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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

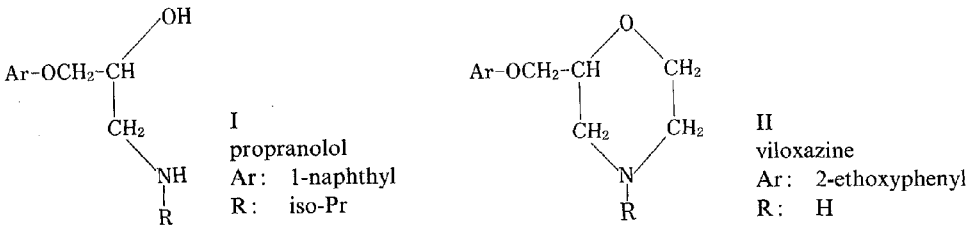

Fig. 1

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**)

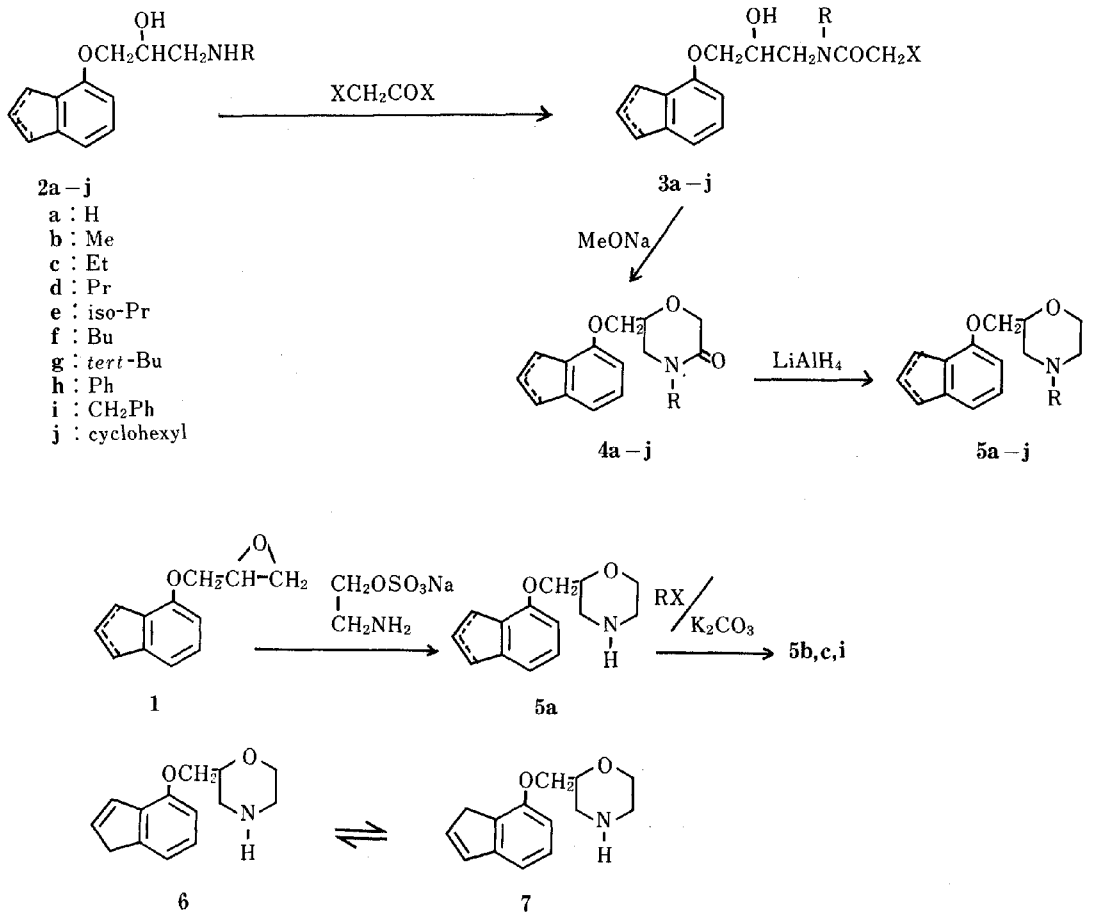

Chart 1

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_2CH_3), 1.9—3.1 (4H, m), 2.4 (2H, q, J=7 Hz, CH_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_2CH_3), 1.5 (2H, m, CH_2CH_3), 1.9—3.1 (4H, m), 2.2 (2H, t, J=7 Hz, $CH_2CH_2CH_3$), 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, $CH_2CH_2CH_3$), 1.9—3.1 (4H, m), 2.3 (2H, t, J=6 Hz, $NCH_2CH_2CH_2$–), 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–CH–), 3.3—3.4 (2H, m), 3.6—4.3 (5H, m), 6.3—6.9 (2H, m), 7.0—7.3 (3H, m)

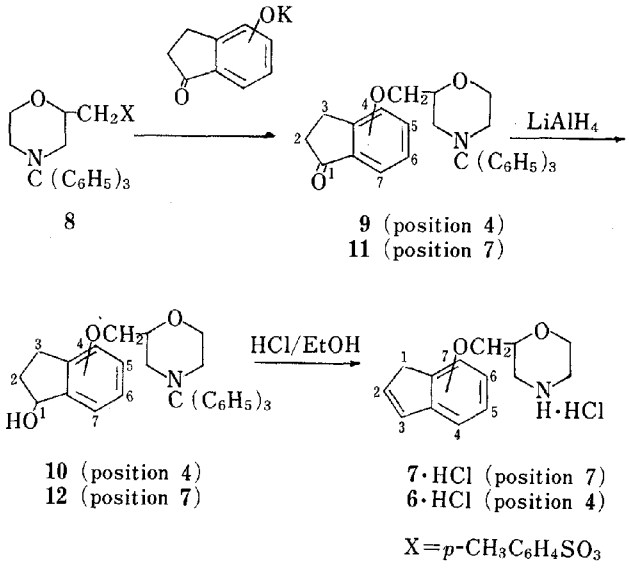

Chart 2

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.

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