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Asymmetric α-Substituted Phenethylamines. III.[1] The Synthesis and Analgesic Activity of optically Pure (*S*)- and (*R*)-1-Aryl-2-phenylethylamines

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(1*S*, 1′*S*)- and (1*R*, 1′*R*)-1-aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-(4-substituted phenyl)ethylamines (**7**—**13** and **18**—**23**) were synthesized by the asymmetric reaction of (*E*)-(*S*)- and (*E*)-(*R*)-*N*-(2-hydroxy-1-isopropylethyl)arylmethylideneamines with Grignard reagents. The products showed 100% optical purities; their absolute configurations were determined by means of circular dichroism.

These optically pure chiral amines were converted into hydrochlorides and then evaluated for analgesic activity in the acetic acid-induced mouse-writhing assay. Among these compounds, the hydrochlorides of **9** (1*S*: 1′*S*, Ar=2-thienyl, R=H), **13** (1*S*: 1′*S*, Ar=2-thienyl, R=MeO), **19** (1*R*: 1′*R*, Ar=4-methoxyphenyl, R=H), **20** (1*R*: 1′*R*, Ar=2-thienyl, R=H), and **23** (1*S*: 1′*S*, Ar=2-thienyl, R=OH) showed inhibition of the writhing; they were about equipotent with (−)-pentazocine hydrochloride.

Moreover, the hydrochlorides of **8** (1*S*: 1′*S*, Ar=4-methoxyphenyl, R=H), **13** (1*S*: 1′*S*, Ar=2-thienyl, R=MeO), **18** (1*R*: 1′*R*, Ar=phenyl, R=H), **19** (1*R*: 1′*R*, Ar=4-methoxyphenyl, R=H), **20** (1*R*: 1′*R*, Ar=2-thienyl, R=H), and **21** (1*R*: 1′*R*, Ar=2-thienyl, R=MeO) were not antagonized by (−)-naloxone hydrochloride.

Keywords——absolute configuration; analgesic activity; chiral azomethine; Cotton effect; Grignard reaction; optically pure amine; naloxone antagonism; phenethylamine moiety; quadrant rule; (*S*)- valinol; (*R*)-valinol

The configuration of the asymmetric carbon atom at the α-position of the phenylethylamine structure plays an important role in determining the analgesic activity. The absolute configuration at the 9-position of (−)-morphine, the 2-position of (−)-pentazocine, or the 1-position of *N*,*N*-dimethyl-1,2-diphenylethylamine is expressed as *R* chirality, and these isomers have more potent analgesic activity than *S* chiral compounds. Nakamura *et al.*[3] reported that the chirality of the 1-position of *N*-[2-(3-hydroxyphenyl)-1-phenylethyl]piperidines is very important for the analgesic potencies and narcotic antagonist properties. However, the synthesis of optically pure asymmetric compounds having defined chirality is required in order to investigate in more detail the relationship between the chirality and the pharmacological activity of the agents.

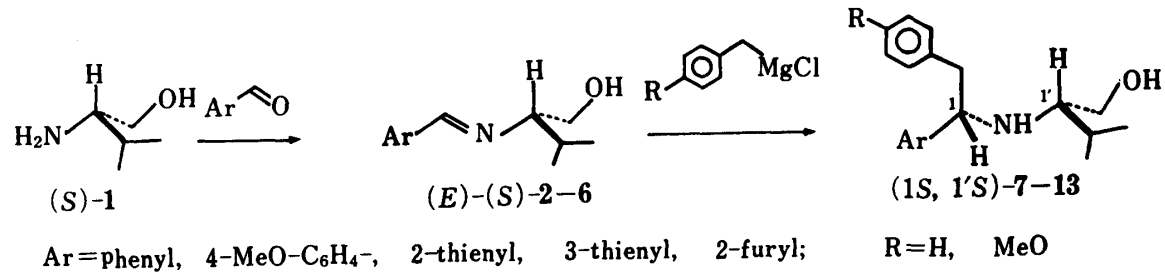
In this work, we will describe the synthesis of asymmetric α-aryl-substituted phenethylamines and the evaluation of the analgesic activity of these compounds.

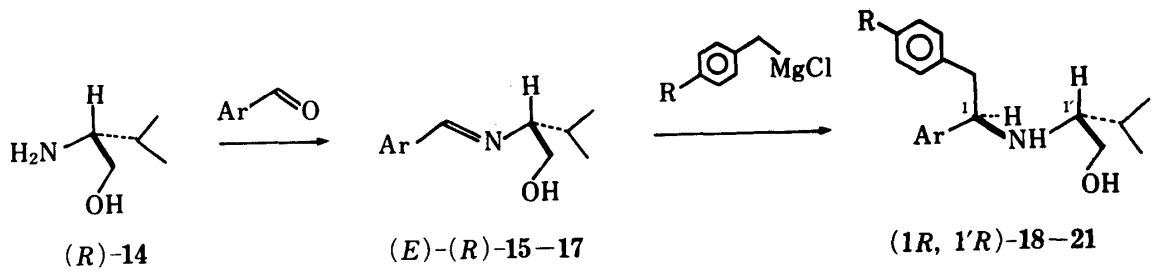
Chemistry

The chiral azomethines, *N*-(2-hydroxy-1-isopropylethyl)arylmethylideneamines (**4**—**6**), were synthesized in good yields by the condensation of (*S*)-valinol with 2-thiophenecarbaldehyde, 3-thiophenecarbaldehyde, and 2-furancarbaldehyde. *N*-(2-Hydroxy-1-isopropylethyl)-benzylideneamine (**2**) and *N*-(2-hydroxy-1-isopropylethyl)-(4-methoxyphenyl)methylideneamine (**3**) have been reported previously.[4] These compounds were moderately stable, colorless oils or crystals, and were confirmed to consist of one isomer by the observation of their proton nuclear magnetic resonance (^{1}H-NMR) spectra; the structures of these compounds were

established by means of infrared (IR), mass (MS), and ^{1}H-NMR spectral analyses.

The C=N bond was presumed to have the *E* configuration because of the difference in bulkiness between the hydrogen atom and the aryl group. It has been reported that the hydroxy group is located on the *si-si* face of the C=N bond because of the difference in bulkiness between the alkyl group, *i.e.*, methyl, isopropyl, isobutyl, or *sec*-butyl, and the hydroxymethyl group.[1)]





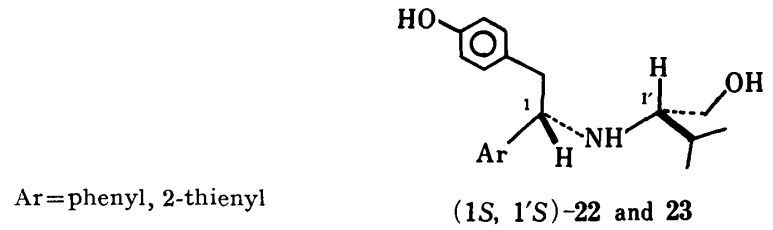


Chart 1

The chiral amine compounds, (1*S*, 1'*S*)-*N*-2'-hydroxy-1'-isopropylethyl-1,2-diphenylethylamine (**7**) and (1*S*, 1'*S*)-*N*-2'-hydroxy-1'-isopropylethyl-1-(4-methoxyphenyl)-2-phenylethylamine (**8**), were obtained by the reaction of the chiral azomethines (**2** and **3**) with benzylmagnesium chloride.[4)] *N*-2'-Hydroxy-1'-isopropylethyl-1-(2-thienyl)-2-phenylethylamine (**9**), *N*-2'-hydroxy-1'-isopropylethyl-1-(3-thienyl)-2-phenylethylamine (**10**), and *N*-2'-hydroxy-1'-isopropylethyl-1-(2-furyl)-2-phenylethylamine (**11**) were prepared by the treatment of *N*-(2-hydroxy-1-isopropylethyl)arylmethylideneamines (**4**—**6**) with benzylmagnesium chloride in tetrahydrofuran (THF) under a nitrogen atmosphere at 40—45°C for 3—5 h. The reactions of 4-methoxybenzylmagnesium chloride with the azomethines (**2** and **4**) in THF under a nitrogen atmosphere gave 1-aryl-*N*-2'-hydroxy-1'-isopropylethyl-2-(4-methoxyphenyl)-1-phenylethylamines (**12** and **13**) in good yields.

This asymmetric reaction of **2**—**6** with the Grignard reagents is diastereoface-differentiating, and the configurations of the resulting amines are either (1*S*, 1'*S*) or (1*R*, 1'*S*), since the reagent attacks azomethine from either the *si-si* or *re-re* face of the C=N bond. The products

of these reactions were chromatographed on a silica gel column in order to remove the 1,2-diarylethane. The eluates containing chiral amines were carefully collected, and no other diastereomer was detected by ^{1}H-NMR spectroscopy in any case.[5] This result indicated that the asymmetric reaction occurred with an extremely high diastereomeric specificity to yield optically pure chiral amines. These chiral amines (**9**—**13**) were colorless crystals or liquids; their structures were confirmed by means of IR, mass, and ^{1}H-NMR spectral analyses.

The chiral amines (**9**—**13**) were treated with a hydrogen chloride methanol solution to yield colorless crystals of the hydrochlorides. The experimental data are summarized in Table I.

TABLE I. (1*S*, 1′*S*)- and (1*R*, 1′*R*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamine Hydrochlorides

Compd. No.	Ar	R	mp (°C)	Recrystn solvent[a]	Method	Yield[b] (%)	Formula	Analysis, (%) Calcd (Found) C	H	N	$[\alpha]_D^{20}$[c]	Absolute configuration
9	2-Thienyl	H	207	BE	A	75	$C_{17}H_{23}NOS\cdot HCl$	62.65 (62.36)	7.42 (7.44)	4.30 (4.30)	+65.3°	(1*S*, 1′*S*)
10	3-Thienyl	H	238—239	E	A	73	$C_{17}H_{23}NOS\cdot HCl$	62.65 (62.43)	7.42 (7.22)	4.30 (4.38)	+73.0°	(1*S*, 1′*S*)
11	2-Furyl	H	216—218	E	A	90	$C_{17}H_{23}NO_2\cdot HCl$	65.90 (65.63)	7.81 (7.84)	4.52 (4.62)	+56.3°	(1*S*, 1′*S*)
12	Phenyl	MeO	234	E	B	75	$C_{20}H_{27}NO_2\cdot HCl$	68.65 (68.68)	8.07 (8.20)	4.00 (3.94)	+89.6°	(1*S*, 1′*S*)
13	2-Thienyl	MeO	224	BE	B	70	$C_{18}H_{25}NO_2S\cdot HCl$	60.74 (60.54)	7.36 (7.43)	3.94 (3.99)	+79.2°	(1*S*, 1′*S*)
19	4-MeO-C_6H_4-	H	206	E	A	69	$C_{20}H_{27}NO_2\cdot HCl$	68.65 (68.67)	8.07 (8.20)	4.00 (3.95)	−113.6°	(1*R*, 1′*R*)
20	2-Thienyl	H	208	BE	A	72	$C_{17}H_{23}NOS\cdot HCl$	62.65 (62.52)	7.42 (7.49)	4.30 (3.98)	−65.2°	(1*R*, 1′*R*)
21	2-Thienyl	MeO	223—224	BE	B	69	$C_{18}H_{25}NO_2S\cdot HCl$	60.74 (60.62)	7.36 (7.42)	3.94 (3.88)	−76.3°	(1*R*, 1′*R*)
22	Phenyl	HO	209—210	BE	C	85	$C_{19}H_{25}NO_2\cdot HCl$	67.94 (67.98)	7.80 (7.92)	4.14 (4.05)	+104.0°	(1*S*, 1′*S*)
23	2-Thienyl	HO	214	BE	C	90	$C_{17}H_{23}NO_2S\cdot HCl$	59.72 (60.03)	7.08 (7.32)	4.10 (3.91)	+52.1°	(1*S*, 1′*S*)

a) E=ethanol; BE=benzene-ethanol.
b) The yields are for isolated purified products; the yields of **9**—**11**, **19**, and **20** are based on Method A; those of **12**, **13**, and **21**, on Method B, and those of **22** and **23**, on Method C.
c) Concentration, 0.4% in 95% ethanol.

On the other hand, (1*R*, 1′*R*)-*N*-2′-hydroxy-1′-isopropylethyl-1,2-diphenylethyl-amine (**18**) has been synthesized by the reaction of (*E*)-(*R*)-*N*-(2-hydroxy-1-isopropylethyl)-benzylideneamine (**15**) with benzylmagnesium chloride.[4] (1*R*, 1′*R*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamines (**19** and **20**) and *N*-2′-hydroxy-1′-isopropylethyl-2-(4-methoxyphenyl)-1-(2-thienyl)ethylamine (**21**) were obtained from (*E*)-(*R*)-*N*-(2-hydroxy-1-isopropylethyl)arylmethylideneamines (**16** and **17**) in a manner similar to that described for the (*S*)-compounds. The IR, mass, and ^{1}H-NMR spectra of these amines (**19**—**21**) were indistinguishable from those of the corresponding *S* isomers. These amines were treated with a hydrogen chloride methanol solution to yield the hydrochlorides. The experimental data are summarized in Table I.

The hydrochlorides of (1*S*, 1′*S*)-1-aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-(4-hydroxyphenyl)ethylamines (**22** and **23**) were obtained from **12** and **13** by treatment with concentrated hydrochloric acid at 140—150°C for 3—5 h.

In order to determine the absolute configuration at the newly created asymmetric carbon atom of these amines, we attempted to measure the circular dichroism (CD) spectra of the hydrochlorides of the amines (**10**—**13**, **22**, and **23**). The observed CD spectral data are summarized, along with the ultraviolet (UV) spectral data, in Table II.

The aromatic quadrant-sector rule[6] was applied for the determination of the absolute configurations of 1,2-diphenylethylamine hydrochloride.[7] We have previously reported that the absolute configurations of hydrochlorides of **7**—**9** could be elucidated by the application of

TABLE II. CD and UV Spectral Data for 1-Aryl-2-phenylethylamine Hydrochlorides in 95% Ethanol [CD, Maximum $\Delta\epsilon$ (nm)[a] ; UV, λ_{max} nm ($\epsilon\times10^{-3}$)[b]]

Compd. No.		A-Band		B-Bamd				
10	CD	+4.43(216)	+2.68(238)	+0.21(258)	+0.18(265)			
	UV	207(10.17)	235(5.22)	258(0.20)	264(0.13)			
11	CD	+12.00(224)		+0.11(251)	+0.09(256)	−0.01(261)	+0.06(264)	−0.04(267)
	UV	209(13.30)		252(0.12)	258(0.17)	264(0.12)	268*(0.05)	
12	CD	+0.93(217)	+8.30(231)	+0.43(252)	+0.59(259)	+0.55(266)		
	UV	226(10.14)		254*(0.42)	259*(0.66)	266*(0.98)	276(1.45)	283(1.24)
13	CD	+12.33(233)		+0.15(267)	+0.09(280)			
	UV	228(9.01)		268*(0.65)	276(0.94)	283(0.80)		
22	CD	+1.71(219)	+8.60(229)	+0.50(251)	+0.53(258)	+0.51(266)		
	UV	226(9.31)		253*(0.40)	259*(0.64)	265*(0.96)	278(1.58)	283*(1.38)
23	CD	+13.11(235)		+0.15(268)	+0.05(282)			
	UV	227(14.19)		268*(1.02)	276(1.35)	282(1.17)		

a) Concentration, 2.5—3.5×10^{-3}M ; temperature, 25—28°C; cell length, 0.1—0.2 cm.
b) Asterisk indicates a shoulder.

the aromatic quadrant-sector rule,[1] and the configurations of the newly created chiral center in the amines (**7** and **18**) were elucidated by synthesis *via* an alternative route using materials of known absolute configuration.[4]

The quadrant projections of the hydrochlorides of **12** and **22** showed that the 2′-hydroxy-1′-isopropylethylamino group lies in the positive quadrant, while the CD spectra of these compounds showed positive Cotton effects at both the ^1L_a and ^1L_b bands. In the case of 2-thienyl, 3-thienyl, and 2-furyl compounds (**10**, **11**, **13**, and **23**), the CD spectra for the 210—240 nm region bands showed positive Cotton effects, and the quadrant projections of these compounds showed that the 2′-hydroxy-1′-isopropylethylamino group lies in the positive quadrant. These results on the Cotton effects and the quadrant projections were similar to those for the hydrochlorides of **7**—**9**, which were previously reported.[1] Accordingly, the absolute configurations of these amines (**10**—**13**, **22**, and **23**) were confirmed to be (1*S*, 1′*S*). The absolute configurations of the amines (**19**—**21**) synthesized from (*R*)-valinol were concluded to be (1*R*, 1′*R*).

Pharmacological Results

(1) Analgesic Activity

The hydrochloride of chiral amines thus obtained were evaluated for analgesic activity in the acetic acid-induced mouse-writhing assay. No significant morphine-like analgesic activity was found by the tail-flick method, but it is known that this test is generally insensitive to narcotic antagonist analgesics, such as (−)-nalorphine or (−)-pentazocine.

Male ddY mice were used; they weighed 18—22 g, and each group included 8 mice. The test compounds were dissolved in saline and the solutions were administered intraperitoneally to animals. Thirty min later, writhing was induced by the intraperitoneal injection of a 0.7% acetic acid aqueous solution into mice treated with each compound; the number of writhings was counted for 10 min beginning from 10 min after the challenge with acetic acid. The fifty percent inhibition dose (ID_{50}) of each compound was determined, *i.e.*, the amount required to decrease by 50% the number of writhes compared with the number in the vehicle-control group. The ID_{50} values and the 95% confidence limits (CL) were estimated by the method of Litchfield and Wilcoxon.[8] The ID_{50} values of the hydrochlorides of chiral amines (**7**—**13** and **18**—**23**) are summarized in Table III; (−)-morphine hydrochloride and (−)-pentazocine hydrochloride are included for purposes of comparison.

TABLE III. Analgesic Activities of 1-Aryl-2-phenylethylamine Hydrochlorides as Determined by the Acetic Acid Writhing Method in Mice

Compd. No.	ID_{50},[a] μmol/kg, *i.p.* (95% CL)	Compd. No.	ID_{50},[a] μmol/kg, *i.p.* (95% CL)
7	118 (83—167)	**19**	80 (51—123)
8	89 (68—117)	**20**	81 (64—104)
9	79 (55—113)	**21**	101 (79—129)
10	136 (77—240)	**22**	202 (153—265)
11	218 (156—304)	**23**	43 (18—105)
12	91 (60—138)	(−)-Pentazocine HCl	80 (56—114)
13	46 (23— 93)	(−)-Morphine HCl	5.81 (4.11—8.24)
18	105 (88—125)		

a) ID_{50} represents a dose producing 50% inhibition of writhing induced by 0.7% acetic acid.

A promising analgesic action was observed with hydrochlorides of **9**, **13**, **19**, **20**, and **23**, as shown in Table III; these compounds were about equipotent with (−)-pentazocine hydrochloride. When the substituent at the α-position of phenethylamines was the 2-thienyl group among these chiral amines, the potency of analgesic activity was increased. The analgesic potencies of the optical isomers with the (1*S*, 1′*S*) and (1*R*, 1′*R*) chiralities were similar.

(2) Naloxone Antagonism of Analgesic Activity

The hydrothlorides of **7**—**9**, **13**, **18**—**21**, and **23** were tested for antagonistic activity against naloxone,using the acetic acid-induced writhing method.[9] (−)-Naloxone hydrochloride (5mg/kg) was administered subcutaneously to mice 20 min after injection of each compound. The mice were treated with a 0.7% acetic acid aqueous solution at 10 min after the naloxone injection, and the number of writhings was counted for 10 min beginning from 10 min after the acetic acid challenge. The analgesic activity of **7**, **9**, and **23** was antagonized by naloxone, while that of **8**, **13**, and **18**—**21** was not, as shown in Fig. 1.

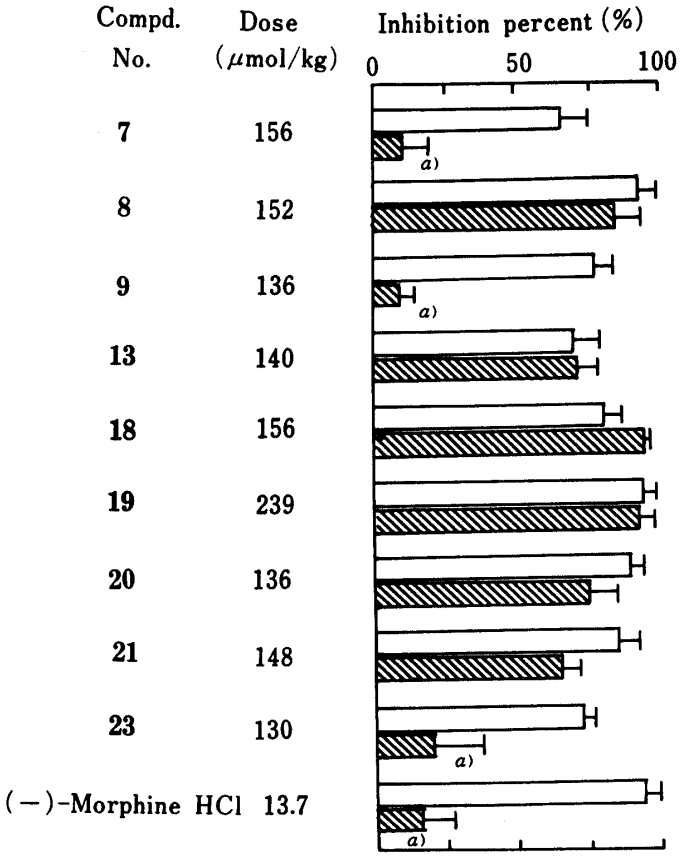


Fig. 1. Naloxone Antagonism of Analgesic Activities of 1-Aryl-2-phenylethylamine Hydrochlorides in Mice as Determined Using the Acetic Acid Writhing Method

▨ : naloxone HCl (5 mg/kg, *s.c.*) was administered at 20 min after test compound injection (*i.p.*).
□ : without naloxone HCl injection.
—| : standard error.
a) : $p<0.01$ (Student's *t*-test).

The hydrochloride of **13**, **19**, and **20** were about equipotent with (−)-pentazocine hydrochloride, and the analgesic activity was not antagonized by naloxone. We are continuing to study the analgesic activity of these asymmetric α-substituted phenethylamines in an attempt to evaluate the significance of these results.

Experimental

The IR spectra were recorded with a Hitachi 215 spectrometer; the MS, with a JEOL JMS-D300 spectrometer; the UV spectra, with a Hitachi 124 spectrometer, and the ^{1}H-NMR spectra, with a JEOL FX100 spectrometer. The melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected. The optical rotations were measured with a Jasco DIP-180 polarimeter. The gas chromatography (GC) was carried out with a Hitachi 164F gas chromatograph, using silicone SE-30.

The CD spectra were measured at 25—28°C using a Jasco J-40 spectropolarimeter; the magnitudes of the bands were calibrated with D-10-camphorsulfonic acid (at 289 nm) and D-pantolactone (at 221 nm) as standards.

(*E*)-(*S*)-*N*-(2-Hydroxy-1-isopropylethyl)-(2-thienyl)methylideneamine (4)——A mixture of **1** (5.15 g, 50 mmol) and 2-thiophenecarbaldehyde (5.60 g, 50 mmol) in benzene (100 ml) was refluxed for 4 h using a Dean-Stark trap. The mixture was then concentrated under reduced pressure, and the residue was allowed to stand at room temperature to give 18 g (91%) of crystals of **4**; this product was recrystallized from *n*-hexane to give colorless needles of mp 80—81°C. IR (KBr): 3300 (OH), 1625 (C=N) cm^{-1}. MS *m/e*: 197 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 0.94 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 6.9—7.4 (3H, aromatic H), 8.35 (1H, s, CH=N).

(*E*)-(*S*)-*N*-(2-Hydroxy-1-isopropylethyl)-(3-thienyl)methylideneamine (5)——The condensation of **1** (3.1 g, 30 mmol) and 3-thiophenecarbaldehyde (3.36 g, 30 mmol) in a manner similar to that used for **4** gave 5.3 g (90%) of crystals of **5**; this product was recrystallized from *n*-heptane to yield colorless columns of mp 73—74°C. IR (KBr): 3300 (OH), 1645 (C=N) cm^{-1}. MS *m/e*: 197 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 0.94 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 7.2—7.6 (3H, aromatic H), 8.15 (1H, s, CH=N).

(*E*)-(*S*)-*N*-(2-Hydroxy-1-isopropylethyl)-(2-furyl)methylideneamine (6)——A mixture of **1** (3.1 g, 30 mmol) and 2-furancarbaldehyde (2.9 g, 30 mmol) in benzene (70 ml) was refluxed for 3 h using a Dean–Stark trap. The mixture was then concentrated under reduced pressure, and the residue was distilled under reduced pressure. A colorless oil of bp 141—143°C/12 mmHg was thus obtained. Yield, 4.1 g (76%). IR (film): 3300 (OH), 1630 (C=N) cm^{-1}. MS *m/e*: 181 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.87 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 0.95 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 6.4—7.5 (3H, aromatic H), 8.02 (1H, s, CH=N).

(1*S*, 1′*S*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamines (9—11); Method A——A suspension of benzylmagnesium chloride (100 mmol in 100 ml of THF) was slowly added, drop by drop, to a solution of a chiral azomethine (**4—6**) (20 mmol) in THF (50 ml) under a nitrogen atmosphere. The resulting mixture was stirred at 40—45°C for 5—8 h. The reaction mixture was treated with a small amount of water, the resulting white precipitate was filtered off, and the mixture was extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed over silica gel using CH_2Cl_2, 1,2-diphenylethane was removed, and the chiral amine (**9—11**) was obtained as a colorless oil.

9: IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 289 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 0.83 (3H, d, J=6.6 Hz, CH–C$\underline{H}_3$), 2.99 (2H, d, J=7.1 Hz, PhC$\underline{H}_2$–CH), 3.28 (1H, dd, J=4.4 and 11.0 Hz, C$\underline{H}_2$–OH), 3.47 (1H, dd, J=3.9 and 11.0 Hz, C$\underline{H}_2$–OH), 4.16 (1H, t, J=7.1 Hz, ArC$\underline{H}$–CH$_2$).

10: IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 289 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.7 Hz, CH–C$\underline{H}_3$), 0.82 (3H, d, J=6.7 Hz, CH–C$\underline{H}_3$), 2.94 (2H, d, J=7.1 Hz, PhC$\underline{H}_2$–CH), 3.28 (1H, dd, J=4.4 and 11.0 Hz, C$\underline{H}_2$–OH), 3.50 (1H, dd, J=4.2 and 11.0 Hz, C$\underline{H}_2$–OH), 4.00 (1H, t, J=7.1 Hz, ArC$\underline{H}$–CH$_2$).

11: IR (film): 3400 (OH) cm^{-1}. MS *m/e*: 273 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.79 (6H, d, J=6.6 Hz, CH–(C$\underline{H}_3$)$_2$), 3.03 (2H, d, J=7.6 Hz, PhC$\underline{H}_2$–CH), 3.27 (1H, dd, J=4.4 and 10.8 Hz, C$\underline{H}_2$–OH), 3.52 (1H, dd, J=3.9 and 10.8 Hz, C$\underline{H}_2$–OH), 3.86 (1H, t, J=7.6 Hz, ArC$\underline{H}$–CH$_2$).

The free bases were treated with a hydrogen chloride methanol solution to give the hydrochlorides of **9—11**. The experimental data for these compounds are summarized in Table I.

(1*S*, 1′*S*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-(4-methoxyphenyl)ethylamines (12 and 13); Method B——A suspension of 4-methoxybenzylmagnesium chloride (100 mmol in 100 ml of THF) was slowly added, drop by drop, to a solution of chiral azomethine (**4** and **6**) (20 mmol) in THF (50 ml) under a nitrogen atmosphere, after which stirring was continued at 40—45°C for 5 h. The reaction mixture was worked up as described above to obtain **12** and **13** as colorless oils.

12: IR (film): 3350 (OH) cm^{-1}. MS *m/e*: 313 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.78 (3H, d, J=6.8 Hz, CH–C$\underline{H}_3$), 0.82 (3H, d, J=6.8 Hz, CH–C$\underline{H}_3$), 3.31 (1H, dd, J=4.4 and 11.0 Hz, C$\underline{H}_2$–OH), 3.47 (1H, dd, J=4.2 and 11.0 Hz, C$\underline{H}_2$–OH), 3.79 (3H, s, OC$\underline{H}_3$), 3.83 (1H, t, J=7.0 Hz, ArC$\underline{H}$–CH$_2$), 2.86 (2H, d, J=7.0 Hz, MeOPhC$\underline{H}_2$–CH).

13: IR (film): 3370 (OH) cm^{-1}. MS *m/e*: 319 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.8 Hz, CH–C$\underline{H}_3$), 0.83 (3H, d, J=6.8 Hz, CH–C$\underline{H}_3$), 3.32 (1H, dd, J=4.4 and 11.0 Hz, C$\underline{H}_2$–OH), 3.45 (1H, dd, J=4.0 and 11.0 Hz, C$\underline{H}_2$–OH), 3.73 (3H, s, OC$\underline{H}_3$), 4.12 (1H, t, J=7.1 Hz, ArC$\underline{H}$–CH$_2$), 2.93 (2H, d, J=7.1 Hz, MeOPhC$\underline{H}_2$–CH).

The free bases were treated with a hydrogen chloride methanol solution to give the hydrochlorides of **12** and **13**. The experimental data for these compounds are summarized in Table I.

(*E*)-(*R*)-*N*-(2-Hydroxy-1-isopropylethyl)arylmethylideneamines (15—17)——The condensation of **14** (5.15 g, 50 mmol) with arylaldehydes (50 mmol) in benzene (100 ml), in the manner described for **2—4**, gave **15—17**. Compounds **15—17** were indistinguishable from **2—4**, respectively, by IR, mass, and ^{1}H-NMR spectral comparisons.

(1*R*, 1′*R*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamines (18—20); Method A——A suspension of benzylmagnesium chloride (50 mmol in 50 ml of THF) was slowly added, drop by drop, to a solution of a chiral azomethine (**15—17**) (10 mmol) in THF (30 ml) at room temperature under a nitrogen atmosphere. After being stirred at 40—45°C for 5 h, the reaction mixture was worked up as described for the *S* compounds. **18—20** were thus obtained as colorless liquids; among these compounds, **19** and **20** were indistinguishable from **8** and **9**, respectively, by IR, mass, and ^{1}H-NMR spectral comparisons.

The free bases were converted into hydrochlorides; the experimental data are summarized in Table I.

(1*R*, 1′*R*)-*N*-2′-Hydroxy-1′-isopropylethyl-2-(4-methoxyphenyl)-1-(2-thienyl)ethylamine (21); Method B——The reaction of **14** (2.0 g, 10 mmol) with 4-methoxybenzylmagnesium chloride (50 mmol in 50 ml of THF) in THF (25 ml), in the manner described for the *S* compounds, gave **21** as a colorless oil. The product was indistinguishable from **13** by IR, mass, and ^{1}H-NMR spectral comparisons. The experimental data for the hydrochloride of **21** are summarized in Table I.

Hydrochlorides of (1*S*, 1′*S*)-1-Aryl-*N*-2′-hydroxy-1′-isopropylethyl-2-(4-hydroxyphenyl)ethylamine (22 and 23); Method C——A solution of a chiral amine (**12** or **13**) (5 mmol) in concentrated hydrochloric acid (20 ml) was heated at 140—150°C in a sealed tube for 4 h. After the reaction, the hydrochloric acid was removed under reduced pressure; colorless crystals of the hydrochloride of **22** or **23** were thus obtained. The experimental data for these compounds are summarized in Table I.

References and Notes

1) Part II: Y. Suzuki and H. Takahashi, *Chem. Pharm. Bull.*, **31**, 31 (1983).
2) Formerly, Hoshi Institute of Pharmaceutical Sciences.
3) H. Nakamura, K. Ishii, Y. Yokoyama, S. Motoyoshi, K. Natsuka, and M. Shimizu, *J. Pharm. Pharmacol.*, **32**, 635 (1980).
4) H. Takahashi, Y. Suzuki, and H. Inagaki, *Chem. Pharm. Bull.*, **32**, 3160 (1982).
5) The ^{1}H-NMR spectra of the (1*S*, 1′*S*) isomers differed from those of the (1*R*, 1′*S*) isomers in the cases of compounds **7** and **8**.
6) M. Legrand and M.J. Rougier, "Stereochemistry: Fundamentals and Methods," Vol. 2, ed. by H.B. Kagan, Georg Thieme Publishers, Stuttgart, 1977, pp. 67—103.
7) H.E. Smith and T.C. Willis, *J. Am. Chem. Soc.*, **93**, 2282 (1971).
8) J.T. Litchfild and F.A. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
9) K.L. McGilliard and A.E. Takemori, *J. Pharmacol. Exp. Ther.*, **207**, 494 (1978).