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Syntheses of (±)-2-[(Inden-7-yloxy)methyl]morpholine Hydrochloride (YM-08054, Indeloxazine Hydrochloride) and Its Derivatives with Potential Cerebral-Activating and Antidepressive Properties

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The synthesis of (±)-2-[(inden-7-yloxy)methyl]morpholine hydrochloride (**7**·HCl, YM-08054, indeloxazine hydrochloride) and its optical resolution into *levo*- and *dextro*-isomers were investigated. A practical synthetic method for **7**·HCl was established by employing preferential crystallization from an equilibrium mixture of **7**·HCl and its tautomer, (±)-2-[(inden-4-yloxy)-methyl]morpholine hydrochloride (**6**·HCl), in the presence of a catalytic amount of base in MeOH. It was found that **7**·HCl and its *levo*-rotatory isomer ((−)-**7**·HCl) showed not only strong antidepressive activities, but also potent cerebral-activating properties. The syntheses and pharmacological activities of related compounds are also discussed briefly.

Keywords——indene; antidepressant; cerebral activator; (±)-2-[(inden-7-yloxy)methyl]morpholine; (±)-2-[(inden-4-yloxy)methyl]morpholine; YM-08054; indeloxazine hydrochloride; isomerization; optical resolution

It is known that β-adrenergic blocking agents such as 1-(1-naphthyloxy)-3-isopropylamino-2-propanol hydrochloride (propranolol, Fig. 1) have various activities on the central nervous system in addition to the main effects.[1] It is also known that a number of 2-aryloxymethylmorpholine derivatives (II), prepared by structural modification of aryloxypropanolamine derivatives (I), show increased antidepressive activitity as compared to I. For example, 2-(2-ethoxyphenoxymethyl)morpholine hydrochloride (viloxazine, Fig. 1) has been shown to have a novel profile of neuropharmacological activity, possessing features in common with tricyclic antidepressants but without the β-adrenergic blocking property.[2] Recently, Yamamoto *et al.*[3] of our laboratories found that (±)-2-[(inden-7-yloxy)-methyl]morpholine hydrochloride (**7**·HCl, YM-08054, indeloxazine hydrochloride) not only showed strong antidepressive properties, but also had an enhancing effect on learning behavior, a protective effect on nitrogen-gas-induced amnesia and some other cerebral-activating properties in rats or mice. These kinds of pharmacological activities, particularly the cerebral-activating properties, are important in connection with the treatment of senile and

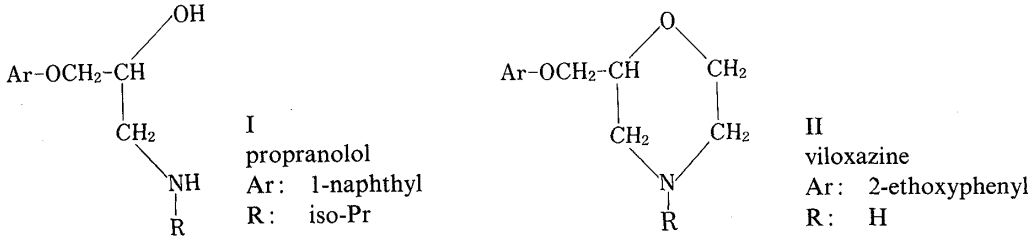

Fig. 1

multi-infarct dementia. However, no report has been published on the cerebral-activating activities of **7**·HCl type compounds.

This report describes the synthesis of **7**·HCl and related compounds and the optical resolution of **7**·HCl, and also presents preliminary findings on the pharmacological activities.

(±)-2-[(Inden-7(or 4)-yloxy)methyl]morpholines (**5a—j**), were first prepared by modifying the method of Turner *et al.*[2a] (Chart 1). Treatment of propanolamine derivatives (**2a—j**)

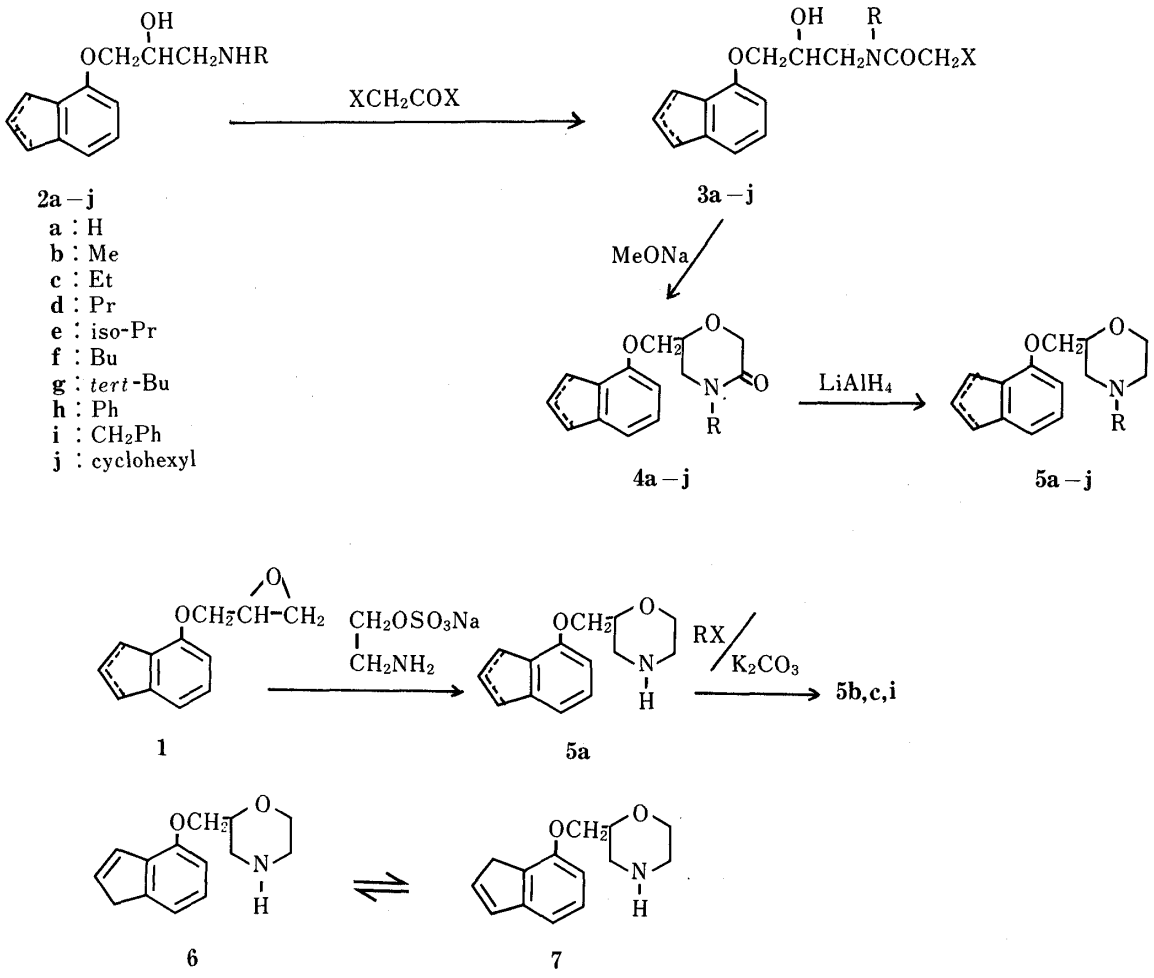

Chart 1

with halogenoacetyl halide in the presence of an appropriate base afforded N-halogenoacetyl compounds (**3a—j**), which were cyclized with MeONa to produce the lactams (**4a—j**). Reduction of **4a—j** with $LiAlH_4$ in tetrahydrofuran (THF) gave the corresponding morpholine derivatives **5a—j**. However, this route was not very convenient and overall yields were generally low. An improved method for the synthesis of compounds **5a—j** involves reaction with epoxide (**1**)[2d] (Chart 1). Treatment of **1** with excess 2-aminoethyl hydrogen sulfate and 70% aqueous NaOH gave **5a** in a good yield. Compound **5a** was easily alkylated with appropriate alkyl halides to give N-substituted derivatives **5b, c, i** in good yields. The physical properties of **4a—j** are listed in Table I and those of **5a—j** are listed in Tables II and III.

All indenyl compounds thus prepared are tautomeric equilibrium mixtures of 4-indenyl and 7-indenyl isomers. For example, **5a** was an equilibrium mixture of the 4-indenyl isomer (**6**) and 7-indenyl isomer (**7**) in a ratio of 1 : 2. The ratio was determined by gas chromatography after converting the compounds to the corresponding N-trifluoroacetyl derivatives. The separation of **5a** into **6** and **7** was achieved by fractional crystallization of its hydrochloride. In

TABLE I. (±)-6-[(Inden-7 (or 4)-yloxy)methyl]morpholin-3-one Derivatives (**4a—j**)

Compd.	Yield (%)	mp (°C) (Solvent)	Formula	Analysis (%) Calcd (Found)			NMR δ ($CDCl_3$)
				C	H	N	
4a	40.5	Oil[a]	$C_{14}H_{15}NO_3$	68.56	6.16	5.71	3.9—4.3 (1H, br s, NH)
				(68.31	6.00	5.52)	
4b	79.0	Oil[a]	$C_{15}H_{17}NO_3$	69.48	6.61	5.40	2.4 (3H, s, CH_3)
				(69.19	6.36	5.35)	
4c	86.0	Oil[a]	$C_{16}H_{19}NO_3$	70.31	7.01	5.12	1.2 (3H, t, J=7 Hz, CH_3)
				(70.10	6.84	5.08)	2.5 (2H, q, J=7 Hz, CH_2CH_3)
4d	88.2	Oil[a]	$C_{17}H_{21}NO_3$	71.06	7.37	4.81	1.1 (3H, t, J=7 Hz, CH_3)
				(70.94	7.10	4.57)	1.5 (2H, m, CH_2CH_3)
4e	86.0	Oil[a]	$C_{17}H_{21}NO_3$	71.06	7.37	4.81	1.2 (6H, d, J=7 Hz, $CH_3 \times 2$)
				(71.31	7.51	4.90)	
4f	78.5	Oil[a]	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	1.0 (9H, t, J=7 Hz, $CH_3 \times 3$)
				(71.46	7.43	4.59)	1.0—1.8 (4H, m, $CH_2CH_2CH_3$)
							2.4 (2H, t, $CH_2CH_2CH_2CH_3$)
4g	46.1	Oil[a]	$C_{18}H_{23}NO_3$	71.73	7.69	4.65	1.5 (9H, s, CH_3)
				(71.51	7.46	4.55)	
4h	84.6	Oil[a]	$C_{20}H_{19}NO_3$	74.75	5.96	4.36	7.4 (5H, m, Ph-H)
				(74.99	6.07	4.13)	
4i	91.5	Oil[a]	$C_{21}H_{21}NO_3$	75.20	6.31	4.18	3.6 (2H, s, CH_2Ph)
				(74.91	6.45	4.40)	7.4 (5H, m, Ph-H)
4j	82.6	106—107	$C_{20}H_{25}NO_3$	73.37	7.70	4.28	0.8—2.0 (10H, m)
		(EtOH)		(73.08	7.51	4.00)	4.6 (1H, m, N–CH–)

a) Oily compounds were purified by column chromatography on silica gel.

TABLE II. (±)-2-[(Inden-7 (or 4)-yloxy)methyl]morpholine Derivatives (**5a—j**)

Compd.	Yield[a] (%)	Salt	mp (°C) (Solvent)	Formula	Analysis (%) Calcd (Found)			
					C	H	N	Cl
5a	42.0	HCl	143—155	$C_{14}H_{17}NO_2 \cdot HCl$	62.80	6.78	5.23	13.24
			(Acetone)		(62.53	6.70	4.99	12.91)
5b	38.0	Oxalate	146—147	$C_{15}H_{19}NO_2 \cdot C_2H_2O_4$	60.89	6.31	4.18	
			(EtOH–Et_2O)		(60.90	6.29	4.21)	
5c	91.3	Citrate	84—86	$C_{16}H_{21}NO_2 \cdot C_6H_8O_7$	58.53	6.47	3.10	
			(EtOH–Et_2O)		(58.70	6.55	3.07)	
5d	89.5	Oxalate	201—202	$C_{17}H_{23}NO_2 \cdot C_2H_2O_4$	62.80	6.93	3.85	
			(EtOH–Et_2O)		(62.99	6.90	3.64)	
5e	87.9	Citrate	107—109	$C_{17}H_{23}NO_2 \cdot C_6H_8O_7$	59.35	6.71	3.01	
			(EtOH–Et_2O)		(59.78	6.66	3.01)	
5f	84.0	Oxalate	200	$C_{18}H_{25}NO_2 \cdot C_2H_2O_4$	63.65	7.21	3.71	
			(EtOH–Et_2O)		(63.90	6.93	3.68)	
5g	60.4	Citrate	114—116	$C_{18}H_{25}NO_2 \cdot C_6H_8O_7$	60.11	6.94	2.92	
			(EtOH–Et_2O)		(60.30	6.91	2.94)	
5h	76.4	HCl	160—163	$C_{20}H_{21}NO_2 \cdot HCl$	69.86	6.45	4.07	10.31
			(EtOH–Et_2O)		(70.01	6.36	4.03	10.31)
5i	89.0	Oxalate	206—208	$C_{21}H_{23}NO_2 \cdot C_2H_2O_4$	67.14	6.12	3.40	
			(EtOH–Et_2O)		(66.95	6.07	3.40)	
5j	73.06	HCl	216—218	$C_{20}H_{27}NO_2 \cdot HCl$	68.65	8.07	4.00	10.13
			(EtOH–Et_2O)		(68.58	8.00	4.23	10.49)

a) Yield of free base.

TABLE III. NMR Spectra Data for (±)-2-[(Inden-7 (or 4)-yloxy)methyl]morpholine Derivatives (**5a—j**)

Compd.	NMR δ ($CDCl_3$)
5a	1.9—3.1 (4H, m), 2.4 (1H, s, NH), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)
5b	1.9—3.1 (4H, m), 2.3 (3H, s, CH_3), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)
5c	1.1 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.9—3.1 (4H, m), 2.4 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)
5d	0.9 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.5 (2H, m, $C\underline{H}_2CH_3$), 1.9—3.1 (4H, m), 2.2 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_3$), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)
5e	1.5 (6H, d, J=7 Hz, $CH_3\times2$), 1.9—3.1 (5H, m), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)
5f	0.9 (3H, t, J=6 Hz, CH_3), 1.1—1.7 (4H, m, $CH_2C\underline{H}_2CH_3$), 1.9—3.1 (4H, m), 2.3 (2H, t, J=6 Hz, $NC\underline{H}_2CH_2CH_2$–), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)
5g	1.1 (9H, s, $CH_3\times3$), 1.9—3.1 (4H, m), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)
5h	1.9—3.1 (4H, m), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 6.3—7.4 (5H, m, Ph-H), 7.0—7.3 (3H, m)
5i	1.9—3.1 (4H, m), 3.3—3.4 (2H, m), 3.6 (2H, s, CH_2Ph), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m), 7.4 (5H, s, Ph-H)
5j	1.0—2.0 (10H, m, cyclohexyl-H), 1.9—3.1 (4H, m), 2.0—2.4 (1H, m, N–$\underset{\vert}{C}$H–), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)

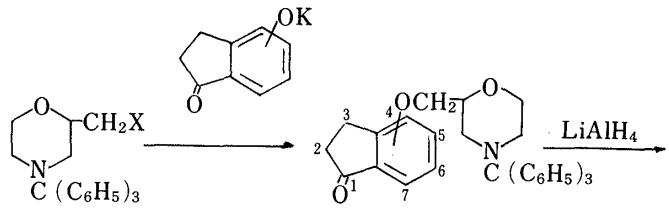

Chart 2

order to confirm the strucures of **6**·HCl and **7**·HCl thus obtained, each of the authentic samples was also synthesized by the route illustrated in Chart 2.

The starting material (**8**) (prepared from 2-hydroxymethylmorpholine[4]) was allowed to react with the potassium salt of 4-hydroxy-1-indanone[5c] in dimethylsulfoxide (DMSO) to furnish (±)-2-(1-oxoindan-4-yloxymethyl)-4-triphenylmethylmorpholine (**9**) in 73.5% yield. Reduction of **9** with $LiAlH_4$ in THF gave the hydroxyindanyl derivative (**10**) in a good

yield. Dehydration and deprotection of **10** with aqueous ethanolic HCl under reflux gave the corresponding 7-indenyl derivative **7**·HCl, which was recrystallized from MeOH to yield pale yellow needles melting at 169—170 °C in 73.4% yield. Similarly, the 4-indenyl derivative **6**·HCl was synthesized from **8** and 7-hydroxy-1-indanone,[5c] and recrystallized from iso-PrOH to yield pale yellow prisms melting at 175—176 °C.

In general, it is known that prototropic tautomerization in indene occurs under basic conditions to afford an equilibrium mixture.[5] A similar double bond isomerization between **6**·HCl and **7**·HCl in a methanol solution was observed in the presence of base and the equilibrium ratio of **6** to **7** was 1 : 2, as described above. However, interestingly enough, it was found that **6**·HCl was predominantly isomerized to **7**·HCl when a suspension of the crystalline equilibrium mixture of **6**·HCl and **7**·HCl in a small volume of MeOH was treated with a catalytic amount of base; the ratio of the crystals were changed to 0.3 : 9.7. It is likely that less soluble **7**·HCl crystallized out preferentially from a solution of the suspension system. Accordingly, the isolation of **7**·HCl could be easily performed in good yield simply by direct filtration of crystals from the reaction mixture. This method affords a simple and practical route for the manufacturing synthesis of **7**·HCl.

In order to investigate differences in biological activities between the two optical antipodes, **7**·HCl was resolved into its optically active isomers, (−)-**7**·HCl and (+)-**7**·HCl by using D-(+)- and L-(−)-dibenzoyl tartaric acid, respectively.

The pharmacological activities of **7**·HCl, its optical isomers and related derivatives are shown in Table IV. These compounds inhibited the uptake of norepinephrine (NE) and serotonin (5-HT) by rat brain synaptosomes, antagonized the reserpine-induced hypothermia in mice and potentiated the 5-hydroxytriptophan (5-HTP)-induced behavioral change in rats. The secondary amines (**6**·HCl and **7**·HCl) were found to be markedly more potent than the tertiary amine derivatives (**5b—j**) and as active as the known tricyclic antidepressants, imipramine and amitriptyline. In particular, **7**·HCl was the most potent in respect of both 5-HT uptake inhibition *in vitro* and 5-HTP potentiation *in vivo*. It is also very interesting that

TABLE IV. Biochemical and Pharmaceutical Effects of (±)-2-[(Inden-7 (or 4)-yloxy)methyl]morpholine Derivatives

Compd.	IC_{50} (μM)[a]		MED (mg/kg)	
	NE	5-HT	Reserpine[a]	5-HTP[a]
5a·HCl	1.8	1.3	3	25
6·HCl	2.2	1.3	3	25
7·HCl	3.2	0.71	3	20
(+)-**7**·HCl	11.0	0.83	—	20
(−)-**7**·HCl	1.3	0.65	—	20
5b·oxalate	42	5.1	30	50
5c·citrate	47	6.8	30	50
5d·oxalate	44	6.8	30	75
5e·citrate	37	9.0	10	50
5f·oxalate	25	8.8	30	75
5g·citrate	—	—	100	—
5h·HCl	—	—	100	—
5i·oxalate	—	—	100	—
5j·HCl	—	—	—	—
Imipramine	5.8	0.42	10	50
Amitriptyline	2.9	0.70	3	25
Viloxazine	19	66	3	100

a) See Experimental.

TABLE V. Cerebral-Activating Properties of 7·HCl (Indeloxazine Hydrochloride)

Pharmacological activities	Species	Injection route	Dose (MED, mg/kg)
			7·HCl
Enhancing effect on learning behavior	Rat	*i.p.*	3
Desynchronization of spontaneous EEG	Rat	*i.p.*	3
Protective effect against nitrogen-gas-induced lethality	Mice	*i.v.*	3
Protective effect against nitrogen-gas-induced amnesia	Rat	*i.p.*	1
Facilitatory effect on recovery from experimental concussion	Mice	*i.v.*	3

EEG, electroencephalogram in the cerebral cortex.

(−)-7·HCl showed an NE uptake inhibitory effect which was 10 times as potent as that of (+)-7·HCl, though in the 5-HT uptake inhibition, such enantioselectivity was not observed (Table IV). These serotonergic and noradrenergic activities have been reported to be responsible for mood elevation and increased activities in humans,[6] respectively. Thus, 7·HCl and (−)-7·HCl may have clinically useful activities as antidepressants. It is important to note that viloxazine, a compound structurally analogous to 6·HCl or 7·HCl, exhibited the least effect on 5-HT uptake and had no effect on 5-HTP responses (Table IV). The difference in the serotonergic actions of the two types of compounds may be related to the difference of chemical structures between 6·HCl or 7·HCl (indenyl) and viloxazine (2-ethoxyphenyl).

Furthermore, Yamamoto *et al.*[3] of our laboratories recently found that 7·HCl showed an enhancing effect on learning behavior, a protective effect on nitrogen-gas-induced amnesia and some other cerebral-activating properties in rats or mice (Table V). These cerebral-activating effects of 7·HCl might be attributed, at least in part, to inhibitory effects on the uptake of the biogenic amines in the cerebral nervous system. Thus, 7·HCl appears to be promising as a cerebral activator as well as an antidepressant, and it is currently under clinical evaluation for efficacy and safety.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a JNM-FX100 Fourier transform (FT)-NMR (^{1}H; 100 MHz) spectrometer using Me_4Si as an internal standard. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad singlet (br s), double doublet (dd) and double triplet (dt). Mass (MS) spectra were measured with a Hitachi M-80 mass spectrometer. Gas chromatography was done on a Hewlett Packard 5711A gas chromatograph (column, 3% OV-22 on Chromosorb W AW, glass, 1.8 m × 1.8 mm i.d.; temperature of column, 190 °C; temperature of flame ionization detector, 250 °C; carrier gas, 43 ml/min of He). Specific optical rotations were measured on a Perkin-Elmer (model 241) polarimeter. Column chromatography was carried out on Wako gel C-200 (Wako Pure Chemical Ind., Ltd.). Thin layer chromatography (TLC) was performed on Silica gel 60 F_{254} plates (Merck). Solutions were concentrated in rotary evaporators under reduced pressure.

(±)-6-[(Inden-7(or 4)-yloxy)methyl]-4-isopropylmorpholin-3-one (4e)——Bromoacetyl bromide (2.0 g, 0.01 mol) was added dropwise to a solution of 1-(inden-7(or 4)-yloxy)-3-isopropylamino-2-propanol (**2e**) (2.5 g, 0.01 mol) and Et_3N (1.2 g, 0.013 mol) in CH_2Cl_2 (30 ml) with stirring at 0—5 °C, and the mixture was stirred at room temperature for 6 h. The reaction mixture was washed with 5% HCl (10 ml × 2) and H_2O (10 ml × 2), dried over $MgSO_4$, and concentrated *in vacuo*. The residue (3.6 g) was dissolved in MeOH (30 ml), this solution was added to a solution of MeONa (0.7 g, 0.013 mol) in MeOH (20 ml), and the mixture was refluxed for 6 h, then concentrated *in vacuo*. The residue was extracted with $CHCl_3$ (50 ml), and the extract was washed with 10% HCl (10 ml × 2) and H_2O (10 ml × 2), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (60 g) using $CHCl_3$–EtOAc (5 : 1, v/v) as an eluent to afford **4e** (2.5 g, 86%) as an oil.

The following compounds were similarly prepared. The physical data and total yields of (±)-6-[(inden-7(or 4)-yloxy)methyl]morpholin-3-one derivatives (**4a—j**) are shown in Table I.

Citric Acid Salt of (±)-2-[(Inden-7(or 4)-yloxy)methyl]-4-isopropylmorpholine (5e·Citrate)——A solution of **4e** (2.0 g, 0.007 mol) in THF (30 ml) was added dropwise with stirring to a cooled suspension of $LiAlH_4$ (0.5 g, 0.013 mol) in THF (30 ml) at 5—10 °C. The reaction mixture was stirred at 40—50 °C for 10 h and then cooled. Excess reagent was decomposed with H_2O and the resulting precipitates were filtered off. The filtrate was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (30 g) using $CHCl_3$–EtOAc (5 : 1, v/v) as an eluent to afford **5e** (1.5 g, 78.9%) as an oil.

The oily product **5e** (1.1 g, 0.004 mol) was treated with a solution of citric acid (1.0 g, 0.005 mol) in EtOH (10 ml) to give 5e·citrate (1.7 g, 89.9%).

The physical data and yields of (±)-2-[(inden-7(or 4)-yloxy)methyl]morpholine derivatives (**5a—j**) are shown in Tables II and III.

(±)-2-[(Inden-7(or 4)-yloxy)methyl]morpholine Hydrochloride (5a·HCl)——A solution of 1-(inden-7(or 4)-yloxy)-2,3-epoxypropane (**1**) (9.4 g, 0.05 mol) in MeOH (50 ml) was added dropwise to a solution of 70% aqueous NaOH (29 ml) and 2-aminoethyl hydrogen sulfate (35 g, 0.25 mol) with stirring at 50—55 °C. The mixture was stirred for 1 h and then 70% aqueous NaOH (50 ml) was added. The reaction mixture was stirred for 16 h at 50—55 °C, then diluted with H_2O (300 ml) followed by extraction with toluene (100 ml × 2). The extract was washed with H_2O (100 ml × 2), and dried over $MgSO_4$. After removal of the solvent, the oily residue was distilled under reduced pressure to afford **5a** (6.7 g, 58%) as a viscous oil, bp 146—156 °C (0.5 mmHg).

The oily product **5a** (3.0 g, 0.013 mol) in acetone (30 ml) was treated with a solution of 5% HCl in iso-PrOH (15 ml) to give the salt (2.8 g, 82%), mp 143—155 °C (recrystallized from acetone). *Anal.* Calcd for $C_{14}H_{17}NO_2 \cdot HCl$: C, 62.80; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 62.63; H, 6.79; N, 5.05; Cl, 13.51. The NMR spectrum, melting point and *Rf* value on TLC were identical with those of **5a**·HCl obtained by the alternative route described above (listed in Tables II and III).

Isolation of (±)-2-[(Inden-4-yloxy)methyl]morpholine Hydrochloride (6·HCl) and (±)-2-[(Inden-7-yloxy)-methyl]morpholine Hydrochloride (7·HCl) from 5a·HCl——A solution of **5a** (3.0 g, 0.013 mol) in acetone (70 ml) was acidified with a solution of 10% HCl in iso-PrOH and the resulting solution (equilibrium mixture of **6**·HCl and **7**·HCl in a ratio of 1 : 2) was allowed to stand at 0—5 °C for 15 min. The precipitated crystals were collected by filtration and washed with acetone to provide **6**·HCl (1.1 g, containing 15% of **7**·HCl). Repeated recrystallization from iso-PrOH afforded isomer-free **6**·HCl (0.6 g, 17%), mp 175—176 °C. *Anal.* Calcd for $C_{14}H_{17}NO_2 \cdot HCl$: C, 62.80; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 62.87; H, 6.75; N, 5.35; Cl, 13.49. The mother liquor and washings were combined and evaporated to dryness *in vacuo*. The residual salt dissolved in acetone (30 ml) was allowed to stand overnight at room temperature. The precipitated crystals were collected by filtration and washed with acetone to provide **7**·HCl (1.7 g, containing 10% **6**·HCl). Repeated recrystallization from MeOH afforded isomer-free **7**·HCl (1.1 g, 31%), mp 169—170 °C. *Anal.* Calcd for $C_{14}H_{17}NO_2 \cdot HCl$: C, 62.80; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 62.82; H, 6.77; N, 5.20; Cl, 13.46. The structures of **6**·HCl and **7**·HCl were confirmed by comparison of their NMR spectra, MS and melting points with those of authentic samples synthesized by an alternative route described later. The purities were checked by gas chromatography after trifluroacetylation (*N*-trifluoroacetyl-**6**, t_R 17′57″; *N*-trifluoroacetyl-**7**, t_R 15′24″).

Isomerization of 5a·HCl into 7·HCl——A suspension of **5a**·HCl (10.0 g, 0.037 mol, equilibrium mixture of **6**·HCl and **7**·HCl in a ratio of 1 : 2) in acetone (30 ml) containing a catalytic amount of **5a** (0.9 g, 0.0038 mol) as a base was stirred vigorously at room temperature for 24 h. The precipitated salts were collected by filtration and washed thoroughly with acetone. The resulting salts (9.8 g, containing 3% **6**·HCl) were recrystallized from MeOH (35 ml) to provide isomer-free **7**·HCl (7.3 g, 73%), mp 169—170 °C. Free base **5a** recovered from the filtrate was shown to be an equilibrium mixture of **6** and **7** in a ratio of 1 : 2.

Preparation of Authentic 7·HCl——(a) A solution of (±)-4-triphenylmethyl-2-(*p*-toluenesulfonyloxymethyl)morpholine (**8**) (10 g, 0.019 mol) and the potassium salt of 4-hydroxy-1-indanone (3.6 g, 0.019 mol) in dimethylformamide (DMF, 120 ml) were stirred at 100—105 °C for 17 h. The reaction mixture was concentrated *in vacuo*. The residue was poured into ice water and the precipitated crystals were collected by filtration and washed with water to provide (±)-2-[(1-oxoindan-4-yloxy)methyl]-4-triphenylmethylmorpholine (**9**) (7.0 g, 73.5%), mp 213—215 °C (recrystallized from EtOAc–hexane). MS *m/z*: 489 (M^+). NMR ($CHCl_3$) δ: 1.4—1.9 (2H, m), 2.8—3.3 (2H, m), 2.5—3.0 (4H, m), 3.8—4.1 (4H, m), 4.1—4.3 (1H, m), 6.9—7.6 (18H, m). *Anal.* Calcd for $C_{33}H_{31}NO_3$: C, 80.95; H, 6.38; N, 2.86. Found: C, 81.21; H, 6.57; N, 2.79.

(b) A solution of **9** (10 g, 0.02 mol) in THF (100 ml) was added dropwise to a suspension of $LiAlH_4$ (1.17 g, 0.03 mol) in THF (100 ml) at 5—10 °C and the reaction mixture was stirred at room temperature for 3 h and then cooled. Next, H_2O (1.2 ml), 15% aqueous NaOH (1.2 ml) and H_2O (3.6 ml) were successively added dropwise to the reaction mixture. The resulting precipitates were filtered off. The filtrate was concentrated to dryness under reduced pressure. The residue was triturated with EtOAc (3 ml) to give (±)-2-[(1-hydoxyindan-4-yloxy)methyl]-4-triphenylmethylmorpholine (**10**) (7.8 g, 77.7%), mp 222—224 °C (recrystallized from EtOAc). MS *m/z*: 491 (M^+). NMR ($CDCl_3$) δ: 1.4—1.7 (1H, m), 1.6—1.8 (1H, br s), 1.7—2.0 (1H, m), 2.2—2.5 (1H, m), 2.5—3.0 (3H, m), 2.8—

3.3 (2H, m), 3.8—4.0 (4H, m), 4.1—4.3 (1H, m), 5.2 (1H, t, J=6 Hz), 6.6—7.6 (18H, m). *Anal.* Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 80.84; H, 6.81; N, 2.59.

(c) A mixture of **10** (2.0 g, 0.004 mol) and 0.5 N HCl (140 ml) in EtOH (60 ml) was refluxed with stirring for 17 h and then cooled. The reaction mixture was concentrated to half the initial volume under reduced pressure and washed with Et_2O. The aqueous layer was saturated with NaCl and extracted with $CHCl_3$ (50 ml × 3). The extract was dried over $MgSO_4$ and concentrated under reduced pressure to give **7**·HCl (0.8 g, 73.4%). Recrystallization of the salt from either MeOH or acetone was performed to give isomer-free **7**·HCl, mp 169—170 °C (from MeOH) and mp 155—156 °C (from acetone); these products were polymorphs. MS m/z: 231 (M^+). NMR (DMSO-d_6) δ: 2.8—3.6 (4H, m), 3.32 (2H, m), 3.6—4.3 (3H, m), 4.12 (2H, m), 6.56 (1H, dt, J=2, 5 Hz), 6.86 (1H, dt, J=2, 5 Hz), 6.7—7.3 (3H, m), 9.64 (2H, br s). *Anal.* Calcd for $C_{14}H_{17}NO_2$·HCl: C, 62.80; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 62.73; H, 6.52; N, 5.09; Cl, 13.49.

Preparation of Authentic 6·HCl——(a) (±)-2-[(1-Oxoindan-7-yloxy)methyl]-4-triphenylmethylmorpholine (**11**) was prepared from 7-hydroxy-1-indanone in the same manner as described for **9**. Recrystallization from EtOAc afforded **11** (87.8%), mp 170—171 °C. MS m/z: 489 (M^+). NMR ($CDCl_3$) δ: 1.4—1.9 (2H, m), 2.8—3.3 (2H, m), 2.5—3.2 (4H, m), 3.8—4.2 (4H, m), 4.2—4.4 (1H, m), 6.6—7.6 (18H, m). *Anal.* Calcd for $C_{33}H_{31}NO_3$: C, 80.95; H, 6.38; N, 2.86. Found: C, 81.09; H, 6.44; N, 2.71.

(b) (±)-2-[(1-Hydroxyindan-7-yloxy)methyl]-4-triphenylmethylmorpholine (**12**) was prepared from **11** in the same manner as described for **10**. Recrystallization from EtOAc afforded **12** (89.3%), mp 221—222 °C. MS m/z: 491 (M^+). NMR ($CDCl_3$) δ: 1.6—1.8 (1H, m), 1.9—2.1 (1H, m), 2.2—2.4 (1H, m), 2.4—2.9 (3H, m), 2.9—3.1 (1H, br s), 2.9—3.2 (2H, m), 3.8—4.1 (4H, m), 4.1—4.4 (1H, m), 5.36 (1H, dd, J=7, 7 Hz), 6.5—6.6 (18H, m). *Anal.* Calcd for $C_{33}H_{33}NO_3$: C, 80.62; H, 6.77; N, 2.85. Found: C, 80.73; H, 6.59; N, 2.64.

(c) **6**·HCl was prepared from **12** in the same manner as described for **7**·HCl. Recrystallization from iso-PrOH afforded **6**·HCl (81.8%), mp 175—176 °C. MS m/z: 231 (M^+). NMR (DMSO-d_6) δ: 2.8—3.6 (4H, m), 3.4 (2H, m), 3.6—4.3 (3H, m), 4.10 (2H, m) 6.48 (1H, dt, J=2, 5 Hz), 6.86 (1H, dt, J=2, 5 Hz), 6.7—7.2 (3H, m), 9.67 (2H, br s). *Anal.* Calcd for $C_{14}H_{17}NO_2$·HCl: C, 62.80; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 62.64; H, 6.71; N, 5.14; Cl, 13.40.

(±)-2-Hydroxymethylmorpholine——(±)-2-Hydroxymethyl-4-benzylmorpholine[2c] (10.0 g, 0.048 mol) was hydrogenated over 10% Pd–C (500 mg) in MeOH (100 ml) at room temperature until H_2 uptake ceased. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was distilled to give 2-hydroxymethylmorpholine (8.1 g, 95%), as a colorless oil, bp 92—93 °C (1.1 mmHg). NMR ($CDCl_3$) δ: 2.18 (2H, s), 2.5—3.0 (4H, m), 3.2—4.0 (5H, m). *Anal.* Calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.08; H, 9.35; N, 12.06.

(±)-2-Hydroxymethyl-4-triphenylmethylmorpholine——A solution of triphenylchloromethane (4.3 g, 0.015 mol) in CH_2Cl_2 (20 ml) was added to a solution of (±)-2-hydroxymethylmorpholine (1.8 g, 0.015 mol) and Et_3N (1.6 g, 0.016 mol) in CH_2Cl_2 (30 ml) with stirring at 0—5 °C. After being stirred at room temperature for 10 h, the reaction mixture was diluted with H_2O. The organic layer was separated and washed with H_2O. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography using $CHCl_3$ as an eluent to afford (±)-2-hydroxymethyl-4-triphenylmethylmorpholine (5.3 g, 96.4%) as an oil. NMR ($CDCl_3$) δ: 1.2—1.9 (2H, m). 1.5 (1H, s), 2.9 (2H, d, J=10 Hz), 3.5 (2H, m), 3.7—4.2 (3H, m), 7.0—7.6 (15H, m). *Anal.* Calcd for $C_{24}H_{25}NO_2$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.36; H, 6.89; N, 3.87.

(±)-4-Triphenylmethyl-2-(*p*-toluenesulfonyloxymethyl)morpholine (8)——A solution of *p*-toluenesulfonyl chloride (2.8 g, 0.015 mol) in CH_2Cl_2 (50 ml) was added dropwise to a solution of (±)-2-hydroxymethyl-4-triphenylmethylmorpholine (5.2 g, 0.015 mol) and pyridine (1.2 g, 0.015 mol) in CH_2Cl_2 (150 ml) with stirring at 0—5 °C. After being stirred for 15 h at room temperature, the reaction mixture was diluted with H_2O. The organic layer was separated and washed successively with H_2O, saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from $ClCH_2CH_2Cl$ to give **8** (5.2 g, 70%), mp 232—233 °C. NMR ($CDCl_3$) δ: 1.2—1.8 (2H, m), 2.4 (3H, s), 2.8 (2H, d, J=10 Hz), 3.6—4.1 (5H, m), 7.0—7.5 (17H, m), 7.6 (2H, d, J=8 Hz). *Anal.* Calcd for $C_{31}H_{31}NO_4S$: C, 72.49; H, 6.08; N, 2.73; S, 6.24. Found: C, 72.53; H, 5.97; N, 2.85; S, 6.44.

(+)-2-[(Inden-7-yloxy)methyl]morpholine Hydrochloride ((+)-7·HCl)——(a) A solution of LiOH H_2O (42 g, 1 mol) in abs. MeOH (800 ml) was added dropwise to a solution of L-(−)-dibenzoyltartaric acid monohydrate (452 g, 1.2 mol) in abs. MeOH (1600 ml) at −10 to −20 °C with stirring. Then **7**·HCl (268 g, 1 mol) was added at room temperature and the whole was stirred at 2—5 °C for 60 h. The precipitated crystals were collected by filtration and repeated recrystallizations from abs. MeOH (g/10 ml volume) afforded the L-(−)-dibenzoyltartaric acid salt of (+)-2-[(inden-7-yloxy)methyl]morpholine (93.5 g, 15.6%), mp 181—182 °C. $[\alpha]_D^{20}$ −71.7 (c=1, MeOH). MS m/z: 231 (M^+). NMR (CD_3OD) δ: 2.8—3.5 (4H, m), 3.6—4.2 (5H, m), 5.9 (2H, s), 6.5 (1H, dt, J=2, 5 Hz), 6.8 (1H, dt, J=2, 5 Hz), 6.7 (1H, q, J=2, 8 Hz), 6.9—7.3 (2H, m), 7.3—7.7 (6H, m), 8.0—8.2 (4H, m). *Anal.* Calcd for $C_{14}H_{17}NO_2 \cdot C_{18}H_{14}O_8 \cdot 1/2H_2O$: C, 64.21; H, 5.39; N, 2.34. Found: C, 64.44; H, 5.28; N, 2.32.

(b) The L-(−)-dibenzoyltartaric acid salt of (+)-2-[(inden-7-yloxy)methyl]morpholine (60 g, 0.1 mol) was stirred with 0.1 N HCl (1000 ml) and Et_2O (500 ml) at 0—5 °C for 3 h. The aqueous layer was separated and washed with Et_2O (500 ml × 5). After removal of the solvent, the residue was crystallized from iso-PrOH (70 ml). The crystals were collected by filtration and recrystallized from EtOH (50 ml) to give (+)-**7**·HCl (12 g, 44.9%), mp 112—113 °C. $[\alpha]_D^{21}$

+4.9 ($c=5$, MeOH). MS m/z: 231 (M^+). NMR (CD_3OD) δ: 3.0—3.6 (6H, m), 3.7—4.3 (5H, m), 6.6 (1H, dt, $J=6$, 2 Hz), 6.7—6.9 (2H, m), 7.0 (1H, dd, $J=7$, 1 Hz), 7.2 (1H, t, $J=7$ Hz). *Anal.* Calcd for $C_{14}H_{17}NO_2 \cdot HCl$: C, 62.80; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 62.67; H, 6.71; N, 5.27; Cl, 13.24.

(−)-2-[(Inden-7-yloxy)methyl]morpholine Hydrochloride ((−)-7·HCl)——(a) The D-(+)-dibenzoyltartaric acid salt of (−)-2-[-inden-7-yloxy)methyl]morpholine was prepared from **7**·HCl (268 g, 1 mol) and D-(+)-dibenzoyltartaric acid in the same manner as described for (+)-**7**·HCl. Yield 65 g (10.9%), mp 181—182 °C. $[\alpha]_D^{20}$ +71.6 ($c=1$, MeOH). MS m/z: 231 (M^+). NMR (CD_3OD) δ: 2.8—3.5 (4H, m), 3.6—4.2 (5H, m), 5.9 (2H, s), 6.5 (1H, dt, $J=2$, 5 Hz), 6.8 (1H, dt, $J=2$, 5 Hz), 6.7 (1H, q, $J=2$, 8 Hz), 6.9—7.3 (2H, m), 7.3—7.7 (6H, m), 8.0—8.2 (4H, m). *Anal.* Calcd for $C_{14}H_{17}NO_2 \cdot C_{18}H_{14}O_8 \cdot 1/2H_2O$: C, 64.21; H, 5.39; N, 2.34. Found: C, 64.44; H, 5.28; N, 2.32.

(b) (−)-**7**·HCl was prepared from the D-(+)-dibenzoyltartaric acid salt of (−)-2-[(inden-7-yloxy)-methyl]morpholine (58 g, 0.1 mol) in the same manner as described for (+)-**7**·HCl. Recrystallization from iso-PrOH (70 ml) afforded (−)-**7**·HCl (12.5 g, 46.6%), mp 142—142.5 °C. $[\alpha]_D^{20}$ −4.9 ($c=5$, MeOH). MS m/z: 231 (M^+). NMR (CD_3OD) δ: 3.0—3.6 (6H, m), 3.7—4.3 (5H, m), 6.6 (1H, dt, $J=6$, 2 Hz), 6.7—6.9 (2H, m), 7.0 (1H, dd, $J=7$, 1 Hz), 7.2 (1H, t, $J=7$ Hz). *Anal.* Calcd for $C_{14}H_{17}NO_2 \cdot HCl$: C, 62.80; H, 6.78; N, 5.23; Cl, 13.24. Found: C, 63.06; H, 6.83; N, 5.27; Cl, 13.48.

(±)-2-[(Inden-7(or 4)-yloxy)methyl]-4-methylmorpholine (5b) from 5a——A mixture of **5a** (5.0 g, 0.021 mol), MeI (3.0 g, 0.021 mol) and K_2CO_3 (3.0 g, 0.022 mol) was refluxed in EtOH (100 ml) for 15 h. The solvent was removed under reduced pressure. The residue was extracted with $CHCl_3$ (100 ml). The extract was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by column chromatography on silica gel using $CHCl_3$–EtOAc (5 : 1, v/v) as an eluent to afford **5b** (3.6 g, 67.9%) as an oil.

The following compounds were similarly prepared.

(±)-2-[(Inden-7(or 4)-yloxy)methyl]-4-ethylmorpholine (**5c**): Oil. Yield 73.5%.

(±)-2-[(Inden-7(or 4)-yloxy)methyl]-4-benzylmorpholine (**5i**): Oil. Yield 79.7%. NMR spectra and *Rf* values on TLC of these compounds were identical with those of the product prepared by hydrogenation of **4** (**4b**, **4c** and **4i**).

Inhibition of NE and 5-HT Uptake by the Rat Brain Synaptosome[7a]——The inhibition of uptake of [^{14}C]norepinephrine (NE) and [^{14}C]hydroxytryptamine (5-HT) by the synaptosomes from rat whole brain was determined using 6 preparations for each concentration of the test compounds. The IC_{50}s, the concentrations of the test compounds required to inhibit the uptake reaction by 50%, were obtained from the dose-response curves.

Antagonism to the Effects of Reserpine[7b]——Reserpine, 10 mg/kg *i.p.*, was given to mice 3 h before oral administration of a test compound (1, 3, 10, 30 or 100 mg/kg). The minimal effective dose (MED; mg/kg) which produced a significant elevation of the rectal temperature (*vs.* that of control animals receiving researpine and saline, $p<0.05$) was determined. For each dose of the test compounds, 10 mice were used.

Facilitation of Behavioral Response to 5-HTP[7b]——(±)-**5**-HTP, 90 mg/kg *i.v.*, was given 1 h after *i.p.* administration of the test compounds. The minimal effective dose (MED; mg/kg) producing behavioral responses, *i.e.* abduction of hind limb and/or tremor, to (±)-**5**-HTP was determined. For each dose of the test compounds 6 mice were used.

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