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Asymmetric α-Substituted Phenethylamines. II.[1] The Enantioselective Synthesis of 1-Aryl-2-phenylethylamines from L- and D-Amino Acids by Means of 1,3-Asymmetric Induction

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Optically pure (1*S*, 1′*S*)-1-aryl-*N*-(1′-alkyl-2′-hydroxyethyl)-2-phenylethylamines (**13**—**21**) were synthesized from L-alanine, L-leucine, and L-isoleucine *via* (*S*)-2-aminoalkanols (**1**—**3**) and (*E*)-(*S*)-*N*-(1-alkyl-2-hydroxyethyl)arylmethylideneamines (**4**—**12**). On the other hand, the amines with (1*R*, 1′*R*) configuration (**33**—**38**) were synthesized from D-amino acids, *i.e.*, D-alanine and D-leucine. The absolute configurations of these amines were confirmed by the aromatic quadrant-sector rule. The asymmetric reactions of chiral azomethines (**7**—**12** and **30**—**32**) with benzylmagnesium chloride were found to be extremely highly stereoselective. However, the reactions of the azomethines (**4**—**6** and **27**—**29**) derived from L- and D-alanine with the Grignard reagent afforded poor stereoselectivity.

Keywords——absolute configuration; alaninol; asymmetric synthesis; azomethine chiral; Grignard reaction; isoleucinol; leucinol; optically pure amine; phenethylamine moiety; quadrant rule

Optically pure medicinal agents are required for pharmacological studies, and it is very important to be able to synthesize easily asymmetric compounds with 100% optical purity. We have previously reported the synthesis of optically pure 1-aryl-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenylethylamines[1] and found that some related compounds have an analgetic activity comparable to that of (*R*)-(−)-pentazocine.[3]

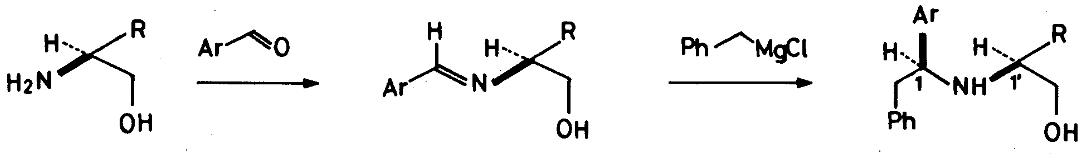
In this work, we have attempted to establish the steric effect of the alkyl group of the amino acids on the enantioselective synthesis of (*S*)- and (*R*)-1-aryl-2-phenylethylamines by means of 1,3-asymmetric induction.

(*S*)- and (*R*)-1-Aryl-2-phenylethylamines

(*S*)-2-Aminoalkanols (**1**—**3**) were prepared from L-amino acids by reduction with lithium aluminium hydride, and their optical purities were confirmed by comparison with the specific rotation values in the literature.[4] The aminoalkanols (**1**—**3**) thus obtained were condensed in benzene with benzaldehyde, 4-methoxybenzaldehyde, and 2-thiophenecarbaldehyde to give (*E*)-(*S*)-*N*-(1-alkyl-2-hydroxyethyl)arylmethylideneamines (**4**—**12**) in good yields. These compounds were moderately stable, colorless crystals or liquids, and were confirmed to consist of one isomer by the observation of their proton nuclear magnetic resonance (^{1}H-NMR) spectra. The infrared (IR) spectra of these compounds showed the typical absorption bands of an OH group at 3400—3200 cm^{-1} and of a C=N group at 1655—1625 cm^{-1}.[5] Moreover, the structures of these compounds were established by means of mass spectrometry (MS) and ^{1}H-NMR spectroscopy. These results are summarized in Tables II and III.

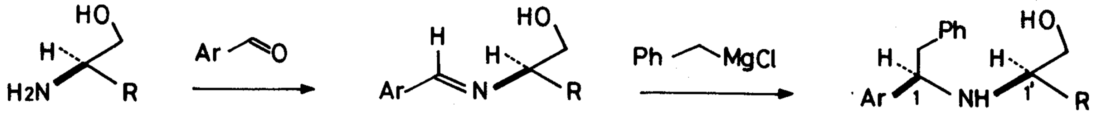
The configuration of the C=N bond of the azomethine was presumed to be the *E* form because of the difference in bulkiness between the hydrogen atom and the aryl group.[6]

(*E*)-(*S*)-*N*-(1-Alkyl-2-hydroxyethyl)arylmethylideneamines (**4**—**12**) were treated with benzylmagnesium chloride in tetrahydrofuran (THF) under a nitrogen atmosphere at 40—45°C for 5 h. These asymmetric reactions of **4**—**12** with the Grignard reagent are diastereoface-differentiating, and the configurations of the resulting amines are either (1*S*, 1′*S*) or (1*R*, 1′*S*),



(*S*)-1—3 (*E*)-(*S*)-4—12 (1*S*, 1′*S*)-13—21

R=methyl, isobutyl, *sec*-butyl
Ar=phenyl, 4-MeO-C_6H_4-, 2-thienyl



(*R*)-25, 26 (*E*)-(*R*)-27—32 (1*R*, 1′*R*)-33—38

R=methyl, isobutyl
Ar=phenyl, 4-MeO-C_6H_4-, 2-thienyl

Chart 1

for the benzyl group 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 column of silica gel in order to remove the 1,2-diphenylethane. The eluates containing 1-aryl-*N*-(1′-alkyl-2′-hydroxyethyl)-2-phenylethylamines were carefully collected, since there was a risk of losing the diastereomer.

In the cases of 1-aryl-*N*-(2′-hydroxy-1′-isobutylethyl)-2-phenylethylamines (**16**—**18**) and 1-aryl-*N*-(1′-*sec*-butyl-2′-hydroxyethyl)-2-phenylethylamines (**19**—**21**), no other diastereomer was detected by ^{1}H-NMR spectroscopy. This result indicated that the asymmetric reaction occurred with an extremely high diastereomeric specificity, and optically pure 1-aryl-*N*-(1′-alkyl-2′-hydroxyethyl)-2-phenylethylamines were obtained. These chiral amines were colorless crystals or liquids, and the structures of these compounds were confirmed by means of MS and ^{1}H-NMR spectroscopy. The results are summarized in Table IV. By contrast, the ^{1}H-NMR spectra of the amines derived from (*S*)-alaninol showed a mixture of two isomers, *i.e.*, two diastereomers having (1*S*, 1′*S*) and (1*R*, 1′*S*) configurations. In the cases of the phenyl (**13**), 4-methoxyphenyl (**14**), and 2-thienyl (**15**) products, the ratios of the major product to the minor product were estimated to be 78:22, 77:23, and 70:30%, respectively. The pure (1*S*, 1′*S*) compounds (**13**—**15**) derived from L-alanine were obtained by the removal of the minor product by means of rechromatography on a silica gel column.

On the other hand, 1-aryl-*N*-(2′-hydroxy-1′-methylethyl)-2-phenylethylamines (**23** and **24**) were obtained by the reactions of *N*-(2′-hydroxy-1′-methylethyl)-2-phenylethylideneamine (**22**) with aryllithiums. These compounds were identical with the minor products obtained from the reactions of **4** and **5** with benzylmagnesium chloride; they were the diastereomeric isomers of **13** and **14**, respectively.

The free bases of 1-aryl-*N*-(1′-alkyl-2′-hydroxyethyl)-2-phenylethylamines (**13**—**21**) were treated with a hydrogen chloride methanol solution to yield colorless crystals of the hydrochlorides. The specific rotations and analytical values of these hydrochlorides are summarized in Table V.

(1*R*, 1′*R*)-1-Aryl-*N*-(1′-alkyl-2′-hydroxyethyl)-2-phenylethylamines (**33**—**38**) were synthesized from D-amino acids as starting materials in a manner similar to that described for L-amino acids; *i.e.*, (*R*)-2-aminoalkanols (**25** and **26**) were condensed with benzaldehyde, 4-methoxybenzaldehyde, and 2-thiophenecarbaldehyde to yield (*E*)-(*R*)-*N*-(1-alkyl-2-hydroxyethyl)arylmethylideneamines (**27**—**32**). Then, **33**—**38** were obtained by the reactions of **27**—**32** with benzylmagnesium chloride. The free bases of these amines were treated with a hydrogen chloride methanol solution to yield the hydrochlorides. The gas chromatography (GC), IR, MS, and ^{1}H-NMR spectra of these azomethines (**27**—**32**) and amines (**33**—**38**) were indistinguishable from those of the corresponding *S* isomers.

Discussion

The optically pure 1-aryl-2-phenylethylamines **13**—**21** and **33**—**38**, which do not contain any diastereomer, were synthesized from L- and D-amino acids *via* chiral azomethines.

TABLE I. CD and UV Spectral Data for Hydochlorides of 1-Aryl-2-phenylethylamines in 95% Ethanol [CD, Maximum $\Delta\epsilon$ (nm)[a]; UV, λ_{max} nm ($\epsilon \times 10^{-3}$)]

Compd. No.		^1L_a Band	^1L_b Band				
13	CD	+13.62(217)	+0.16(246)	+0.24(252)	+0.32(257)	+0.21(266)	
	UV	205(15.2)	248[b](0.20)	252(0.28)	258(0.37)	264(0.31)	268(0.20)
14	CD	+2.18(218) +5.64(233)	+0.31(251)	+0.44(258)	+0.45(265)	+0.33(271)	+0.24(279)
	UV	228(11.6)	254[b](0.45) 281(1.06)	260[b](0.72)	266[b](0.96)	270[b](1.07)	275(1.14)
15	CD	+8.66(221) +4.61(236)	+0.15(256)	−0.10(261)	+0.08(265)	−0.13(267)	
	UV	207(10.3) 233(7.85)	265[b](0.23)	268[b](0.13)			
16	CD	+21.24(216)	+0.20(246)	+0.30(251)	+0.39(258)	+0.27(265)	
	UV	205(15.6)	248[b](0.19)	253(0.27)	258(0.36)	265(0.29)	268(0.19)
17	CD	+3.18(219) +8.87(232)	+0.33(251)	+0.42(257)	+0.45(265)	+0.25(270)	+0.16(279)
	UV	228(12.4)	254[b](0.49) 281(1.13)	259[b](0.76)	265[b](1.01)	270[b](1.12)	274(1.31)
18	CD	+9.68(222) +6.91(232)	+0.20(256)	−0.07(260)	+0.09(265)	−0.09(267)	
	UV	207(10.9) 234(8.09)	263[b](0.16)	265[b](0.09)			
19	CD	+21.03(217)	+0.17(247)	+0.27(252)	+0.34(258)	+0.25(265)	
	UV	205(17.1)	247[b](0.19)	253(0.27)	258(0.37)	254(0.31)	268(0.21)
20	CD	+3.64(218) +7.00(233)	+0.37(251)	+0.48(258)	+0.49(265)	+0.28(270)	+0.16(279)
	UV	229(12.4)	254[b](0.52) 281(1.18)	260[b](0.77)	265[b](1.05)	270[b](1.18)	275(1.36)
21	CD	+10.04(223) +6.26(233)	+0.24(256)	−0.08(261)	+0.10(264)	−0.11(267)	
	UV	207(9.74) 233(7.32)	264[b](0.16)	268(0.08)			
39[c]	CD	+20.36(217)	+0.21(245)	+0.30(252)	+0.41(258)	+0.28(265)	
	UV	205(14.9)	249[b](0.21)	252(0.30)	258(0.38)	264(0.32)	268(0.22)
40[c]	CD	+4.80(218) +6.48(233)	+0.36(252)	+0.47(258)	+0.52(265)	+0.33(270)	+0.22(278)
	UV	229(11.3)	255[b](0.48) 281(1.06)	260[b](0.73)	266[b](0.97)	270[b](1.06)	275(1.23)
41[c]	CD	+10.12(221) +5.96(234)	+0.49(256)	−0.19(261)	+0.21(265)	−0.23(268)	
	UV	208(9.71) 232(7.31)	264[b](0.18)	268[b](0.09)			

a) Concentration, 2.5—3.5×10^{-3} M; temperature, 25—28°C; cell length, 0.1—0.5 cm.
b) Shoulder.
c) Hydrochlorides of (1*S*, 1′*S*)-(+)-1-aryl-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenylethylamines prepared by the method of refs. 1 and 3.

In order to determine the absolute configurations of these optically pure amines, we attempted to measure the circular dichroism (CD) spectra of the hydrochlorides of the amines **13**—**21** and the hydrochlorides of (1*S*, 1′*S*)-(+)-*N*-(2′-hydroxy-1′-isopropylethyl)-1,2-diphenyletylamine (**39**),1) (1*S*, 1′*S*)-(+)-*N*-(2′-hydroxy-1′-isopropylethyl)-1-(4-methoxyphenyl)-2-phenylethylamine (**40**),1) and (1*S*, 1′*S*)-(+)-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenyl-1-(2-thienyl)ethylamine (**41**).3) The observed CD spectral data are summarized, along with the utraviolet (UV) spectral data, in Table I.

The aromatic quadrant-sector rule7) was applied for the determination of the absolute configurations of tetrahydroisoquinolines,8) morphine, and related compounds.9) Smith *et al.*10) reported the relationship between the Cotton effect and the absolute configurations of 1,2-diphenylethylamine hydrochlorides, and suggested that (1) the two phenyl chromophores do not interact with each other because they are connected through three σ bonds, and (2) the

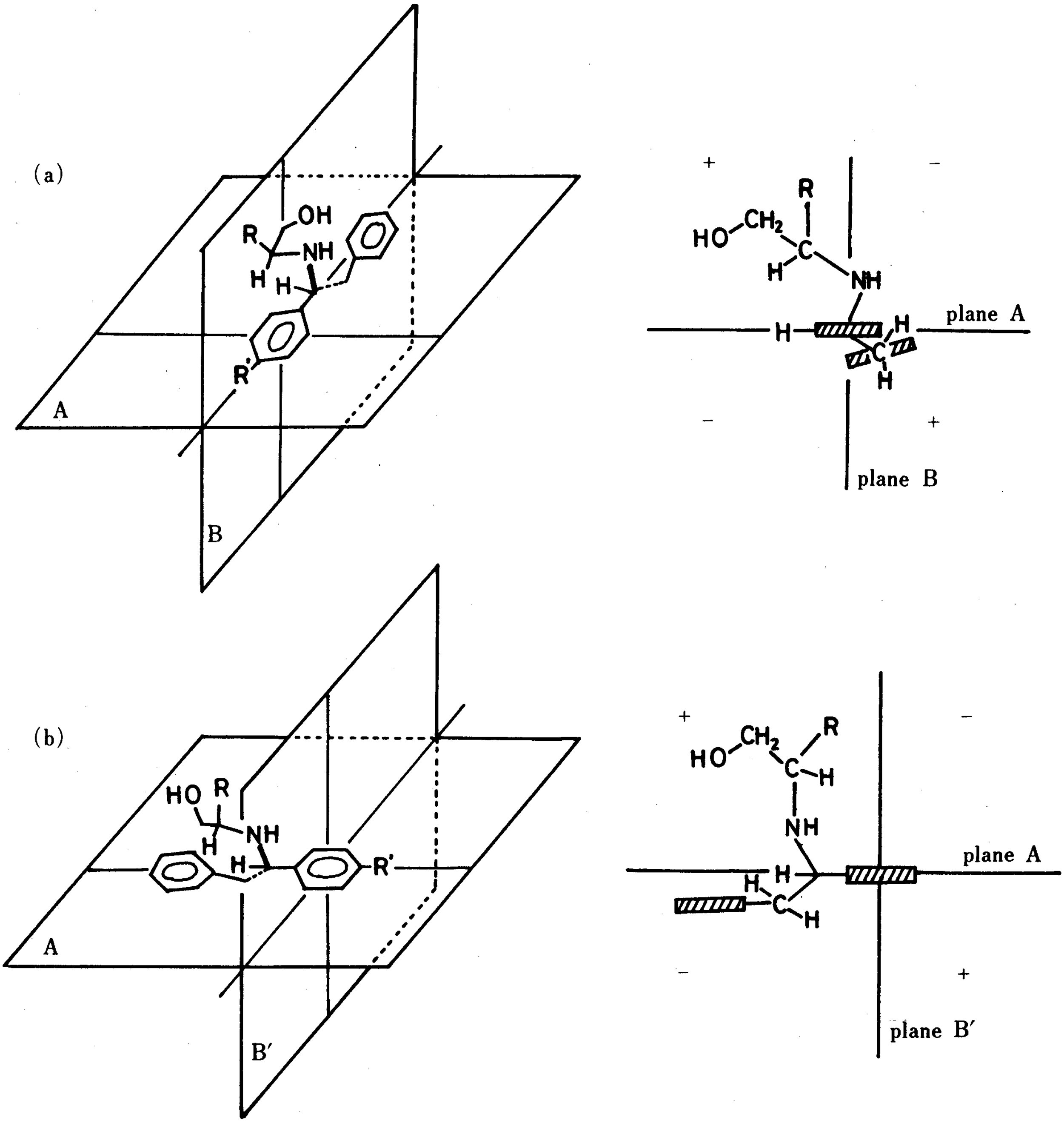


Fig. 1. Quadrant Projection of 1-Aryl-2-phenylethylamines for (a) 210—240 nm Band; (b) 240—280 nm Band

phenyl group at the α-position of the asymmetric carbon atom dominates the CD spectrum, while the phenyl group at the β-position weakly affects it.

We have previously reported that the hydrochlorides of (+)-1-aryl-*N*-(2′-hydroxy-1′-isopropylethyl)-2-phenylethylamines (**39**—**41**) derived from L-valine possess an *S* absolute configuration at the 1-position.[1,3] In this work, we attempted to apply the aromatic quadrant-sector rule to these compounds. The aromatic ring at the 1-position lies on plane A and is bisected by plane B through the 1- and 4-carbon of the aromatic ring, as shown in Fig. 1 (a). These Cotton-effect peaks were observed in the shorter-wavelength region (210—240 nm) and are designated as ^1L_a bands. The other quadrant projection is shown in Fig. 1 (b); here, plane A is placed on the aromatic ring, while plane B′ bisects the aromatic ring through the 2–3 and 5–6 bonds. These Cotton-effect peaks were observed in the longer-wavelength region (240—280 nm) and are designated as ^1L_b bands.

The application of the quadrant-sector rule to these compounds (hydrochlorides of **39**—**41**) predicts that the Cotton effects at the ^1L_a and ^1L_b bands are positive, because the 2′-hydroxy-1′-isopropylethylamino group lies in the positive quadrant and the benzyl group is almost on plane A in each case. Actually, the CD spectra of these compounds showed positive Cotton effects, in accord with the prediction based on the quadrant rule.

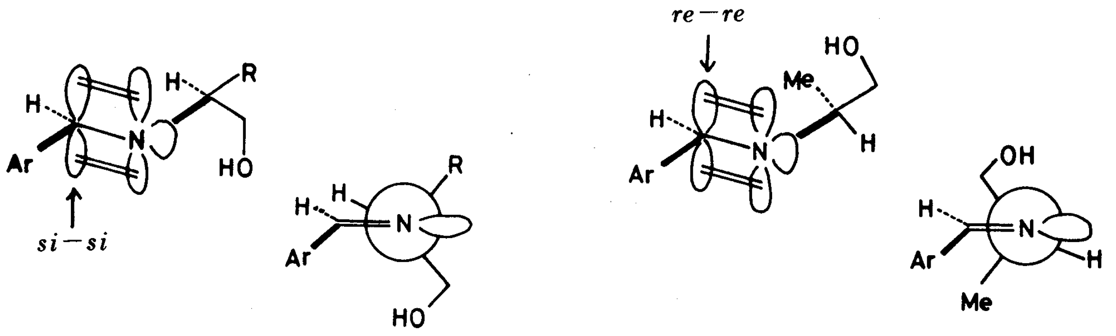
By analogy with **39**—**41**, the quadrant projections of these amines (**13, 14, 16, 17, 19,** and **20**) showed that the 1′-alkyl-2′-hydroxyethylamino group lies in the positive quadrant in Fig. 1 (a) and (b); in fact, the CD spectra of these amines showed positive Cotton effects. Accordingly, the absolute configurations were confirmed to be *S*, and the absolute configurations of the amines (**33, 34, 36,** and **37**) synthesized from D-amino acids were concluded to be *R*.

In the cases of the 2-thienyl compounds (**15, 18,** and **21**) prepared from L-amino acids, the CD spectra for the 220—240 nm bands showed positive Cotton effects as in the cases of the phenyl and 4-methoxyphenyl compounds. The transitions in the 220—240 nm region seemed to be more coherent than those in the 250—270 nm region, which showed that some bands were positive, while others were negative.[7] The aromatic quadrant-sector rule for these compounds (**15, 18,** and **21**) indicates that the 1′-alkyl-2′-hydroxyethylamino group lies in the positive quadrant. Accordingly, the absolute configurations were concluded to be *S*, and it was confirmed that the compounds (**35** and **38**) synthesized from D-amino acids possessed the *R* absolute configuration.

Next, let us discuss the mechanism of this reaction. There seem to be two important factors in this asymmetric reaction. One is the approach of the magnesium atom of the Grignard reagent to the hydroxy group and the nitrogen atom, and the attack of the benzyl anion on the carbon atom at the C=N bond. The other is the restriction of the orientation of the hydroxy group; that is, the hydroxy group was located on either the *si-si* or *re-re* face of the C=N bond. Consideration of a CPK molecular model suggested that the preferred conformations of the C–N bonds are not B-form, but A-form, because of the steric effect of the alkyl and hydroxymethyl groups in the Newman projection for the C–N bond, as shown in Fig. 2.

The chiral azomethines with isopropyl,[1] isobutyl, or *sec*-butyl groups at the α-position reacted with benzylmagnesium chloride to yield optically pure chiral amines with extremely high diastereomer excess. The configurations of the amines obtained from (*E*)-(*S*)-azomethines were (1*S*, 1′*S*), and the amines derived from (*E*)-(*R*)-azomethines had the (1*R*, 1′*R*) configuration. These results confirmed that the attack of the benzyl anion on the (*E*)-(*S*)-azomethines occurred from the *si-si* face, whereas the attack on the (*E*)-(*R*)-compounds occurred from the *re-re* face, because the conformations of the C–N bonds of the azomethines exist in the A-form, as discussed above.

On the other hand, the azomethines having a methyl group at the α-position reacted with benzylmagnesium chloride to give the diastereomeric mixtures. The change of the alkyl group from isopropyl, isobutyl, or *sec*-butyl to methyl affected the stereoselectivity because of the decrease in the bulkiness of the alkyl group. Hence, it seems that the azomethines (**4**—**6**) derived from (*S*)-alaninol (**1**) exist partly in the B-form; *i.e.*, the hydroxy group is located on the *re-re* face of the C=N bond, as shown in Fig. 2.



(*E*)-(*S*) A-form

(*E*)-(*S*) B-form

Fig. 2

Experimental

The IR spectra were recorded with a Hitachi 260-10 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 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.

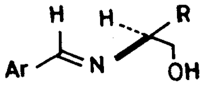
(*E*)-(*S*)-*N*-(2-Hydroxy-1-methylethyl)arylmethylideneamines (4—6)——Anhydrous $MgSO_4$ (5 g) was added to a mixture of **1** (1.5 g, 20 mmol) and arylaldehyde (20 mmol) in ether (20 ml), and the whole was gently stirred at room temperature for 18 h. The solid was then filtered off, and the solvent was removed under reduced pressure. The residue was allowed to stand at room temperature to give colorless crystals. The experimental data for **4**—**6** are summarized in Tables II and III.

(*E*)-(*S*)-*N*-(2-Hydroxy-1-isobutylethyl)arylmethylideneamines (7—9)——A mixture of **2** (2.34 g, 20 mmol) and arylaldehyde (20 mmol) in benzene (50 ml) was refluxed for 3 h using a Dean-Stark trap. The mixture was then concentrated under reduced pressure, and the residual oily product was distilled under reduced pressure. The experimental data for **7**—**9** are summarized in Tables II and III.

(*E*)-(*S*)-*N*-1-(*sec*-Butyl-2-hydroxyethyl)arylmethylideneamines (10—12)——A mixture of **3** (2.34 g, 20 mmol) and arylaldehyde (20 mmol) in benzene (5 ml) was refluxed for 3 h as described above. After the removal of the solvent, a colorless oily product was distilled under reduced pressure. The experimental data for **10**—**12** are summarized in Tables II and III.

(1*S*, 1′*S*)-1-Aryl-*N*-(2′-hydroxy-1′-methylethyl)-2-phenylethylamines (13—15)——A suspension of benzylmagnesium chloride (20 mmol in 7 ml of THF) was slowly added, drop by drop, to a solution of an azomethine (**4**—**6**) (5 mmol) in THF (5 ml) at −5—0 °C under a nitrogen atmosphere. The resulting mixture was maintained at the same temperature and stirred for 5 h. The mixture was then poured into an ammonium chloride solution (5 ml) and extracted with ether. The extract was dried over anhydrous $MgSO_4$, the solvent was evaporated off, and the oily residue was chromatographed on a column of silica gel, using CH_2Cl_2–ether (9:1); colorless crystals were thus obtained. By observation of their ^{1}H-NMR spectra, these crystals were confirmed to consist of a mixture of two diastereomeric isomers. The mixture was fractionated by rechroma-

TABLE II. (*E*)-(*S*)-*N*-(1-Alkyl-2-hydroxyethyl)arylmethylideneamines (**4**—**12**)



Compd. No.	R	Ar	mp[a] (°C)	bp (°C/mmHg)	Yield[b] (%)	IR, cm^{-1}[c]	
						ν_{OH}	$\nu_{C=N}$
4	Methyl	Phenyl	78—79		85	3200	1645
5	Methyl	4-MeO-C_6H_4-	81—82		83	3250	1635
6	Methyl	2-Thienyl	98—99		78	3225	1625
7	Isobutyl	Phenyl		135/0.4	87	3360	1655
8	Isobutyl	4-MeO-C_6H_4-		161/0.4	83	3340	1645
9	Isobutyl	2-Thienyl		140/0.5	75	3360	1635
10	*sec*-Butyl	Phenyl		135/0.5	88	3360	1655
11	*sec*-Butyl	4-MeO-C_6H_4-		175/2	85	3360	1645
12	*sec*-Butyl	2-Thienyl		148/1	73	3380	1635

a) Recrystallized from *n*-heptane.
b) Isolated yield.
c) Measured in KBr (for solid products) or as a film (for liquid products).

TABLE III. (*E*)-(*S*)-*N*-(1-Alkyl-2-hydroxyethyl)arylmethylideneamines (**4**—**12**)

Compd. No.	MS (*m/e*) M^+	^{1}H-NMR ($CDCl_3$) δ			$[\alpha]_D^{20}$ (*c*, ethanol)
		CH=N[a]	CH_2OH[b]	Others[c]	
4	163	8.31	3.70	1.22(3H, d, 6.3, $CH-C\underline{H}_3$)	+43.3°(0.47)
5	193	8.25	3.68	1.20(3H, d, 6.3, $CH-C\underline{H}_3$); 3.84(3H, s, OCH_3); 6.90(2H, d, 8.8, aromatic H); 7.66(2H, d, 8.8, aromatic H);	+47.1°(0.45)
6	169	8.41	3.68	1.20(3H, d, 6.3, $CH-C\underline{H}_3$);	+73.3°(0.38)
7	205	8.27	3.70	0.87(3H, d, 6.1, $CH-C\underline{H}_3$); 0.91(3H, d, 6.1, $CH-C\underline{H}_3$)	−67.1°(0.56)
8	235	8.12	3.68	0.86(3H, d, 6.1, $CH-C\underline{H}_3$); 0.90(3H, d, 6.1, $CH-C\underline{H}_3$); 3.83(3H, s, $OC\underline{H}_3$); 6.89(2H, d, 8.8, aromatic H); 7.63(2H, d, 8.8, aromatic H);	−55.2°(0.50)
9	211	8.37	3.68	0.87(3H, d, 6.1, $CH-C\underline{H}_3$); 0.90(3H, d, 6.1, $CH-C\underline{H}_3$)	−83.0°(0.54)
10	205	8.25	3.80	0.92(3H, t 6.3, $CH_2-C\underline{H}_3$); 0.95(3H, d, 6.3, $CH-C\underline{H}_3$)	−68.3°(0.56)
11	235	8.13	3.81	0.90(3H, t, 6.3, $CH_2-C\underline{H}_3$); 0.94(3H, d, 6.3, $CH-C\underline{H}_3$); 3.83(3H, s, OCH_3); 6.89(2H, d, 8.8, aromatic H); 7.63(2H, d, 8.8, aromatic H);	−68.2°(0.63)
12	211	8.32	3.76	0.90(3H, t, 6.3, $CH_2-C\underline{H}_3$); 0.93(3H, d, 6.3, $CH-C\underline{H}_3$)	−87.0°(0.54)

a) One proton and singlet.
b) Two protons and AB_2 pattern.
c) Proton numbers, splitting patterns, coupling constant (Hz), and assignment in parentheses.

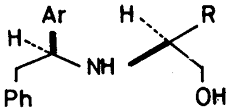
tography on a column to give the pure (1*S*, 1′*S*) compound. The experimental data for **13**—**15** are summarized in Table IV.

The free bases were treated with a hydrogen chloride methanol solution to give the hydrochlorides of **13**—**15**. The experimental data are summarized in Table V.

(1*S*, 1′*S*)-1-Aryl-*N*-(2′-hydroxy-1′-isobutylethyl)-2-phenylethylamines (16—18)———A suspension of benzylmagnesium chloride (20 mmol in 7 ml of THF) was slowly added, drop by drop, to a solution of an azomethine (7—9) (5 mmol) in THF (5 ml) at room temperature under a nitrogen atmosphere, after which stirring was continued at 45°C for 5 h. The reaction mixture was then worked-up as described above. **16—18** were thus obtained as colorless crystals. These free bases were treated with a hydrogen chloride methanol solution to give the hydrochlorides of **16—18**. The experimental data for these compounds are summarized in Tables IV and V.

(lS, 1′S)-1-Aryl-*N*-(1′-*sec*-butyl-2′-hydroxyethyl)-2-phenylethylamines (19—21)——A suspension of benzylmagnesium chloride (20 mmol in 7 ml of THF) was slowly added, drop by drop, to a solution of an azomethine (**10—12**) (5 mmol) in THF (5 ml) under a nitrogen atmosphere. The resulting mixture was stirred at 45°C for 5 h. After treatment as described above, **19—21** were obtained as colorless oils. The base compounds were converted into the hydrochlorides of **19—21** by treatment with a hydrogen chloride methanol solution. The experimental data for these compounds are summarized in Tables IV and V.

TABLE IV. (1*S*, 1′*S*)-1-Aryl-*N*-(1′-alkyl-2′-hydoxyethyl)-2-phenylethylamines (**13—21**)



Compd. No.	R	Ar	Appearance[a]	mp (°C)	Yield[b] (%)	MS(*m*/*e*) M$^+$
13	Methyl	Phenyl	Nee	66—67	53	255
14	Methyl	4-MeO-C_6H_4-	Col	80—81	51	285
15	Methyl	2-Thienyl	Pri	68—69	44	261
16	Isobutyl	Phenyl	Pla	79—80	85	297
17	Isobutyl	4-MeO-C_6H_4-	Nee	67—68	84	327
18	Isobutyl	2-Thienyl	Pri	73—74	76	303
19	*sec*-Butyl	Phenyl	Oil		83	297
20	*sec*-Butyl	4-MeO-C_6H_4-	Oil		80	327
21	*sec*-Butyl	2-Thienyl	Oil		75	303

Compd. No.	^{1}H-NMR ($CDCl_3$) δ			
	ArCH-N[c]	CH_2-O[d]	$PhCH_2$[e]	Others[f]
13	3.86(7.0)	3.48(3.9, 10.5) 3.09(5.1, 10.5)	2.91(7.0)	0.90(3H, d, 6.4, CH–C$\underline{H}_3$)
14	3.84(6.8)	3.45(4.2, 10.7) 3.10(5.2, 10.7)	2.87(6.8)	0.88(3H, d, 6.6, CH–C$\underline{H}_3$) 3.73(3H, s, OCH_3)
15	4.18(7.1)	3.47(3.9, 10.5) 3.13(4.9, 10.5)	2.99(7.1)	0.95(3H, d, 6.3, CH–C$\underline{H}_3$)
16	3.86(7.1)	3.52(3.9, 10.5) 3.09(4.1, 10.5)	2.91(7.1)	0.64(3H, d, 6.3, CH–C$\underline{H}_3$) 0.77(3H, d, 6.3, CH–C$\underline{H}_3$)
17	3.82(7.0)	3.53(3.9, 10.7) 3.11(4.2, 10.7)	2.89(7.0)	0.66(3H, d, 6.4, CH–C$\underline{H}_3$) 0.78(3H, d, 6.4, CH–C$\underline{H}_3$) 3.79(3H, s, OCH_3)
18	4.17(7.1)	3.52(3.7, 11.0) 3.13(3.9, 11.0)	3.00(7.1)	0.70(3H, d, 6.6, CH–C$\underline{H}_3$) 0.80(3H, d, 6.6, CH–C$\underline{H}_3$)
19	3.86(7.1)	3.50(4.2, 11.0) 3.24(5.1, 11.0)	2.93(7.1)	0.74(3H, d, 6.6, CH–C$\underline{H}_3$) 0.73(3H, t, 7.3, CH_2–C$\underline{H}_3$)
20	3.81(7.1)	3.50(4.2, 10.7) 3.24(5.4, 10.7)	2.90(7.1)	0.74(3H, d, 6.6, CH–C$\underline{H}_3$) 0.75(3H, t, 7.2, CH_2–C$\underline{H}_3$) 3.78(3H, s, OCH_3)
21	4.17(7.1)	3.50(3.9, 11.0) 3.28(4.9, 11.0)	3.01(7.1)	0.78(3H, d, 6.6, CH–C$\underline{H}_3$) 0.77(3H, t, 7.1, CH_2–C$\underline{H}_3$)

a) Recrystallized from *n*-heptane. Nee = needles; Col = columns; Pri = prisms; Pla = plates.
b) Isolated yield.
c) One proton and triplet; coupling constant (Hz) in parentheses.
d) Double doublet; coupling constant (Hz) in parentheses.
e) Two protons and doublet; coupling constant (Hz) in parentheses.
f) Proton numbers, splitting patterns, coupling constant (Hz) and assignment in parentheses.

TABLE V. Hydrochlorides of (1*S*, 1′*S*)-1-Aryl-*N*-(1′-alkyl-2′-hydroxyethyl)-2-phenylethylamines (**13**—**21**)

Compd. No.	mp (°C)	Appearance[a]	$[\alpha]_D^{20}$ (*c*, ethanol)	Formula	Analysis, (%) Calcd (Found) C	H	N
13	246—247	Col	+82.9°(0.51)	$C_{17}H_{21}NO \cdot HCl$	69.96	7.60	4.80
					(69.72	7.62	4.63)
14	235—236	Nee	+116.9°(0.48)	$C_{18}H_{23}NO_2 \cdot HCl$	67.17	7.52	4.35
					(67.43	7.72	4.38)
15	236—237	Nee	+50.4°(0.42)	$C_{15}H_{19}NOS \cdot HCl$	60.49	6.77	4.70
					(60.31	6.90	4.73)
16	267—268	Nee	+88.6°(0.45)	$C_{20}H_{27}NO \cdot HCl$	71.94	8.45	4.20
					(71.65	8.53	4.08)
17	216	Col	+113.7°(0.48)	$C_{21}H_{29}NO_2 \cdot HCl$	69.31	8.31	3.85
					(69.18	8.37	3.67)
18	239—240	Nee	+62.0°(0.37)	$C_{18}H_{25}NOS \cdot HCl$	63.60	7.71	4.12
					(63.85	7.88	4.05)
19	229—230	Pla	+91.2°(0.46)	$C_{20}H_{27}NO \cdot HCl$	71.91	8.45	4.19
					(72.12	8.64	4.11)
20	195—196	Pla	+121.1°(0.41)	$C_{21}H_{29}NO_2 \cdot HCl$	69.31	8.31	3.85
					(69.01	8.43	3.69)
21	214—215	Pri	+70.0°(0.47)	$C_{18}H_{25}NOS \cdot HCl$	63.60	7.71	4.12
					(63.48	7.79	3.97)

a) Recrystallized from ethanol. Col=columns; Nee=needles; Pla=plates; Pri=prisms.

(*S*)-*N*-(2′-Hydroxy-1′-methylethyl)-2-phenylethylideneamine (22)———A mixture of **1** (0.75 g, 10 mmol) and phenylacetaldehyde (1.2 g, 10 mmol) was stirred at room temperature for 10 min. Ether (10 ml) was then added, and the solution was dried over anhydrous $MgSO_4$. The solvent was quickly evaporated off under reduced pressure to yield a colorless oil (1.65 g, 93%), which showed one peak in GC. IR (film) : 3400 (OH), 1640(C=N)cm^{-1}. MS *m/e*: 177 (M$^+$). ^{1}H-NMR ($CDCl_3$) δ: 1.17(3H, d, *J*=6.1 Hz, CH-C$\underline{H}_3$).

(1*R*, 1′*S*)-*N*-(2′-Hydroxy-1′-methylethyl)-1,2-diphenylethylamine (23)———A phenyllithium ethereal solution [prepared from lithium wire (0.37 g, 53 mmol) and bromobenzene (3.93 g, 25 mmol) in ether (20 ml)] was slowly added, drop by drop, into a solution of **22** (0.89 g, 5 mmol) in ether (10 ml) under a nitrogen atmosphere. After being stirred at room temperature for 5 h, the mixture was poured into ice water; the organic layer was then extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure, and the residue was chromatographed over silica gel with CH_2Cl_2–ether (9 : 1). **23** (0.3 g) was thus obtained as a colorless oil. IR (film): 3350 (OH) cm^{-1}. MS *m/e*: 255 (M$^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, *J*=6.4 Hz, CH-C$\underline{H}_3$), 2.87 (2H, AB_2 pattern, *J*=9.3 Hz, $PhCH_2$), 3.05 (1H, dd, *J*=8.3 and 10.3 Hz, CH_2-O), 3.33 (1H, dd, *J*=4.4 and 10.3 Hz, CH_2-O), 4.02 (1H, AB_2 pattern, *J*=9.3 Hz, PhCH-N).

This compound was treated with a hydrogen chloride methanol solution to give the hydrochloride of **23**. Recrystallization from THF gave colorless plates, mp 244—245°C. $[\alpha]_D^{25}$ −85.1° (*c*=0.42, ethanol).

(1*R*, 1′*S*)-*N*-(2′-Hydroxy-1′-methylethyl)-1-(*p*-methoxyphenyl)-2-phenylethylamine (24)———An ethereal solution (25 ml) of *n*-butyllithium (2 M, 12.5 ml) was added, drop by drop, to *p*-iodoanisole (5.85 g, 25 mmol) in ether (20 ml). After being stirred at room temperature for 1 h, the *p*-methoxyphenyllithium ethereal solution was added, drop by drop, to **22** (0.89 g, 5 mmol) in ether (10 ml) at −10°C over 30 min under a nitrogen atmosphere. Stirring was continued for 5 h at −15—−10°C, then the mixture was poured into ice water and extracted with ether. After the removal of the solvent, the residue was chromatographed over silica gel with CH_2Cl_2–ether (4 : 1). **24** (0.2 g) was thus obtained as a colorless oil. IR (film): 3350(OH) cm^{-1}. MS *m/e*: 285 (M$^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.82 (3H, d, *J*=6.3 Hz, CH-C$\underline{H}_3$), 2.87 (2H, AB_2 pattern, *J*=11.8 Hz, $PhCH_2$), 3.04 (1H, dd, *J*=8.3 and 10.5 Hz, CH_2-O), 3.33 (1H, dd, *J*=4.4 and 10.5 Hz, CH_2-O), 3.79 (3H, s, OCH_3), 3.97(1H, AB_2 pattern, *J*=11.8 Hz, ArCH-N), 6.85(2H, d, *J*=8.8 Hz, aromatic H), 7.23 (2H, d, *J*=8.8 Hz, aromatic H), 7.2(5H, aromatic H).

The hydrochloride of **24** was recrystallized from cyclohexane–benzene to give colorless prisms, mp 185—188°C. $[\alpha]_D^{25}$ −46.3° (*c*=0.25, ethanol).

(*E*)-(*R*)-*N*-2-Hydroxy-1-methylethyl)arylmethylideneamines (27—29)———Anhydrous $MgSO_4$ (5 g) was added to a mixture of **25** (1.5 g, 20 mmol) and arylaldehyde (20 mmol) in ether (20 ml), after which the mixture was stirred at room temperature for 7 h. The reaction mixture was then treated in the manner described for *S* compounds to give colorless crystals (**27**—**29**). The structures of **27**—**29** were indistinguishable from those of

4—**6**, respectively, by comparison of their IR, MS, and ^{1}H-NMR spectra. The specific rotations of **27**, **28**, and **29** in ethanol were $[\alpha]_D^{20}$ $-44.0°$ (c=0.47), $-49.8°$ (c=0.49), and $-74.2°$ (c=0.47) respectively.

(*E*)-(*R*)-*N*-(2-Hydroxy-1-isobutylethyl)arylmethylideneamines (30—32)——The condensation of **26** (2.34 g, 20 mmol) with arylaldehyde (20 mmol) in benzene (50 ml) in the manner described for **7**—**9** gave **30**—**32**. The structures of **30**—**32** were indistinguishable from those of **7**—**9**, respectively, by comparison of their IR, MS, and ^{1}H-NMR spectra. The specific rotations of **30**, **31**, and **32** in ethanol were $[\alpha]_D^{25}$ $+65.9°$ (c=0.66), $+55.1°$ (c=0.49), and $+83.2°$ (c=0.50) respectively.

(1*R*, 1′*R*)-1-Aryl-*N*-(2′-hydroxy-1′-methylehyl)-2-phenylethylamines (33—35)——A suspension of benzylmagnesium chloride (20 mmol in 7 ml of THF) was added, drop by drop, into a solution of an azomethine (**27**—**29**) (5 mmol) in THF (5 ml) at room temperature under a nitrogen atmosphere. After being stirred at 45 ° for 5 h, the reaction mixture was worked-up as described for the *S* compounds. **33**—**35** were thus obtained as colorless crystals; the structures of these compounds were indistinguishable from those of **13**—**15**, respectively, by comparison of their IR, MS, and ^{1}H-NMR spectra.

The free bases were converted into hydrochlorides; the specific rotations of the hydrochlorides of **33**, **34**, and **35** in ethanol were $[\alpha]_D^{20}$ $-83.5°$ (c=0.48), $-117.0°$ (c=0.44), and $-51.2°$ (c=0.44), respectively.

(1*R*, 1′*R*)-1-Aryl-*N*-(2′-hydroxy-1′-isobutylethyl)-2-phenylethylamines (36—38)——The reaction of an azomethine (**30**—**32**) (5 mmol) with benzylmagnesium chloride (20 mmol in 7 ml of THF) in THF (5 ml), in the manner described for the *S* compounds, gave colorless crystals (**36**—**38**). The structures of **36**—**38** were indistinguishable from those of **16**—**18** respectively, by comparison of their IR, MS, and ^{1}H-NMR spectra.

The free bases were converted into hydrochlorides; the specific rotations of the hydrochlorides of **36**, **37**, and **38** in ethanol with $[\alpha]_D^{20}$ $-94.8°$ (c=0.49), $-110.3°$ (c=0.41), and $-63.0°$ (c=0.42), respectively.

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