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Syntheses and Biological Activities of Optical Isomers of 3-Chloro-5-[3-(2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidino)propyl]-10,11-dihydro-5*H*-dibenz[*b*, *f*]azepine (Mosapramine1)) Dihydrochloride

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Mosapramine (1) is a new neuroleptic drug with an asymmetric carbon atom (8a) in its imidazopyridine ring. The enantiomers of this agent were synthesized to compare their biological activities, such as antiapomorphine activity, affinity for dopamine D_2 receptor and acute toxicity. The key intermediates, (*R*)-(−)- and (*S*)-(+)-2-oxo-1,2,3,5,6,-7,8,8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidines, were prepared by optical resolution of the corresponding (±)-compound and were treated with 3-chloro-5-(3-methanesulfonyloxypropyl)-10,11-dihydro-5*H*-dibenz[*b*, *f*]azepine to afford (*R*)-(−)-1 and (*S*)-(+)-1, respectively. There were few differences in the examined biological activities of the two enantiomers as thier dihydrochlorides.

Keywords mosapramine; biological activity; enantiomer; synthesis; resolution; *N*-acetyltryptophan

Mosapramine, [(±)-3-chloro-5-[3-(2-oxo-1,2,3,5,6,7,8,-8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidino)propyl]-10,11-dihydro-5*H*-dibenz[*b*, *f*]azepine (**1**)],1) (Cremin® as the dihydrochloride) has an asymmetric carbon atom (8a) in the imidazopyridine ring of the amine moiety. The stereo structure of **1** has been established by X-ray crystallographic analysis.2) The ORTEP drawing showed the presence of disorder at four carbon locations in the pyridine part of the imidazopyridine ring. This suggested the presence of *cis* and *trans* conformers of the ring.

The location of the asymmetric carbon atom of **1** is on the outside of the circle formed by connecting the three pharmacologically active functional groups, *i.e.*, the 3-chloro-10,11-dihydro-5*H*-dibenz[*b*, *f*]azepine ring, the piperidine ring and the –C(=O)–NH– moiety of the imidazopyridine ring, as discussed in our previous report.1) Mosapramine is the first drug which has an asymmetric carbon atom outside the pharmacologically active functional groups.

We aimed to synthesize the enantiomers of **1** to evaluate influence on the biological activities of the spatial relationship between the functional groups and the asymmetric carbon atom. In this paper, we describe (1) the syntheses of key intermediates, (−)-2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidine {(−)-**2**} and (+)-2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]-pyridine-3-spiro-4′-piperidine {(+)-**2**}, which were prepared by optical resolution of the corresponding racemate (**2**), (2) the indirect estimation of the optical purity of the enantiomers, (3) the indirect determination of the absolute configuration of (−)-**2** by X-ray crystallographic analysis, (4) the syntheses of the enantiomers of **1** by coupling 3-chloro-5-(3-methanesulfonyloxypropyl)-10,11-dihydro-5*H*-dibenz[*b*, *f*]azepine (**3**)1) with (−)-**2** or (+)-**2**, and (5) the evaluation of the biological activities of the dihydrochloride of each enantiomer.

Synthesis Optical resolution of **2** was performed at first by recrystallization of its diastereomeric salts with D- or L-mandelic acid, and a mixture of three polymorphic crystals (fine needles, large pillars and large cubic crystals) was obtained, presumably due to the presence of *cis* and *trans* conformation of the imidazopyridine ring. The results of a study on *cis* and *trans* conformation of **2** will be reported elsewhere.

Resolution was achieved by recrystallization of the diastereomeric salts with *N*-acetyl-L- and *N*-acetyl-D-tryptophan followed by neutralization with alkali to afford (−)-**2** {$[\alpha]_D$ −25.8 (c=1, H_2O)} and (+)-**2** {$[\alpha]_D$ +25.3 (c=1, H_2O)}, respectively (Chart 1).

The optical purity of (+)-**2** was indirectly measured by HPLC, because **2** has weak UV absorption (254 nm). It was converted to the 3,5-dinitrobenzamide derivative (**4**) by coupling with 3,5-dinitrobenzoyl chloride. The optical purity of **4** was determined as 97% ee.

The absolute configulation of the asymmetric carbon atom of (−)-**2** was indirectly determined to be *R*. This was inferred on the basis of the absolute configuration of

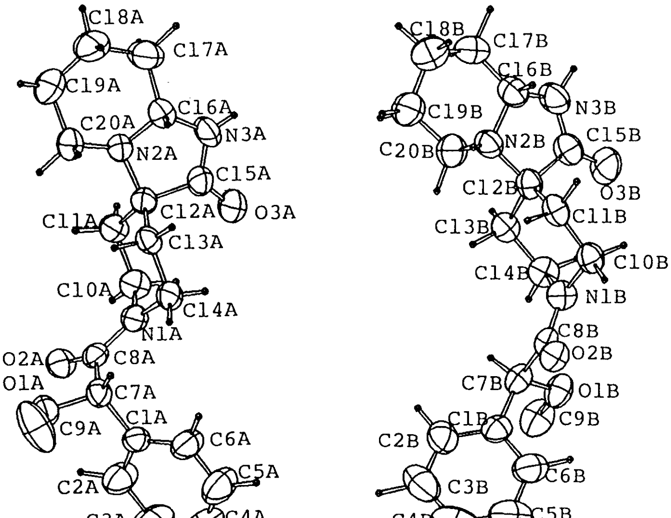

Fig. 1. ORTEP Drawing of **5**

Two independent molecules exist.

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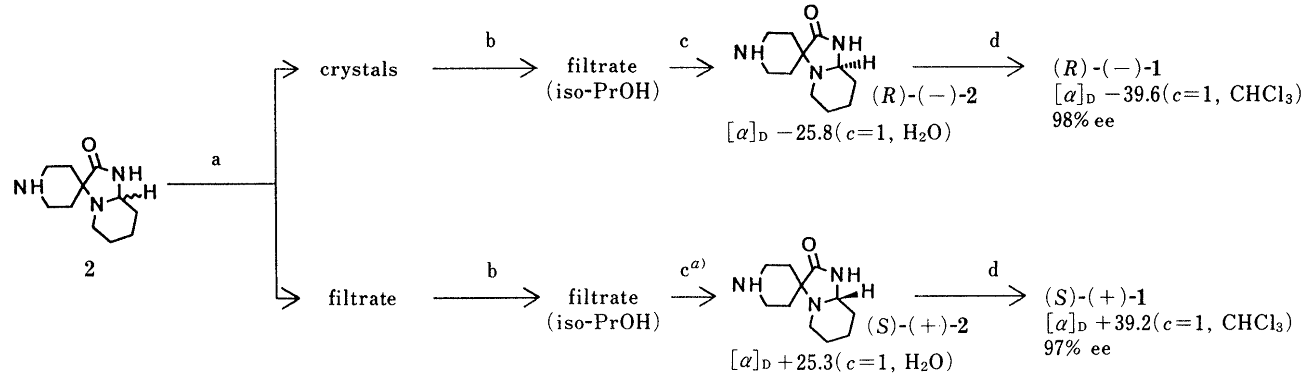

a : *N*-acetyl-L-tryptophan b : 1) aqueous NH_4OH ; 2) $CHCl_3$ extraction ; 3) iso-PrOH with seed crystals of **2**
c : 1) *N*-acetyl-L-tryptophan (*N*-acetyl-D-tryptophan)[a] 2) aqueous NH_4OH ; 3) $CHCl_3$ extraction d : 3-chloro-5-(3-methansulfonyloxypropyl)-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (**3**)

Chart 1

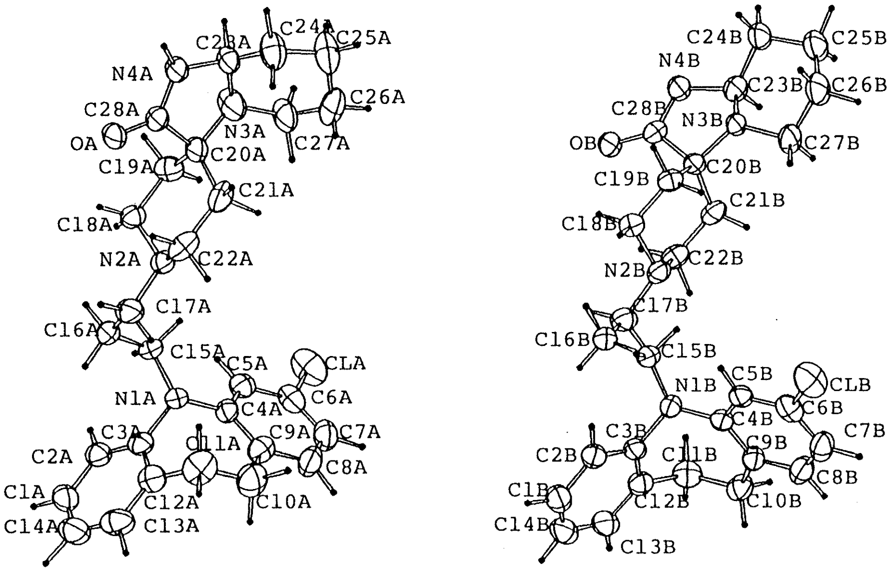

Fig. 2. ORTEP Drawing of (*R*)-(−)-**1**
A: *cis* form (left), B: *trans* (right).

(*S*)-α-methoxyphenylacetic acid by the X-ray crystallographic analysis of the (*S*)-α-methoxyphenylacetamide derivative (**5**) as shown in Fig. 1.

Compounds (*R*)-(−)-**2** and (*S*)-(+)-**2** were coupled with **3** to afford the enantiomers of mosapramine [(*R*)-(−)-**1** and (*S*)-(+)-**1**], respectively. The optical purities and the values of optical rotation of (*R*)-(−)-**1** and (*S*)-(+)-**1** were determined to be 98% ee, {[α]$_D$ −39.6 (*c*=1, $CHCl_3$)} and 97% ee, {[α]$_D$ 39.2 (*c*=1, $CHCl_3$)} by HPLC and polarimetry, respectively.

An ORTEP drawing of the molecule of (*R*)-(−)-**1** is shown in Fig. 2. The imidazopyridine ring of the amine moiety exhibited *cis* and *trans* structures. The lattice constants of crystals of (*R*)-(−)-**1** and (*S*)-(+)-**1** are given in the experimental section.

Biological Activities and Discussion The pharmacological and toxicological activities of the dihydrochlorides of (*R*)-(−)-**1** and (*S*)-(+)-**1**, and **1** were compared by means of antiapomorphine tests (locomotor activities, gnawing behavior and vomiting), dopamine D_2 receptor affinity test, and acute toxicity test. The biological activities of these three compounds showed few differences as summarized in Table I. However, the affinity of (*R*)-(−)-**1**·2HCl for dopamine D_2 receptors was 1.5 times stronger than that of (*S*)-(+)-**1**·2HCl.

The three-dimensional arrangement of the three pharmacologically active functional groups of (*R*)-(−)-**1** and (*S*)-(+)-**1** is identical and the arrangement is not affected by the asymmetric carbon atom C(23), as shown in Fig. 2. With respect to the plane which is formed by connecting the three functional groups, the asymmetric atom affects only the stereo arrangement of four carbon atoms of the pyridine part of the molecule, in particular C(24). This is presumably why little difference was observed in the biological activities of the enantiomers.

The activity ratios of the optical isomers were within 2 fold as regards the pharmacokinetic parameters in rats (25 mg/kg) and dogs (2.5 mg/kg) after oral administration as shown in Table II.[3] In schizophrenic patients, who were orally administered 75 mg of **1**, the ratios of C_{max} and area

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Table I. Biological Activities of the Enantiomers and Mosapramine

	Antiapomorphine Hyperactivity Mice	Gnawing Rats	Emesis Dogs$^{a)}$	Affinity for dopamine D_2 recep.	Acute toxicity Mice
	ED_{50} mg/kg		(1 mg/kg)	([^{3}H]Spiperone)	LD_{50} mg/kg
	p.o.	*p.o.*	*p.o.*	K_i (nM)	i.p.
(*R*)-(−)-**1**·2HCl	10.0	5.8	80	0.14	79.0
(*S*)-(+)-**1**·2HCl	9.4	6.4	73	0.21	82.1
1·2HCl	9.6	8.5	64	0.19	79.4

a) Protection %.

Table II. Pharmacokinetic Parameter of Enantiomers of Mosapramine

Parameter	Rat (25 mg/kg, *p.o.*)		Dog$^{a)}$ (2.5 mg/kg, *p.o.*)	
	(*R*)-(−)-**1**	(*S*)-(+)-**1**	(*R*)-(−)-**1**	(*S*)-(+)-**1**
$t_{\max}$ (h)	1.0	1.0	0.9± 0.3	0.9± 0.3
$C_{\max}$ (ng/ml)	96.1	161.0	44.2±20.3	31.2± 23.0
$t_{1/2}$ (h)	2.8	3.1	2.7± 0.4	2.9± 0.7
$AUC_{(0-12)}$ (ng·h/ml)	424.1	754.1	150.2±59.9	134.3±108.5

a) Mean±S.D., *n*=4.

under the curve (*AUC*) of the isomers (*R*)-(−)-**1**/(*S*)-(+)-**1** were both 1.6 as determined by HPLC analysis of the plasma.[3] From these data, it is suggested that the two isomers have almost the same pharmacological, toxicological and pharmacokinetic characteristics. The racemic mixture, mosapramine, is therefore adequate for use as a neuroleptic drug.

Experimental

Melting points were determined with a Yamato MP-3 apparatus and values were not corrected. Infrared (IR) spectra were taken on a JASCO IR-810 spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JNM-GSX 400 spectrometer and chemical shifts are given in δ with tetramethylsilane as the internal standard. Optical rotations were determined with a JASCO DIP-181 polarimeter. X-Ray crystallographic analyses were carried out on a Enraf-Nonius CAD4 diffractometer. Diffraction measurements were carried out using graphite-monochromated CuK_α radiation. The structures were solved by the direct method using the program MULTAN 82. All coordinates, with anisotropic thermal parameters for non-H and isotropic ones for H atoms, were refined by a block-diagonal least squares method; $\sum w(|F_o|-|F_c|)^2$ minimized, $w=1.0$.

HPLC Conditions for Determination of the Optical Purity of Enantiomers HPLC analysis was conducted with a Japan-Waters ALC/GPC 204 (column, Sumipax OA-2000 (4.6×250 mm): room temperature; detection, UV at 254 nm). For compound **4**: mobile phase, hexane–dichloromethane–MeOH (90 : 18 : 2); flow rate 2 ml/min. For compound **1**: hexane–dichloromethane–MeOH (300 : 60 : 25); flow rate 1.2 ml/min.

Resolution of (±)-2-Oxo-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidine (2). (*R*)-(−)-Enantiomer of 2 The racemate (**2**) (60 g, 0.30 mol) and *N*-acetyl-L-tryptophan (75 g, 0.31 mol) were dissolved in warmed iso-PrOH (2 l). The precipitated jelly-like crystals were collected (the filtrate was used in the next experiment), and recrystallized from iso-PrOH. The product was dissolved in H_2O, and concentrated NH_4OH was added to make pH 10. The solution was thoroughly extracted with $CHCl_3$. The $CHCl_3$ layer was dried (K_2CO_3), and concentrated. The residue was taken up in iso-PrOH (120 ml), and the solution was seeded with crystals of **2**. The crystals formed were filtered off, and *N*-acetyl-L-tryptophan was added to the mother liquid. The precipitated crystals were collected, and dissolved in H_2O. Concentrated NH_4OH was added to make pH 10, and the solution was thoroughly extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$), and concentrated, then the residue was recrystallized from iso-PrOH to give 10 g of (*R*)-(−)-**2**, $[\alpha]_D$ −25.8 ($c=1$, H_2O). mp 125—127 °C. *Anal.* Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 63.04; H, 8.94; N, 19.88.

(S)-(+)-Enantiomer of 2 Concentrated NH_4OH was added to the filtrate mentioned above to make pH 10 and the solution was thoroughly extracted with $CHCl_3$. The chloroform layer was dried (K_2CO_3) and concentrated. The residue was taken up in iso-PrOH (120 ml), and the solution was seeded with crystals of **2**. The separated crystals were filtered off, and *N*-acetyl-D-tryptophan was added to the mother liquid. Thereafter, the procedure was as described above, providing 11 g of (*S*)-(+)-**2**. $[\alpha]_D$ +25.3 ($c=1$, H_2O). mp 125—127 °C (iso-PrOH). *Anal.* Calcd for $C_{11}H_{19}N_3O$: C, 63.13; H, 9.15; N, 20.08. Found: C, 62.87; H, 8.96; N, 19.96.

(*S*)-(+)-1′-(3,5-Dinitrobenzoyl)-2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidine (4) The enantiomer {(*R*)-(−)-**2**} (0.5 g) was dissolved in $CHCl_3$ (15 ml), then Et_3N (1.0 ml) was added, and the mixture was cooled to below 5 °C. To this solution, 3,5-dinitrobenzoyl chloride (0.58 g) was added slowly with stirring over 1 h, and the mixture was stirred for 2 h at room temperature. The mixture was washed with H_2O and aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The crude crystals were recrystallized from MeOH to give 0.8 g of **4** as yellowish white crystals. mp 234—236 °C. $[\alpha]_D$ +67.0 ($c=1$, $CHCl_3$). *Anal.* Calcd for $C_{18}H_{21}N_5O_6$: C, 53.60; H, 5.25; N, 17.36. Found: C, 53.35; H, 5.19; N, 17.23. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3200, 3100, 2890, 1705, 1640, 1550, 1340. ^{1}H-NMR ($CDCl_3$) δ: 9.10 (1H, s), 8.60 (2H, s), 6.35 (1H, s), 4.67—4.58 (1H, m), 4.31—4.25 (0.6H, m), 4.02—3.88 (1.4H, m), 3.76—3.69 (0.4H, m), 3.54—3.46 (1.6H, m), 3.41—3.35 (1H, m), 2.80 (1H, m), 2.47 (1H, m), 1.95—1.35 (9H, m).

The optical purity of **4** was determined to be 97% ee by HPLC (t_R: 47.2 min).

(*R*)-(−)-1′-[(*S*)-α-Methoxyphenylacetyl]-2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidine (5) The enantiomer {(*R*)-(−)-**2**} (0.8 g) was dissolved in $CHCl_3$ (25 ml), and Et_3N (1.5 ml) was added. The mixture was cooled to below 5 °C. To this solution was added (*S*)-α-methoxyphenylacetyl chloride (1 ml) with stirring over 1 h, and the mixture was stirred for 3 h at room temperature. It was then washed with H_2O, dried ($MgSO_4$), and evaporated. The crude solid was triturated with isopropyl ether–hexane (1 : 1), and recrystallized from toluene–iso-propyl ether (1 : 1) for X-ray analysis to give 0.9 g of **5** as light rod crystals, mp 153—156 °C, $[\alpha]_D$ −48.2 ($c=0.5$, $CHCl_3$). *Anal.* Calcd for $C_{20}H_{27}N_3O_3$: C, 67.20; H, 7.61; N, 11.75. Found: C, 67.21; H, 7.64; N, 11.67. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3300 (NH), 2930 (NH), 1710 (C=O), 1635 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 7.45—7.28 (5H, m), 6.54 (1H, m), 5.09 (0.5H, s), 5.02 (0.5H, s), 4.59—4.45 (1H, m), 4.05—3.72 (2H, m), 3.49 (3H, d, $J=5.1$ Hz), 3.28 (0.5H, m), 3.06 (0.5H, m), 2.56—2.05 (1H, m), 1.82—1.31 (10H, m), 1.00—0.73 (1H, m).

X-Ray Analysis of 5 Intensities were measured in the ω–2θ ($0 \leqq \theta \leqq 60$) scan mode, and 2798 unique reflections with $I \geqq 2.3\sigma$ (I) were used for the refinement. The crystal data are as follows: $C_{20}H_{27}N_3O_3 \times 2$, $M_r=357.46\times 2$. Conformational isomers exsit (molecules A and B). $a=15.383$ (1), $b=12.313(1)$, $c=10.728(1)$ Å, $\beta=108.208(7)°$, $V=1930.2$ (5) Å^3; space group $P2_1$ (monoclinic); $Z=2$; D_{calcd} 1.229 Mg m^{-3}. The final *R* factor was 0.042 by the method mentioned above. The final parameters are listed in Table III.

(*R*)-(−)-3-Chloro-5-[3-(2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidino)propyl]-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine {(*R*)-(−)-1} A solution of (*R*)-(−)-**2** (10 g), 3-chloro-5-(3-methanesulfonyloxypropyl)-10,11-dihydro-5*H*-dibenz[*b*,*f*]azepine (19.2 g) and Et_3N (9 g) in $CHCl_3$ (200 ml) was refluxed for 5 h. The reaction mixture was washed, and extracted with aqueous sulfamic acid. The solution was neutralized with K_2CO_3, and extracted with $CHCl_3$ (80 ml). The organic solution was, dried ($MgSO_4$), and concentrated *in vacuo*. The (*R*)-(−)-**1** was obtained by recrystallization from AcOEt as white crystals (17.5 g), mp 145—147 °C, $[\alpha]_D$ −39.6 ($c=1$, $CHCl_3$), 98% ee (HPLC, t_R: 31.0 min). *Anal.* Calcd for $C_{28}H_{35}ClN_4O$: C, 70.20; H, 7.36; N, 11.69. Found: C, 70.18; H, 7.39; N, 11.87. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: 3180, 3090, 2930, 1700, 1485. ^{1}H-NMR ($CDCl_3$) δ: 7.15—6.83 (7H, m), 5.72 (1H, s), 3.92—3.89 (1H, m), 3.73 (2H, t, $J=6.8$ Hz), 3.15—3.07 (3H, m), 2.86—2.83 (3H, m), 2.70 (1H, m), 2.46—2.34 (3H, m), 1.83—1.64 (10H, m), 1.52—1.48 (1H, m), 1.37—1.33 (2H, m).

The dihydrochloride of (*R*)-(−)-**1** was obtained by adding HCl–EtOH to the EtOH solution of (*R*)-(−)-**1**, yield 93%, mp 270—272 °C (dec.), $[\alpha]_D$ +8.6 ($c=0.5$, H_2O). *Anal.* Calcd for $C_{28}H_{35}ClN_4O\cdot 2HCl$: C, 60.93; H, 6.76; N, 10.15. Found: C, 60.81; H, 6.79; N, 10.17. IR $\nu_{\max}^{\mathrm{KBr}}$ cm^{-1}: ^{1}H-NMR (DMSO-d_6) ppm: 9.34 (1H, s), 7.18—6.95 (7H, m), 4.55 (1H, m), 3.80 (2H, t, $J=6.8$ Hz), 4.0—2.7 (12H, m), 2.4—1.4 (12H, m).

X-Ray Analysis of (*R*)-(−)-1 A transparent rod crystal of (*R*)-(−)-**1**

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TABLE III. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors (Å^2) of **5** for Non-H Atom

	x	y	z	B_{eqv}
O1A	6977 (2)	3676 (2)	4130 (2)	4.64 (6)
O2A	7859 (2)	2832 (2)	2647 (2)	4.39 (6)
O3A	10450 (2)	−549 (2)	5018 (3)	5.67 (8)
N1A	8566 (2)	1561 (2)	4134 (2)	3.83 (7)
N2A	11415 (2)	1946 (2)	6109 (3)	3.90 (7)
N3A	11653 (2)	194 (3)	6605 (3)	5.06 (9)
C1A	6463 (2)	1804 (3)	3946 (3)	3.66 (8)
C2A	5852 (3)	1912 (4)	2687 (4)	6.08 (12)
C3A	5122 (3)	1206 (5)	2221 (4)	7.05 (15)
C4A	5015 (3)	359 (5)	3015 (5)	6.75 (15)
C5A	5619 (3)	260 (5)	4270 (5)	7.26 (16)
C6A	6334 (3)	957 (4)	4726 (4)	5.49 (12)
C7A	7256 (2)	2577 (3)	4420 (3)	3.63 (8)
C8A	7937 (2)	2355 (3)	3682 (3)	3.45 (8)
C9A	6658 (4)	4147 (5)	5066 (5)	8.66 (21)
C10A	9190 (2)	1274 (3)	3395 (3)	4.31 (9)
C11A	10137 (2)	1743 (3)	4052 (3)	4.04 (9)
C12A	10531 (2)	1409 (3)	5495 (3)	3.57 (8)
C13A	9817 (2)	1608 (3)	6204 (3)	3.61 (8)
C14A	8883 (2)	1128 (3)	5477 (3)	4.08 (9)
C15A	10851 (2)	224 (3)	5644 (3)	4.05 (9)
C16A	11958 (2)	1248 (3)	7155 (4)	4.68 (10)
C17A	12959 (3)	1507 (4)	7439 (5)	6.77 (14)
C18A	13104 (3)	2709 (4)	7837 (6)	7.14 (16)
C19A	12459 (3)	3437 (4)	6818 (5)	6.58 (14)
C20A	11470 (3)	3080 (3)	6502 (4)	5.21 (11)
O1B	3287 (2)	−1154 (2)	760 (2)	4.72 (6)
O2B	2178 (2)	−2589 (2)	2316 (2)	4.42 (6)
O3B	−291 (2)	876 (2)	−511 (3)	6.39 (9)
N1B	1460 (2)	−1296 (3)	861 (3)	4.21 (7)
N2B	−1282 (2)	−1638 (3)	−1584 (3)	4.35 (8)
N3B	−1681 (2)	96 (3)	−1495 (3)	5.45 (10)
C1B	3458 (2)	−3113 (3)	1057 (3)	4.32 (9)
C2B	3437 (3)	−3995 (4)	242 (4)	5.58 (12)
C3B	4048 (3)	−4833 (5)	633 (6)	7.40 (18)
C4B	4703 (3)	−4797 (5)	1866 (6)	7.88 (18)
C5B	4741 (3)	−3925 (5)	2699 (5)	7.28 (16)
C6B	4118 (3)	−3088 (5)	2283 (4)	6.01 (12)
C7B	2816 (2)	−2182 (3)	589 (3)	3.94 (8)
C8B	2112 (2)	−2038 (3)	1319 (3)	3.63 (8)
C9B	3861 (3)	−1059 (4)	−68 (4)	5.93 (13)
C10B	780 (2)	−1056 (3)	1517 (3)	4.43 (10)
C11B	−165 (2)	−1470 (3)	707 (3)	4.22 (9)
C12B	−456 (2)	−1103 (3)	−741 (3)	3.91 (9)
C13B	332 (2)	−1258 (3)	−1308 (3)	4.18 (9)
C14B	1233 (2)	−798 (3)	−442 (3)	4.36 (10)
C15B	−776 (3)	82 (3)	−885 (4)	4.52 (10)
C16B	−2073 (2)	−986 (3)	−1628 (4)	4.94 (11)
C17B	−2838 (3)	−1220 (4)	−2873 (5)	6.19 (13)
C18B	−3087 (3)	−2415 (5)	−2869 (6)	7.44 (17)
C19B	−2246 (3)	−3131 (4)	−2654 (5)	6.79 (15)
C20B	−1459 (3)	−2785 (3)	−1467 (4)	5.47 (12)

$B_{eqv}=4/3\Sigma_i\Sigma_j\beta_{ij}\boldsymbol{a}_i\cdot\boldsymbol{a}_j$.

for X-ray diffraction study was grown from EtOH solution. Intensities were measured in the ω–2θ ($0\leqq\theta\leqq60$) scan mode, and 3649 unique reflections with $I\geqq2.3\sigma$ (I) were used for the refinement. The crystal data are as follows: $C_{28}H_{35}ClN_4O\times2$, $M_r=479.07\times2$, $a=11.557(1)$, $b=11.868(1)$, $c=10.775(1)$ Å, $\alpha=92.73(1)°$, $\beta=112.65(1)°$, $\gamma=68.26(1)°$, $V=1259.1(3)$ Å^3; space group $P1$(triclinic); $Z=1$; D_{calcd} 1.263 Mg m^{-3}. The final R factor was 0.046 by the method described above. The final parameters are listed in Table IV.

(*S*)-(+)-3-Chloro-5-[3-(2-oxo-1,2,3,5,6,7,8,8a-octahydroimidazo[1,2-*a*]pyridine-3-spiro-4′-piperidino)propyl]-10,11-dihydro-5*H*-dibenz[*b*,*f*]-azepine {(*S*)-(+)-1} Compound (***S***)-(+)-**2** (5 g) was reacted with **3** (9.6 g) to give 9.2 g of (*S*)-(+)-**1** in the same manner as described above, mp 142—143 °C (AcOEt), $[\alpha]_D$ +39.2 ($c=1$, $CHCl_3$), 97% ee (HPLC, t_R: 33.5 min). *Anal.* Calcd for $C_{28}H_{35}ClN_4O$: C, 70.20; H, 7.36; N, 11.69.

TABLE IV. Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Temperature Factors (Å^2) of (*R*)-(−)-**1** for Non-H Atom

	x	y	z	B_{eqv}
ClA	−2892 (1)	5376 (1)	−1407 (2)	6.20 (4)
OA	4407 (3)	4037 (3)	8622 (3)	4.11 (10)
N1A	1433 (3)	1958 (3)	1691 (3)	2.87 (10)
N2A	2807 (3)	3384 (3)	4970 (3)	2.87 (10)
N3A	2192 (5)	6831 (4)	6609 (4)	5.27 (15)
N4A	3802 (4)	6095 (3)	8676 (3)	3.53 (11)
C1A	1620 (6)	−1259 (4)	1571 (5)	4.40 (16)
C2A	1181 (4)	−33 (4)	1690 (4)	3.19 (13)
C3A	1851 (4)	664 (4)	1549 (4)	3.22 (12)
C4A	745 (4)	2731 (4)	460 (4)	2.93 (12)
C5A	−553 (4)	3593 (4)	165 (4)	3.55 (14)
C6A	−1271 (4)	4365 (4)	−1049 (5)	3.84 (14)
C7A	−698 (5)	4274 (4)	−1976 (5)	4.34 (16)
C8A	582 (6)	3421 (5)	−1675 (5)	4.51 (18)
C9A	1350 (5)	2628 (4)	−467 (4)	3.78 (15)
C10A	2793 (6)	1771 (6)	−267 (7)	5.78 (22)
C11A	3657 (5)	916 (6)	1044 (6)	5.30 (19)
C12A	3014 (4)	139 (4)	1262 (4)	3.85 (14)
C13A	3459 (5)	−1133 (5)	1135 (5)	5.24 (18)
C14A	2779 (6)	−1808 (4)	1318 (5)	5.09 (18)
C15A	941 (5)	2351 (4)	2781 (4)	3.38 (14)
C16A	2062 (6)	1670 (4)	4152 (4)	4.46 (18)
C17A	3190 (6)	2090 (4)	4718 (4)	4.59 (17)
C18A	2184 (4)	3656 (4)	5952 (4)	3.09 (13)
C19A	1734 (4)	4986 (4)	6120 (4)	3.50 (13)
C20A	2837 (5)	5489 (4)	6554 (4)	3.55 (14)
C21A	3656 (5)	5053 (5)	5690 (4)	4.24 (17)
C22A	4008 (4)	3694 (5)	5463 (4)	4.00 (15)
C23A	2973 (4)	7222 (4)	7778 (4)	3.48 (13)
C24A	3747 (6)	7936 (5)	7642 (6)	5.45 (19)
C25A	2836 (6)	8931 (5)	6447 (6)	6.16 (22)
C26A	2246 (6)	8417 (5)	5173 (5)	5.48 (19)
C27A	1505 (6)	7664 (5)	5369 (5)	5.54 (20)
C28A	3773 (4)	5105 (4)	8058 (4)	3.21 (12)
ClB	2883 (1)	4624 (1)	1443 (2)	5.73 (4)
OB	−4302 (3)	5847 (3)	−8614 (3)	3.72 (9)
N1B	−1388 (3)	8078 (3)	−1753 (3)	3.05 (10)
N2B	−2829 (3)	6617 (3)	−4960 (3)	3.06 (10)
N3B	−2427 (4)	3147 (3)	−6423 (3)	3.65 (12)
N4B	−4002 (4)	3835 (3)	−8534 (3)	3.33 (11)
C1B	−1563 (5)	11293 (4)	−1732 (5)	4.47 (17)
C2B	−1078 (5)	10022 (4)	−1818 (4)	3.72 (15)
C3B	−1809 (4)	9363 (3)	−1643 (4)	2.87 (12)
C4B	−735 (4)	7331 (4)	−504 (4)	2.92 (12)
C5B	571 (4)	6427 (4)	−153 (4)	3.09 (12)
C6B	1210 (4)	5714 (4)	1035 (5)	3.85 (14)
C7B	625 (5)	5815 (5)	1966 (5)	4.48 (17)
C8B	−652 (5)	6705 (5)	1616 (4)	4.08 (16)
C9B	−1363 (4)	7451 (4)	421 (4)	3.22 (13)
C10B	−2786 (5)	8345 (5)	195 (5)	4.08 (16)
C11B	−3642 (5)	9165 (4)	−1137 (5)	4.00 (15)
C12B	−2959 (4)	9964 (4)	−1383 (4)	3.45 (13)
C13B	−3400 (5)	11197 (4)	−1321 (5)	4.01 (14)
C14B	−2704 (6)	11881 (4)	−1479 (5)	4.84 (17)
C15B	−939 (5)	7661 (4)	−2845 (4)	3.36 (14)
C16B	−1963 (5)	8294 (4)	−4189 (4)	4.08 (17)
C17B	−3198 (4)	7913 (4)	−4766 (4)	3.60 (13)
C18B	−2200 (4)	6290 (4)	−5941 (4)	3.12 (13)
C19B	−1759 (4)	4922 (4)	−6068 (4)	3.24 (13)
C20B	−2954 (4)	4492 (4)	−6503 (4)	2.73 (11)
C21B	−3762 (4)	5024 (4)	−5615 (4)	3.37 (14)
C22B	−4076 (4)	6352 (4)	−5486 (4)	3.47 (13)
C23B	−3432 (4)	2825 (4)	−7498 (4)	3.46 (13)
C24B	−2806 (5)	1563 (4)	−7849 (5)	4.25 (16)
C25B	−2139 (6)	661 (5)	−6598 (5)	5.19 (19)
C26B	−1183 (6)	1061 (4)	−5395 (5)	5.03 (18)
C27B	−1892 (6)	2369 (4)	−5169 (4)	4.61 (17)
C28B	−3827 (4)	4840 (4)	−7996 (4)	2.99 (12)

$B_{eqv}=4/3\Sigma_i\Sigma_j\beta_{ij}\boldsymbol{a}_i\cdot\boldsymbol{a}_j$.

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Found: C, 70.34; H, 7.43; N, 11.65. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3180, 3090, 2940, 2840, 1705, 1490. ^{1}H-NMR ($CDCl_3$) δ: 7.16—6.83 (7H, m), 5.80 (1H, s), 3.92—3.89 (1H, m), 3.74—3.70 (3H, m), 3.15—3.07 (4H, m), 2.89—2.83 (3H, m), 2.69 (1H, m), 2.45—2.34 (3H, m), 1.83—1.63 (10H, m), 1.52—1.48 (1H, m), 1.36—1.29 (2H, m).

The dihydrochloride of (*S*)-(+)-**1** was obtained by the same method as above, yield 91%, mp 269—270 °C (dec.), $[\alpha]_D$ −6.0 ($c=0.5$, H_2O). *Anal.* Calcd for $C_{28}H_{35}ClN_4O \cdot 2HCl$: C, 60.93; H, 6.76; N, 10.15. Found: C, 60.89; H, 6.89; N, 10.27. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3400 (NH), 2950—2900, 2650, 1730 (C=O), 1480. ^{1}H-NMR (DMSO-d_6) ppm: 9.27 (1H, s), 7.18—6.95 (7H, m), 4.52 (1H, m), 3.79 (2H, t, $J=6.8$ Hz), 3.79 (12H, m), 4.0—2.7 (12H, m), 2.4—1.4 (12H, m).

X-Ray Analysis of (*S*)-(+)-1 A transparent rod crystal of (*S*)-(+)-**1** for an X-ray diffraction study was grown from EtOH solution. Intensities were measured in the ω-2θ ($0 \leqq \theta \leqq 60$) scan mode, and 3511 unique reflections with $I \geqq 2.3\sigma(I)$ were used for the refinement. The crystal data are as follows: $C_{28}H_{35}ClN_4O \times 2$, $M_r=479.07 \times 2$, $a=11.562(1)$, $b=11.862(1)$, $c=10.778(2)$ Å, $\alpha=92.72(1)°$, $\beta=112.66(1)°$, $\gamma=68.24(1)°$, $V=1259.0(3)$ Å^3; space group *P*1 (triclinic); $Z=1$; D_{calcd} 1.263 Mg m^{-3}. The final *R* factor was 0.043 by the method as mentioned above.

Pharmacological Activities and Acute Toxicity. 1) Apomorphine-Induced Hyperactivity Groups of three male mice (20—28 g) (four groups for one dose) were given the test drug orally and apomorphine (0.5 mg/kg) was administered subcutaneously 1 h later. The motor activities were measured immediately thereafter for 20 min using a Varimex® (Columbus Co., U.S.A.).

2) Apomorphine-Induced Gnawing Behavior Groups of 7—14 female rats (180—240 g) were given the test drug orally and apomorphine (1.25 mg/kg) was administered intravenously 1 h later. The presence or absence of gnawing behavior was observed for a 5 min period from 5 and 20 min after the apomorphine administration.

3) Apomorphine-Induced Emesis in Dogs Groups of 10—11 dogs (8—15 kg) were used. The test drug in a gelatin capsule was administered orally, and apomorphine (0.1 mg/kg) was given subcutaneously 2 h later. The presence or absence of vomiting within 2 h after the apomorphine injection was observed. The ED_{50}, which inhibited emesis by 50% (in terms of number of animals) was determined.

4) Affinities for Dopamine D_2 Receptor Preparation of crude synaptosomal fraction and [^{3}H]spiperone (specific activity, 40.0 Ci/mmol, Amersham Co.) binding studies were carried out according to the method of Creese *et al.*[4] Binding in the presence of 100 μM unlabelled sulpiride was defined as non-specific binding.

5) Acute Toxicity Groups of 10 male mice (6 weeks, 18—25 g) were intraperitoneally given the test drug suspended in 0.5% methylcellulose solution. The ED_{50} value was calculated from the number of deaths within 7 d using the probit method.

References and Notes

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