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Asymmetric α-Substituted Phenethylamines. VI.[1] Synthesis and Analgesic Activity of Optically Pure (*R*)- and (*S*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamines

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Optically pure (*R*)- and (*S*)-*N*-alkyl-1-cyclohexyl-2-phenylethylamine hydrochlorides (**9a—r**) were synthesized from (*R*)- and (*S*)-phenylglycine by means of a simple procedure. The analgesic activity of these compounds was evaluated by the acetic acid writhing method, and **9e**, **9f**, **9i—k**, and **9m** showed more potent activity than (−)-pentazocine hydrochloride. Moreover, the analgesic activities of **9a—e**, **9h**, **9i**, **9m**, and **9o—r** were not antagonized by naloxone.

Keywords——absolute configuration; acetic acid writhing method; analgesic activity; chiral 1,3-oxazolidine; 1-cyclohexyl-2-phenylethylamine; Grignard reaction; naloxone antagonism; optically pure amine; (*R*)-phenylglycine; (*S*)-phenylglycine

In this paper, we wish to report that new optically pure (*R*)- and (*S*)-*N*-alkyl-1-cyclohexyl-2-phenylethylamines show analgesic activity more potent than that of (−)-pentazocine hydrochloride, and the activities of these compounds were not antagonized by (−)-naloxone hydrochlolide.

Synthesis of Optically Pure Amines

We have reported the synthesis of (*R*)-1-cyclohexyl-*N*-2′-hydroxy-1′-phenylethyl-*N*-methyl-2-phenylethylamine (**4**), *via* condensation of (*R*)-2-*N*-methylamino-2-phenylethanol (**2**) with cyclohexanecarbaldehyde.[1] However, this procedure was considered to be unsuitable for the synthesis of medicinal compounds because the reaction of (2*S*,4*R*)-2-cyclohexyl-*N*-methyl-4-phenyl-1,3-oxazolidine (**3**) with the Grignard reagent proceeds with only 22—62% diastereoselectivity.

Thus, an alternative route was sought for the synthesis of the optically pure compounds. Condensation of (*R*)-2-amino-2-phenylethanol (**1**) with cyclohexanecarbaldehyde gave 2-cyclohexyl-4-phenyl-1,3-oxazolidine (**5**), which was confirmed to consist of two diastereomers (60 : 40), depending on the asymmetric center at the 2-position of the 1,3-oxazolidine ring, by 400 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy. However, this diastereomeric mixture (**5** and **5′**) could be reacted with benzylmagnesium chloride to give (1*R*,1′*R*)-1-cyclohexyl-*N*-2′-hydroxy-1′-phenylethyl-2-phenylethylamine (**6**) as an optically pure single diastereomer. This characteristic reaction was considered to involve attack by one Grignard reagent molecule on the oxygen of **5** and **5′**; after *cis*-imine rearrangement to the *trans*-isomer (**7**), another Grignard reagent molecule attacks from the *re*-face at the carbon–nitrogen double bond of **7**, as shown in Chart 2. Compound **6** was derived to **4** and the absolute configuration of **6** was thus elucidated as *R*, because the structure of **4** has been determined by X-ray analysis.[1]

Compound **6** was hydrogenolyzed with a Pd–carbon catalyst in acetic acid solution to

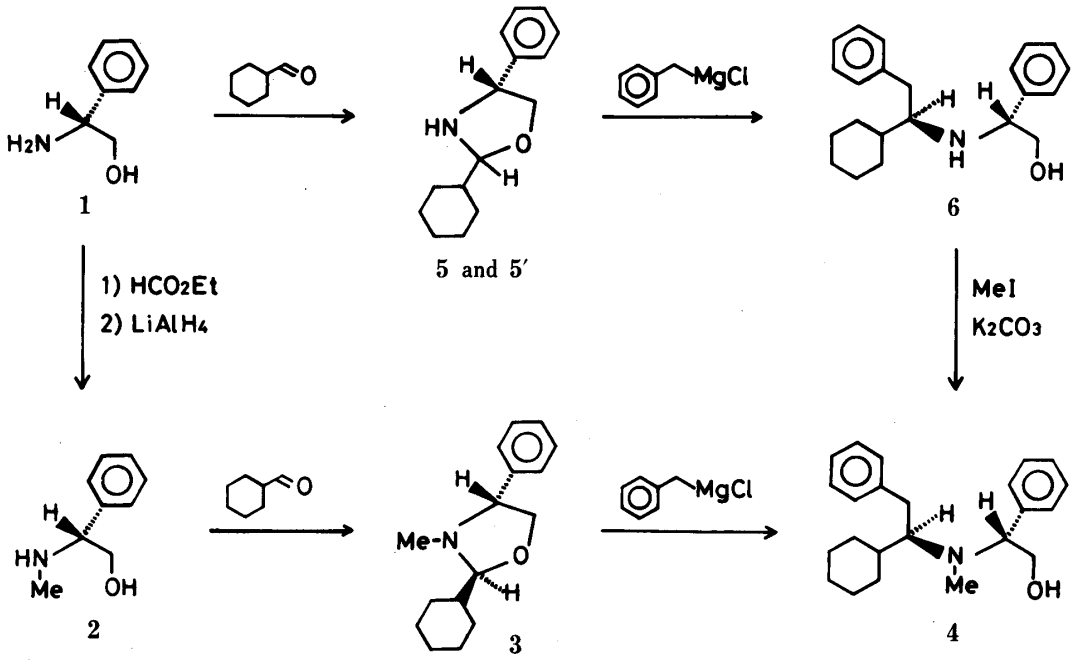

Chart 1

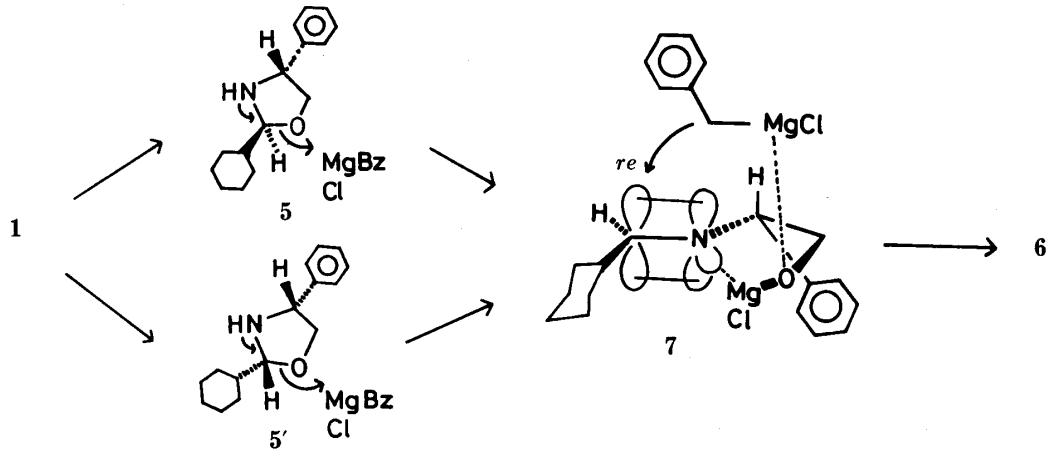

Chart 2

give (*R*)-1-cyclohexyl-2-phenylethylamine (**8a**) in 95.4% yield, while (*R*)-1-cyclohexyl-*N*-methyl-2-phenylethylamine (**8b**) was obtained from **4**.[1] Compounds **8a** and **8b** were derived to (1*S*,1′*R*)-*N*-1′-cyclohexyl-2′-phenylethyl-1-methoxy-1-trifluoromethylphenylacetamide by reaction with (*S*)-1-methoxy-1-trifluoromethylphenylacetyl chloride (Mosher's reagent), and these amines were confirmed to consist of one isomer by ^{1}H-NMR spectroscopy.

Compound **8a** was condensed with alkanals, followed by reduction with sodium borohydride to give (*R*)-*N*-alkyl-1-cyclohexyl-2-phenylethylamines (**8d**, **8f**, **8g**, and **8k**). On the other hand, the reaction of **8b** with alkyl halides gave (*R*)-*N*-alkyl-1-cyclohexyl-*N*-methyl-2-phenylethylamines (**8c**, **8e**, **8h**, **8j**, and **8l**), and the reaction of **8a** with cyclopropylmethyl bromide gave **8i**.

The structures of these amine compounds (**8a**—**l**) were confirmed by mass and ^{1}H-NMR spectroscopic analyses. The experimental data are summarized in Tables I and II. (*S*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamines (**8m**—**r**) were synthesized from (*S*)-1-amino-1-phenylacetic acid by the same procedure as used for the corresponding *R*-isomers.

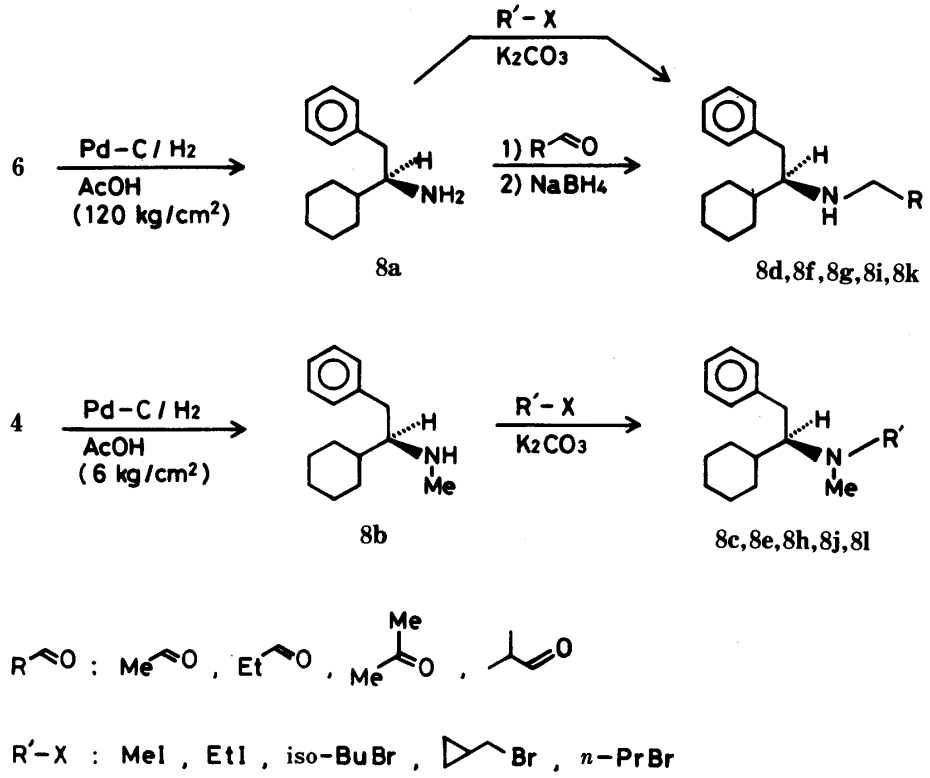

Chart 3

TABLE I. (*R*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamines (**8a**—**l**)

Compd. No.	R^1	R^2	Yield[a] (%)	MS *m/z* CI	MS *m/z* EI		
				($M.H^+$)	($M^+ - PhCH_2$)	($M^+ - C_6H_{11}$)	Others
8a	H	H	95.4	204	112	120	
8b	H	Me	94.6	218	126	134	
8c	Me	Me	85.4	232	140	148	
8d	H	Et	83.7	232	140	148	
8e	Me	Et	92.5	246	154	162	
8f	H	iso-Pr	79.2	246	154	162	230 ($M^+ - CH_3$)
8g	H	iso-Bu	76.9	260	164	176	216 ($M^+ - C_3H_7$)
8h	Me	iso-Bu	88.3	274	182	190	230 ($M^+ - C_3H_7$)
8i	H	$CH_2CH(CH_2)_2$	77.3	258	166	174	216 ($M^+ - C_3H_5$)
8j	Me	$CH_2CH(CH_2)_2$	71.2	271	180	188	230 ($M^+ - C_3H_5$)
8k	H	*n*-Pr	85.3	246	154	162	216 ($M^+ - C_2H_5$)
8l	Me	*n*-Pr	64.0	260	164	176	230 ($M^+ - C_2H_5$)

a) The yields are for purified products isolated by column chromatography.

The free bases (**8a**—**r**) were converted to the hydrochlorides (**9a**—r), colorless needles, by treatment with hydrogen chloride–methanol solution. The experimental data for **9a**—**r** are summarized in Table III.

Analgesic Activity

The optically pure (*R*)- and (*S*)-*N*-alkyl-1-cyclohexyl-2-phenylethylamine hydrochlorides (**9a**—**r**) were evaluated for analgesic activity in mice by using the acetic acid writhing method. The test compounds were dissolved in saline and the solutions were administered sub-

TABLE II. (*R*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamines (**8a—l**)

Compd. No.	^{1}H-NMR (400 MHz) in $CDCl_3$
8a	2.38 (1H, dd, J=9.8, 13.2 Hz, $PhCH_2CH$), 2.88 (1H, dd, J=3.9, 13.2 Hz, $PhCH_2CH$), 2.78 (1H, dt, J=3.9, 9.8 Hz, $NCHCH_2$)
8b	2.17 (3H, s, NCH_3), 2.49 (1H, dd, J=8.6, 13.2 Hz, $PhCH_2CH$), 2.64 (1H, dd, J=4.4, 13.2 Hz, $PhCH_2CH$), 2.43 (1H, dt, J=4.4, 8.6 Hz, $NCHCH_2$)
8c	2.26 (6H, s, NCH_3), 2.56 (1H, dd, J=5.4, 13.9 Hz, $PhCH_2CH$), 2.82 (1H, dd, J=6.1, 13.9 Hz, $PhCH_2CH$)
8d	0.96 (3H, t, J=7.1 Hz, CH_2CH_3), 2.47 (1H, dq, J=7.1, 11.2 Hz, CH_2CH_3), 2.58 (1H, dq, J=7.1, 11.2 Hz, CH_2CH_3)
8e	0.96 (3H, t, J=7.1 Hz, CH_2CH_3), 2.27 (3H, s, NCH_3)
8f	0.83 (3H, d, J=6.1 Hz, $CHCH_3$), 0.95 (3H, d, J=6.1 Hz, $CHCH_3$), 2.52 (1H, dd, J=7.7, 12.9 Hz, $PhCH_2CH$), 2.75 (1H, dd, J=5.4, 12.9 Hz, $PhCH_2CH$), 2.60 (1H, ddd, J=3.7, 5.4, 7.7 Hz, $NCHCH_2$)
8g	0.75 (3H, d, J=6.6 Hz, $CHCH_3$), 0.76 (3H, d, J=6.6 Hz, $CHCH_3$), 2.22 (1H, dd, J=6.6, 11.4 Hz, NCH_2CH), 2.35 (1H, dd, J=6.6, 11.4 Hz, NCH_2CH), 2.51 (1H, dd, J=8.5, 14.7 Hz, $PhCH_2CH$), 2.53 (1H, dd, J=8.5, 14.7 Hz, $PhCH_2CH$)
8h	0.73 (3H, d, J=6.6 Hz, $CHCH_3$), 0.76 (3H, d, J=6.6 Hz, $CHCH_3$), 2.11 (1H, dd, J=7.2, 12.5 Hz, NCH_2CH), 2.15 (1H, dd, J=7.2, 12.5 Hz, NCH_2CH), 2.20 (3H, s, NCH_3), 2.59 (1H, dd, J=6.1, 13.9 Hz, $PhCH_2CH$), 2.79 (1H, dd, J=6.1, 13.9 Hz, $PhCH_2CH$), 2.52 (1H, q, J=6.1 Hz, $NCHCH_2$)
8i	2.19 (1H, dd, J=7.1, 11.8 Hz, NCH_2CH), 2.44 (1H, dd, J=6.6, 11.8 Hz, NCH_2CH), 2.52 (1H, dd, J=8.8, 12.2 Hz, $PhCH_2CH$), 2.57 (1H, dd, J=4.2, 8.8 Hz, $PhCH_2CH$)
8j	2.24 (1H, dd, J=6.4, 12.7 Hz, NCH_2CH), 2.32 (1H, dd, J=6.3, 12.7 Hz, NCH_2CH), 2.34 (3H, s, NCH_3), 2.59 (1H, dd, J=6.1, 13.4 Hz, $PhCH_2CH$), 2.77 (1H, dd, J=6.1, 13.4 Hz, $PhCH_2CH$), 2.66 (1H, q, J=6.1 Hz, $NCHCH_2$)
8k	0.78 (3H, t, J=7.3 Hz, CH_2CH_3), 2.39 (1H, ddd, J=6.6, 7.8, 11.2 Hz, NCH_2CH_2), 2.51 (1H, ddd, J=6.6, 7.8, 11.2 Hz, NCH_2CH_2)
8l	0.79 (3H, t, J=7.3 Hz, CH_2CH_3), 2.23 (3H, s, NCH_3)

cutaneously (s.c.) to the animals.

The fifty percent inhibition dose (ID_{50}) of each compound was determined. The ID_{50} values and the 95% confidence limits (CL) were estimated by the method of Litchfield and Wilcoxon.[2,3] The ID_{50} values of **9a—r** are summarized in Table IV. The results for the hydrochlorides of (−)-pentazocine and (−)-morphine are included for comparison.

The ID_{50} values of **9c—f**, **9h—j**, **9m**, and **9r** were similar to those of (−)-pentazocine hydrochloride. The ID_{50} value of **9k** was about one-tenth of that of (−)-pentazocine hydrochloride. The analgesic activities of the morphine-like *R*-isomers tended to be more potent than those of the *S*-isomers. Interestingly, *S*-isomers such as **9m** and **9n** showed an exciting effect in mice, and appeared to have a potent amphetamine-like activity.

Naloxone Antagonism of Analgesic Activity

These compounds (**9a—r**) were tested for antagonistic activity against naloxone, using the acetic acid writhing method.[2,4] (−)-Naloxone hydrochloride (5 mg/kg) was administered s.c. to mice after injection of each test compound. The naloxone antagonism was estimated from the ratio of the inhibition percent of a test compound together with naloxone to that without naloxone. These results are summarized in Table IV. The analgesic activities of these compounds, except **9f**, **9j**, **9k**, and **9n**, were not antagonized by naloxone. We are continuing the pharmacological evaluation of these compounds.

TABLE III. (*R*)- and (*S*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamine Hydrochlorides (**9a—r**)

Compd. No.	R^1	R^2	mp[a] (°C)	$[\alpha]_D$ (*c*)[b]	Formula	Analysis (%) Calcd (Found)		
						C	H	N
9a	H	H	224—226	+28.5° (0.55)	$C_{14}H_{22}ClN$	70.13	9.25	5.84
						(70.19	9.47	5.89)
9b	H	Me	238—240	+14.9° (0.58)	$C_{15}H_{24}ClN$	70.98	9.53	5.52
						(71.10	9.81	5.53)
9c	Me	Me	193—194	+11.2° (0.53)	$C_{16}H_{26}ClN$	71.75	9.78	5.23
						(71.95	10.07	5.24)
9d	H	Et	195—197	+18.1° (0.59)	$C_{16}H_{26}ClN$	71.75	9.78	5.23
						(71.90	10.06	5.25)
9e	Me	Et	154—155	+11.3° (0.67)	$C_{17}H_{28}ClN$	72.44	10.01	4.97
						(72.42	10.22	4.96)
9f	H	iso-Pr	170—172	+18.0° (0.69)	$C_{17}H_{28}ClN$	72.44	10.01	4.97
						(72.60	10.25	4.97)
9g	H	iso-Bu	153—154	+26.8° (0.73)	$C_{18}H_{30}ClN$	73.07	10.22	4.73
						(73.19	10.41	4.70)
9h	Me	iso-Bu	176—177	+20.6° (0.56)	$C_{19}H_{32}ClN$	73.63	10.41	4.52
						(73.56	10.68	4.47)
9i	H	$CH_2CH(CH_2)_2$	146—148	+23.2° (0.59)	$C_{18}H_{28}ClN$	73.57	9.60	4.77
						(73.59	9.86	4.79)
9j	Me	$CH_2CH(CH_2)_2$	165—167	+13.2° (0.79)	$C_{19}H_{30}ClN$	74.12	9.82	4.55
						(74.35	10.08	4.54)
9k	H	*n*-Pr	163—165	+19.8° (0.66)	$C_{17}H_{28}ClN$	72.44	10.01	4.97
						(72.36	10.19	4.94)
9l	Me	*n*-Pr	172—174	+15.7° (0.68)	$C_{18}H_{30}ClN$	73.07	10.22	4.73
						(73.13	10.49	4.73)
9m	H	H	223—225	−28.3° (0.52)	$C_{14}H_{22}ClN$	70.13	9.25	5.84
						(70.05	9.51	5.78)
9n	H	Me	238—239	−13.8° (0.61)	$C_{15}H_{24}ClN$	70.98	9.53	5.52
						(70.85	9.75	5.47)
9o	H	iso-Pr	169—172	−17.2° (0.73)	$C_{17}H_{28}ClN$	72.44	10.01	4.97
						(72.61	10.28	4.97)
9p	H	$CH_2CH(CH_2)_2$	146—149	−23.4° (0.60)	$C_{18}H_{28}ClN$	73.57	9.60	4.77
						(73.51	9.82	4.73)
9q	Me	$CH_2CH(CH_2)_2$	164—167	−12.5° (0.65)	$C_{19}H_{30}ClN$	74.12	9.80	4.55
						(74.20	10.04	4.57)
9r	H	*n*-Pr	165—167	−20.0° (0.61)	$C_{17}H_{28}ClN$	72.44	10.01	4.97
						(72.48	10.28	4.95)

a) Colorless needles, recrystallized from ethanol. *b*) Measured in water at 20—23 °C, *c*=concentration.

Experimental

The ^{1}H-NMR spectra were obtained with a JEOL JNM-GX400 spectrometer. The mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by using the electron impact (EI) and chemical isonization (CI) (isobutane) methods. The melting points were measured with a Yanagimoto micromelting-point apparatus and are uncorrected. The optical rotations were measured at 20—23 °C with a Jasco DIP-360 digital polarimeter.

Mixture of (2*R*,4*R*)- and (2*S*,4*R*)-2-Cyclohexyl-4-phenyl-1,3-oxazolidines (5 and 5′)——A solution of cyclohexanecarbaldehyde (1.14 g, 10.2 mmol) in CH_2Cl_2 (10 ml) was added dropwise over about 5 min to a solution of (*R*)-2-amino-2-phenylethanol (**1**, 1,41 g, 10.3 mmol) in CH_2Cl_2 (20 ml), and the mixture was stirred in the presence of anhydrous $MgSO_4$ (2 g) at room temperature for 1 h. After removal of the solid, the mixture was concentrated and the residue was distilled *in vacuo* to give a colorless oil (2.36 g, 94.6%). bp 160 °C/2 mmHg. MS *m/z*: CI, 232 ($M.H^+$). The ratio of the diastereomers was estimated by measurement of the peak heights at δ 3.54—3.61 in the ^{1}H-NMR spectrum. ^{1}H-NMR ($CDCl_3$) δ: Major product; 2.46 (1H, s, NH), 3.59 (1H, t, J=7.7 Hz, PhC<u>H</u>CH_2), 4.03—4.42

TABLE IV. Analgesic Activities of (*R*)- and (*S*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamine Hydrochlorides (**9a**—**r**)

Compd. No.	A[a]	The acetic acid writhing method in mice ID_{50},[b] mg/kg s.c. (95% CL)	Naloxone antagonism[c] ratio[d]	Compd. No.	A[a]	The acetic acid writhing method in mice ID_{50},[b] mg/kg s.c. (95% CL)	Naloxone antagonism[c] ratio[d]
9a	*R*	18.6 (12.5—27.6)	1.00	**9k**	*R*	0.81 (0.23— 2.8)	0.53
9b	*R*	10.2 (7.2—14.4)	1.04	**9l**	*R*	>50	
9c	*R*	9.9 (4.6—21.2)	1.06	**9m**	*S*	6.4 (3.4—11.9)	0.97
9d	*R*	8.5 (5.7—12.9)	1.12	**9n**	*S*	14.5 (10.8—19.3)	0.33
9e	*R*	3.4 (1.0—11.7)	1.14	**9o**	*S*	16.8 (10.0—28.3)	0.93
9f	*R*	5.2 (3.2— 8.4)	0.52	**9p**	*S*	24.0 (18.9—30.3)	0.96
9g	*R*	>50		**9q**	*S*	>50	
9h	*R*	9.0 (5.1—15.7)	1.29	**9r**	*S*	9.1 (2.8—29.7)	1.01
9i	*R*	3.7 (1.6— 8.4)	1.40	Pentazocine HCl		7.5 (6.0— 9.4)	
9j	*R*	4.8 (2.4— 9.6)	0.23	Morphine HCl		0.23 (0.06— 0.9)	0.18

a) A: Absolute configuration. *b*) ID_{50} represents the dose producing 50% inhibition of writhing induced by 0.7% acetic acid. *c*) Naloxone antagonism of analgesic activity was determined using the acetic acid writhing method. *d*) Ratio = (inhibition percent by test compound with naloxone HCl)/(inhibition percent by test compound).

(3H, $OCH_2C_6H_{11}$, OCH_2CH), 7.20—7.35 (5H, aromatic H). Minor product; 2.46 (1H, s, NH), 3.56 (1H, dd, J=6.6, 8.1 Hz, $PhCHCH_2$), 4.03—4.42 (3H, $OCH_2C_6H_{11}$, OCH_2CH), 7.20—7.35 (5H, aromatic H).

(1*R*,1′*R*)-Cyclohexyl-*N*-2′-hydroxy-1′-phenylethyl-2-phenylethylamine (6)——A solution of benzylmagnesium chloride (30 mmol in 30 ml of tetrahydrofuran (THF)) was added, drop by drop, to a stirred solution of the mixture of **5** and **5′** (1.85 g, 8 mmol) in THF (30 ml) under a nitrogen atmosphere. After being stirred at room temperature for 4 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 on silica gel with CH_2Cl_2 to give colorless crystals (2.24 g, 87%). The product was recrystallized from *n*-pentane to give colorless columns of mp 59—60 °C. *Anal.* Calcd for $C_{22}H_{29}NO$: C, 81.69; H, 9.04; N, 4.33. Found: C, 81.57; H, 9.11; N, 4.23. $[\alpha]_D$ −52.9° (c=0.46, ethanol). MS m/z: CI, 324 ($M.H^+$); EI, 240 ($M^+ - C_6H_{11}$), 232 ($M^+ - PhCH_2$, base peak). ^{1}H-NMR ($CDCl_3$) δ: 2.56 (1H, dt, J=3.7, 6.6 Hz, $NCHCH_2$), 2.65 (1H, dd, J=6.6, 13.4 Hz, $PhCH_2CH$), 2.73 (1H, dd, J=6.6, 13.4 Hz, $PhCH_2CH$), 3.39 (1H, dd, J=8.3, 10.7 Hz, OCH_2CH), 3.53 (1H, dd, J=4.4, 10.7 Hz, OCH_2CH), 3.71 (1H, dd, J=4.4, 8.3 Hz, $PhCHCH_2$).

***N*-Methylation of 6**——Methyl iodide (10 ml) and anhydrous K_2CO_3 (2 g) were added to a stirred solution of **6** (3.23 g, 10 mmol) in *N*,*N*-dimethylformamide (DMF) (40 ml). After being stirred at room temperature for 12 h, the reaction mixture was poured into water (50 ml) and extracted with ether. The ethereal solution was washed with water and dried over anhydrous $MgSO_4$. The solvent was evaporated off under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give **4** (3.14 g, 93%), and this was identical with an authentic sample on the basis of mass and ^{1}H-NMR spectral comparisons.

(*R*)-1-Cyclohexyl-2-phenylethylamine (8a)——A solution of **6** (5.2 g, 16.1 mmol) in glacial acetic acid (100 ml) was treated with 10% Pd–carbon (1.0 g), and the mixture was shaken in a hydrogen atmosphere at room temperature for 12 h under a pressure of 120 kg/cm^2. The catalyst was then filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give **8a** as a colorless oil (3.1 g, 95%).

Confirmation of Optical Purity for 8a and 8b——A solution of (*S*)-1-methoxy-1-trifluoromethylphenylacetyl chloride (70.2 mg, 0.28 mmol) in dry ether (5 ml) was added to a stirred solution of **8a** or **8b** (0.28 mmol) and Et_3N (28.3 mg, 0.28 mmol) in dry ether (10 ml) at 0 °C. The mixture was stirred at room temperature for 5 h, and the resulting precipitate was filtered off. The solvent was thoroughly evaporated under reduced pressure to give *N*-1′-cyclohexyl-2′-phenylethyl-1-methoxy-1-trifluoromethylphenylacetamide in a quantitative yield. The product was confirmed to consist of one diastereomer by ^{1}H-NMR spectroscopy.

(*R*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamines (8d, 8g, 8k)——A solution of **8a** (2.07 g, 10.2 mmol) and an aldehyde (CH_3CHO, $(CH_3)_2CHCHO$, or CH_3CH_2CHO; 10 mmol) in ether (60 ml) was stirred in the presence of anhydrous $MgSO_4$ (16 g) at room temperature for 2 h. After removal of the solid, the reaction mixture was concentrated under reduced pressure. The residue was dissolved in methanol (20 ml) and treated with $NaBH_4$ (0.38 g). The reaction mixture was stirred at room temperature for 12 h, then concentrated under reduced pressure. The residue was treated with water (30 ml) and extracted with ether. The ethereal solution was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel with

CH_2Cl_2–methanol (100 : 3) to give **8d**, **8g**, or **8k** as a colorless oil.

(*R*)-1-Cyclohexyl-*N*-isopropyl-2-phenylethylamine (8f)——A solution of **8a** (2.09 g, 10.3 mmol) in acetone (100 ml) was refluxed in the presence of a small amount of *p*-toluenesulfonic acid for 3 h. The reaction mixture was worked up, and the residue was reduced with $NaBH_4$ as described above to give **8f**.

(*R*)-*N*-Alkyl-1-cyclohexyl-*N*-methyl-2-phenylethylamines (8c, 8e, 8h, 8j, 8l)——A solution of alkyl halide (methyl iodide, ethyl iodide, isobutyl bromide, cyclopropylmethyl bromide, or *n*-propyl bromide; 15 mmol) and **8b** (1.09 g, 5 mmol) in DMF (10 ml) was stirred in the presence of anhydrous K_2CO_3 (2.07 g, 15 mmol) at 70°C for 12 h. The reaction mixture was poured into water (50 ml), and extracted with ether. The ethereal solution was washed with water and the organic layer was dried over anhydrous Na_2SO_4 then evaporated under reduced pressure. The residue was chromatographed on silica gel with CH_2Cl_2 to give **8c**, **8e**, **8h**, **8j**, or **8l** as a colorless oil.

(*R*)-1-Cyclohexyl-*N*-cyclopropylmethyl-2-phenylethylamine (8i)——A solution of cyclopropylmethyl bromide (0.81 g, 6 mmol) and **8a** (1.01 g, 5 mmol) in DMF (20 ml) was stirred in the presence of anhydrous K_2CO_3 (1.66 g, 12 mmol) at 70 °C for 24 h. The reaction mixture was worked up as described above to give **8i**.

(*S*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamines (8m—r)——Commercially available (*S*)-1-amino-1-phenylacetic acid gave *S*-compounds (**8m—r**) when treated according to the above synthetic procedures for the corresponding *R*-compounds.

Hydrochlorides of (*R*)- and (*S*)-*N*-Alkyl-1-cyclohexyl-2-phenylethylamines (9a—r)——Each free amine (**8a—r**) was treated with hydrogen chloride in methanol to give the corresponding hydrochloride (**9a—r**) as colorless needles.

Acetic Acid Writhing Assay with s.c. Administration——Male ddY mice (18—22 g) were used in groups of eight. The test compounds were dissolved in saline and the solutions were administered s.c. to animals. Twenty minutes later, writhing was induced by the i.p. injection of a 0.7% acetic acid aqueous solution into the mice; the number of writhings was counted for 10 min beginning from 10 min after the challenge with acetic acid.

Naloxone Antagonism of Analgesic Activities——Male ddY mice (18—22 g) were used in groups of eight. The test compounds were administered s.c. to animals. The dose of each compound was sufficient to produce about 80% inhibition of the number of writhings. Fifteen minutes after injection of each compound, naloxone HCl (5 mg/kg) was administered s.c. to mice. 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.

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