ as shown in Chart 4. In the place of 1 eq of HCl in

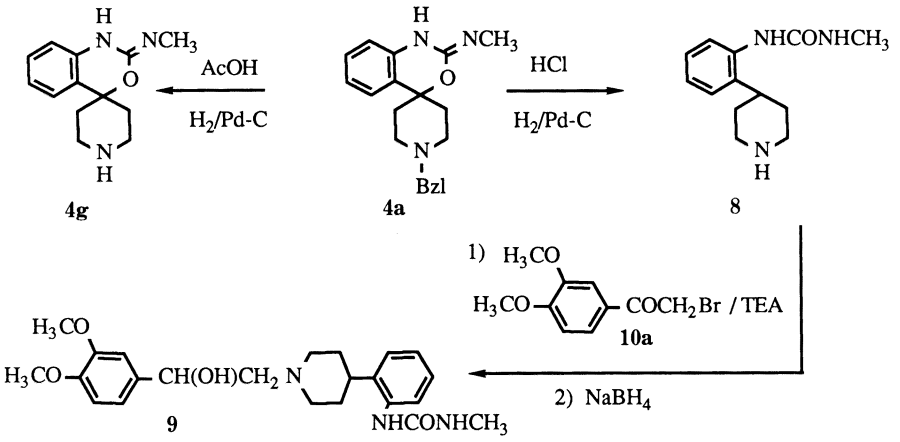


Chart 4

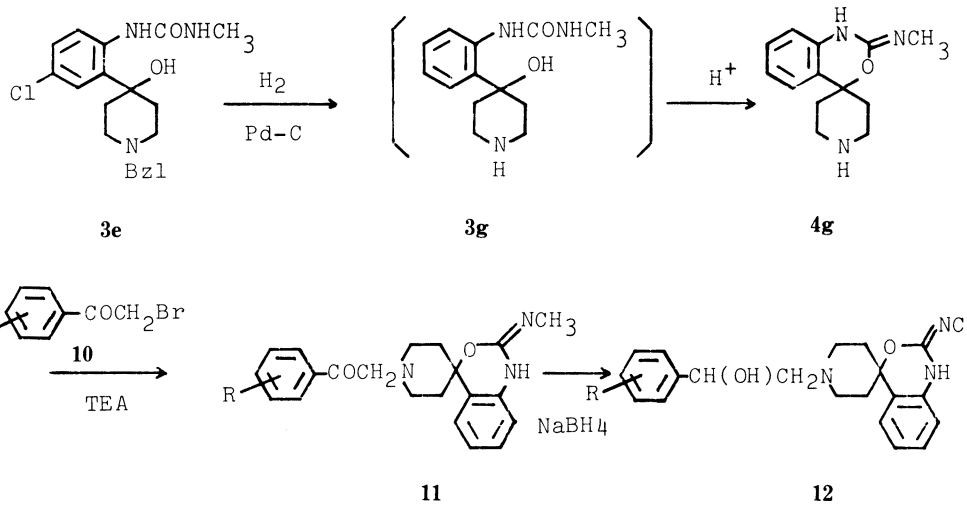
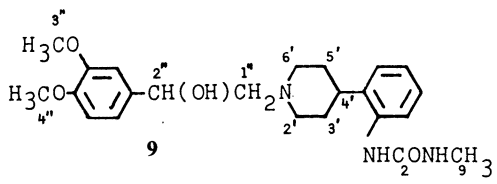


Chart 5

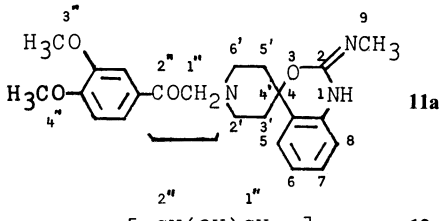
the above reduction, the use of 1 eq of AcOH resulted in the formation of **4g** in 55.6% yield, in addition to the formation of **8**. For the preparation of **4g**, the following procedure gave a better result. Thus, **4g** could be obtained in 63.2% yield by catalytic hydrogenation of **3e** over 10% Pd–C at 40 °C in the presence of 1 eq of HCl in 60% aqueous MeOH for 10.5 h, followed by treatment with 12 N HCl. The reaction of **4g** with an appropriate bromoketone **10** by using TEA in ethanol (EtOH), followed by reduction with $NaBH_4$, gave the aminoalcohol **12** as shown in Chart 5. The structures of **9**, **11a**, and **12a** were confirmed by direct comparison of the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra (Table III). Thus, in the ^{13}C-NMR spectrum of **9** in $CDCl_3$, the signal of the quaternary carbon, which was observed as a singlet at 77.98 ppm in **12a**, had disappeared, while that of a tertiary carbon appeared as a doublet at 36.31 ppm. Accordingly, the structure of this compound (**9**) was confirmed. Physical properties of **12a** and **12b** are summarized in Table IV.

The compounds (**12a, b**) thus obtained were evaluated for antihypertensive activity in the spontaneously hypertensive rat. But, contrary to our expectation, these compounds did not exhibit remarkable antihypertensive activity.

TABLE III. ^{13}C-NMR Spectral Data for **9**, **11a**, and **12a**



9



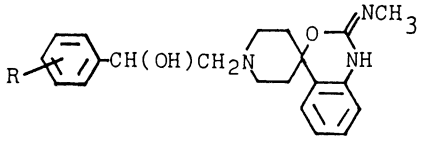
11a

12a

Compd. No.	Chemical shift (ppm) Position C-9	C-2	C-4 (4′)	C-2′,6′	C-3′,5′	C-1″	C-2″	C-3″,4″	Solvent
9	26.85	158.10	36.31	52.49	32.56 32.98	66.62	68.82	55.85	$CDCl_3$
11a	27.92	154.04[a] or 155.28	79.47	48.95	34.60	63.63	195.31	56.14 56.23	$CDCl_3+CD_3OD$
12a	28:24	154.22	77.98	47.21 50.50	34.91 35.21	66.52	68.90	56.02 55.95	$CDCl_3$

a) We could not discriminate between these signals due to the C-2 carbon and one of the aromatic carbons.

TABLE IV. Analytical Data for **12**



Compd. No.	R	Recrystn. solvent	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
12a	3,4-$(CH_3O)_2$	DMF–EtOH	194—195	$C_{23}H_{29}N_3O_4$	67.13 (67.33	7.10 7.09	10.21 10.12)
12b	4-Cl	DMF–MeOH	210—212	$C_{21}H_{24}ClN_3O_2$	65.36 (65.44	6.27 6.37	10.89 10.96)

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. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured on a Varian T-60 spectrometer, a JEOL JNM-PS-100 spectrometer, and a Varian EM 390 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-(*N*-methylcarbamoyl)aminophenyl]piperidine (3a)——Methyl isocyanate (5.50 ml, 93.2 mmol) was added to a solution of 1-benzyl-4-hydroxy-4-(2-aminophenyl)piperidine (**2a**) (17.3 g, 61.3 mmol) in ethyl acetate (AcOEt) (123 ml), and the mixture was stirred at room temperature overnight. Precipitated crystals were collected by filtration and washed with AcOEt to give **3a** (9.30 g, 44.7%). Recrystallization from AcOEt gave an analytical sample, mp 172—173 °C. IR (KBr): 1675 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51—2.92 [12H, piperidine H, OH, and $NHCH_3$ (d, J=4.9 Hz at δ2.80)], 3.56 (2H, s, $C_6H_5CH_2$–), 4.60 (1H, m, –$NHCH_3$), 6.85—7.42 (8H, m, aromatic H), 7.88 (1H, dd, J=8.3 Hz, J'=1.5 Hz, aromatic H), 8.62 (1H, s, ArNH).

1-Substituted 4-Hydroxy-4-[2-(*N*-substituted carbamoyl)amino-6-chlorophenyl]piperidine (3b—f)——These com-

pounds were prepared in the same manner as described for the preparation of **3a** from the corresponding piperidinol (**2**).

1′-Benzyl-2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (4a)——A solution of 1-benzyl-4-hydroxy-4-[2-(*N*-methylcarbamoyl)aminophenyl]piperidine (**3a**) (1.00 g, 2.95 mmol) in 12 N HCl (20 ml) was stirred at 64 °C for 5 h. Then, the reaction mixture was poured into ice water, made basic with aqueous NaOH, and extracted with $CHCl_3$. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give an oily residue. The residue was crystallized from AcOEt–hexane to yield **4a** (0.60 g, 63.3%). Recrystallization from AcOEt–hexane gave an analytical sample, mp 172—173 °C. IR (KBr): 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.96—2.93 [11H, m, piperidine H and N–C$\underline{H}_3$ (s at 2.93 ppm)], 3.57 (2H, s, $C_6H_5C\underline{H}_2$–), 4.74—5.05 (1H, N$\underline{H}$), 6.85—7.40 (9H, m, aromatic H).

1′-Substituted 2-(*N*-Substituted amino)-6-chloro-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (4b—d)——These compounds were prepared in the same manner as described for the preparation of **4a** from the corresponding urea **3**.

1′-Benzyl-6-chloro-2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (4e)——Method A: A solution of 1-benzyl-4-hydroxy-4-[2-(*N*-methylcarbamoyl)amino-5-chlorophenyl]piperidine (**3e**) (3.00 g, 8.02 mmol) in conc. H_2SO_4 (15 ml) was stirred at 65 °C for 2.5 h. Then, the reaction mixture was poured into ice water and made basic with aqueous NaOH. Precipitated white crystals were collected by filtration, and recrystallization from AcOEt–hexane gave **4e** (1.31 g, 45.9%), mp 146—147 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.8—2.94 [11H, m, piperidine H and N–C$\underline{H}_3$ (s at 2.94 ppm)], 3.57 (2H, s, $C_6H_5C\underline{H}_2$), 4.15—5.32 (1H, N$\underline{H}$), 6.86—7.38 (8H, m, aromatic H).

Method B: Methyl thioisocyanate (146 mg, 2.00 mmol) was added to a solution of 1-benzyl-4-hydroxy-4-(2-amino-5-chlorophenyl)piperidine (**2e**) (317 mg, 1.00 mmol) in AcOEt (10 ml) and the mixture was stirred at room temperature for 2 d. Then, the solution was washed with H_2O, dried over $MgSO_4$, and concentrated to give 1-benzyl-4-hydroxy-4-[2-(*N*-methyl-thiocarbamoylamino-5-chlorophenyl]piperidine (**6**) (423 mg) as a crude oil. ^{1}H-NMR ($CDCl_3$) δ: 3.06 (3H, d, J=4.5 Hz, NHC$\underline{H}_3$), H, 3.53 (2H, s, $C_6H_5C\underline{H}_2$), 6.20 (1H, m, N$\underline{H}$CH$_3$), 7.1—7.5 (8H, m, aromatic H), 9.25 (1H, s, N$\underline{H}$CSNHCH$_3$). Then, a mixture of **6** (423 mg) and methyl iodide (1 ml) in EtOH (10 ml) was stirred at room temperarure for 4 h and concentrated. The residue was mixed with EtOH (5 ml) and treated with 2 N aqueous NaOH (1 ml). The reaction mixture was stirred at room temperature for 15 min, poured into water (20 ml), and extracted with AcOEt. The extract was concentrated and the residue was crystallized from AcOEt–hexane. The crystals were collected by filtration to give **4e** (160 mg, 45.0%).

6-Chloro-2-(4-chlorophenyl)amino-1′-methyl-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (4f) and 6-Chloro-1′-methyl-spiro[4*H*-3,1-benzoxazine-4,4′-piperidin]-2(1*H*)-one (7)——A solution of 1-methyl-4-hydroxy-4-[2-[*N*-(4-chlorophenyl)carbamoyl]amino-5-chlorophenyl]piperidine (**3f**) (1.18 g, 2.99 mmol) in 12 N HCl (30 ml) was stirred at 80 °C for 3 h. Then, the reaction mixture was poured into ice-water, and made basic with aqueous NaOH. Precipitated white crystals were collected by filtration to give **4f** (0.91 g, 80.7%). ^{1}H-NMR (CD_3OD) δ: 2.0—2.2 (4H, m, piperidine H), 2.45 (3H, s, N–C$\underline{H}_3$), 2.6—3.0 (4H, m, piperidine H), 6.9—7.7 (7H, m, aromatic H). This compound (**4f**) (800 mg) was dissolved in MeOH (25 ml), and the solution was mixed with 3.5 N HCl/AcOEt (12 ml) and concentrated *in vacuo*. The crystalline residue thus obtained was triturated with AcOEt and collected by filtration to give the HCl salt of **4f** (880 mg), which was dissolved in aqueous EtOH (EtOH : H_2O = 10 : 1, v/v) (50 ml). The solution was refluxed under heating for 1.5 h and concentrated *in vacuo*. The residue was crystallized from MeOH–AcOEt to give **7** (460 mg) as the 1 HCl salt, mp >300 °C.

Stability of 4b—d in Aqueous EtOH——A solution of one of **4b—d** (0.05 mmol as the 2 HCl salt) in aqueous EtOH (EtOH : H_2O = 10 : 1, v/v) (5 ml) was stirred under reflux and the stability of the compound was checked with thin-layer chromatography (TLC).

2-Methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (4g)——Method C: A mixture of 1′-benzyl-2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (**4a**) (1.00 g, 3.11 mmol), 10% Pd–C (270 mg), acetic acid (177 μl, 3.1 mmol), H_2O (10 ml), and MeOH (20 ml) was stirred at 40 °C for 2.75 h under a hydrogen atmosphere. After removal of the catalyst by filtration, the resulting solution was concentrated. Then, the residue was mixed with H_2O, made basic with aqueous NaOH, and extracted with $CHCl_3$. The extract was concentrated to give **4g** as a crude crystalline residue (400 mg, 55.6%), which was recrystallized from EtOH to give pure crystals (120 mg, 16.7%), mp 184—185 °C. IR (KBr): 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.65—2.23 (4H, m, piperidine H), 2.59—3.53 [9H, m, H$\underline{N}$<, –N$\underline{H}C_6H_4$, piperidine H, and N–C$\underline{H}_3$ (s at 2.96 ppm)], 6.85—7.28 (4H, m, aromatic H).

Method D: A mixture of 1-benzyl-4-hydroxy-4-[2-((*N*-methylcarbamoyl)amino-5-chlorophenyl]piperidine (**3e**) (8.27 g, 21.6 mmol), 10% Pd–C (2 g), 1 N HCl (22 ml), H_2O (66 ml), and MeOH (132 ml) was stirred at 40 °C for 10.5 h under a hydrogen atmosphere, and concentrated after removal of the catalyst by filtration to give 4-hydroxy-4-[2-(*N*-methylcarbamoyl)aminophenyl]piperidine (**3g**) as an oily residue, which was mixed with 12 N HCl (50 ml). Then, this mixture was stirred at 76 °C for 3 h, made basic with aqueous NaOH after cooling to room temperature, and extracted with $CHCl_3$. The extract was washed with H_2O and concentrated to give an oily residue, which was concentrated again after addition of MeOH to give **4g** as a crystalline residue. The crude crystals were triturated by AcOEt to give **4g** (3.16 g, 63.2%).

1-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-4-[2-(*N*-methylcarbamoyl)aminophenyl]piperidine (9)——A mixture of 1′-benzyl-2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (**4a**) (643 mg, 2.00 mmol), 10% Pd–C (160 mg), H_2O (6 ml), 1 N HCl (2 ml), and MeOH (12 ml) was stirred at 40 °C for 4.5 h under a hydrogen atmosphere,

and concentrated after removal of the catalyst by filtration. Then, the residue was mixed with H_2O, made basic with aqueous NaOH, and extracted with $CHCl_3$. The extract was concentrated to give 4-[2-(*N*-methylcarbamoyl)aminophenyl]piperidine (**8**) (290 mg, 62.2%) as an oily product, mass spectrum (MS) *m/z*: 233 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.80 (4H, m, piperidine H), 2.7—2.85 [5H, m, piperidine H and NCH_3 (d at 2.80 ppm, J=4.5 Hz)], 2.89—3.01 (1H, m, C_6H_4CH), 3.1—3.2 (2H, m, piperidine H), 4.55 (1H, m, $NHCH_3$), 6.15 (1H, s, NHC_6H_4), 7.2—7.4 (4H, m, aromatic H). This product (290 mg, 1.24 mmol) was mixed with 3,4-dimethoxy-α-bromoacetophenone (324 mg, 1.25 mmol) and TEA (0.175 ml, 1.25 mmol) in EtOH (10 ml). After stirring of the mixture at room temperature for 2 h, $NaBH_4$ (400 mg, 10.6 mmol) was added. The whole was kept at room temperature for 3 h with stirring, and then concentrated. The residue was mixed with H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O and concentrated to give a white crystalline residue, which was recrystallized from EtOH to give **9** (162 mg, 31.6% from **8**), mp 175—177 °C. *Anal.* Calcd for $C_{23}H_{31}N_3O_4$: C, 66.80; H, 7.56; N, 10.16. Found: C, 66.95; H, 7.67; N, 9.88. IR (KBr): 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.48 [2H, d, J=7 Hz, $-CH(OH)CH_2-$], 2.76 (3H, d, J=4.5 Hz, $NHCH_3$), 3.86 and 3.89 (6H, each s, $2\times CH_3O$), 4.55—4.80 [2H, m, $-CH(OH)-$ and $NHCH_3$], 6.43 (1H, s, NH).

1′-[2-(3,4-Dimethoxyphenyl)-2-hydroxyethyl]-2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (12a)——A mixture of 3,4-dimethoxy-α-bromoacetophenone (**10a**) (518 mg, 2.00 mmol), 2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (**4g**) (463 mg, 2.00 mmol), and TEA (0.28 ml, 2 mmol) in EtOH (5 ml) was stirred at room temperature for 5 h. Then, the reaction mixture was concentrated to give a crystalline residue, which was mixed with H_2O and collected by filtration. The crystals of 1′-(3,4-dimethoxybenzoylmethyl)-2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (**11a**) thus obtained were dissolved in EtOH (20 ml), and $NaBH_4$ (860 mg, 22.7 mmol) was added. The reaction mixture was stirred at room temperature overnight and concentrated *in vacuo* to give a crystalline residue, which was mixed with H_2O. Precipitated white crystals were collected by filtration to give **12a** (716 mg, 87.0%). Recrystallization from dimethylformamide (DMF)–EtOH gave an analytical sample, mp 194—195 °C. IR (KBr): 1629 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.96 (3H, s, $N-CH_3$), 3.88 and 3.91 (6H, each s, $2\times CH_3O$), 4.66—4.86 [1H, m, $-CH(OH)-$].

1-[2-(4-Chlorophenyl)-2-hydroxyethyl]-2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (12b)——A mixture of 4-chloro-α-bromoacetophenone (**10b**) (467 mg, 2.00 mmol), 2-methylamino-spiro[4*H*-3,1-benzoxazine-4,4′-piperidine] (**4g**) (463 mg, 2.00 mmol), and TEA (0.28 ml, 2.0 mmol) in MeOH (10 ml) was stirred at room temperature for 4 h. Then, $NaBH_4$ (500 mg, 13.2 mmol) was added under ice cooling and the mixture was stirred for 30 min. This reaction mixture was, after further addition of $NaBH_4$ (500 mg, 13.2 mmol), stirred at room temperature overnight and concentrated *in vacuo*. The crystalline residue was mixed with H_2O and collected by filtration to give **12b** (722 mg, 93.5%). Recrystallization from DMF–MeOH gave an analytical sample, mp 210—212 °C. IR (KBr): 1663 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.95 (3H, s, $N-CH_3$), 4.60—4.83 [1H, m, $-CH(OH)-$].

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