[Chem. Pharm. Bull. 32(7)2714—2723(1984)]

Asymmetric α-Substituted Phenethylamines. IV.[1] The Synthesis and Analgesic Activity of Optically Pure (*S*) and (*R*)-1-Cyclohexyl- and 1-Cyclohexenyl-2-phenylethylamines

HIROSHI TAKAHASHI,* YASUHIRO CHIDA, TSUTOMU SUZUKI, HIRAKU ONISHI, and SAIZO YANAURA

Institute of Medicinal Chemistry, Hoshi University, Ebara, Shinagawa, Tokyo 142, Japan

(Received October 21, 1983)

New optically pure (1*S*,1′*S*)- and (1*R*,1′*R*)-1-cycloalkyl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamine hydrochlorides (**3a**—**j**) were synthesized in good yields. The analgesic activities of these hydrochlorides were evaluated by the acetic acid writhing method and the bradykinin-induced flexor reflex method.

The structure of **3f′**·HCl was elucidated by X-ray analysis. The relationship between the analgesic activity and the conformation of the 1—2 bond of these amines is discussed.

Keywords——acetic acid writhing method; analgesic activity; asymmetric 1,3-induced; bradykinin flexor reflex method; chiral oxazolidine; chiral phenethylamine; Grignard reaction; naloxone antagonism; X-ray analysis

The absolute configuration of the chiral carbon atom at the 9-position of (−)-morphine or at the 1-position of *N*-[2-(3-hydroxyphenyl)-1-phenylethyl]piperidines plays an important role in determining the analgesic activity.[2] Thus, the study of analgesic chiral α-substituted phenylethylamines is of interest. The synthesis and analgesic activity of 1-aryl-2-phenylethylamine derivatives were previously reported.[1] In this paper, we deal with the optically pure (*S*)- and (*R*)-1-cyclohexyl- and 1-3′′-cyclohexenyl-2-phenylethylamines. These compounds can be regarded as derived from the morphinane skeleton by cleavage at the C_{12}–C_{13} and C_{13}–C_{15} bonds, and the configuration of the chiral carbon atom at the 9-position is either retained as shown in Chart 1 or reversed.

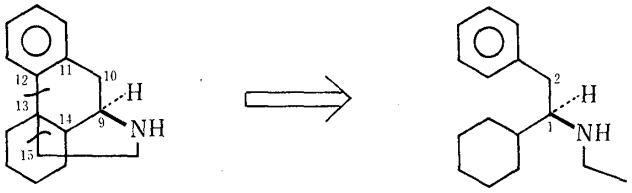


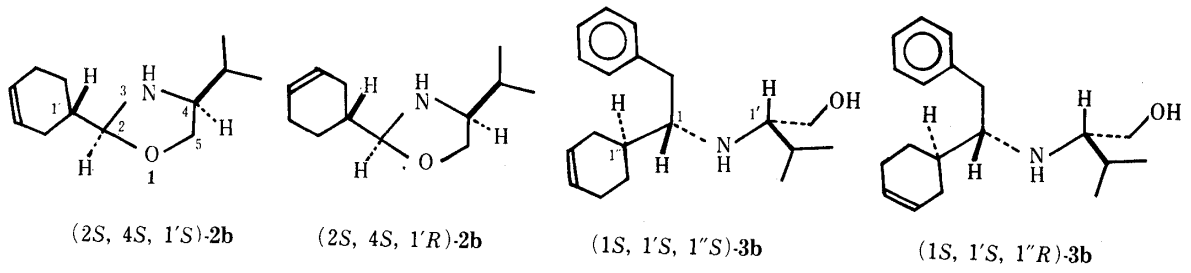
Chart 1

The chiral synthesis and evaluation of the analgesic activity of these compounds were carried out, and the structure of one of the products was confirmed by X-ray analysis.

Chemistry

New chiral heterocyclic compounds, (2*S*,4*S*)-2-cycloalkyl-4-isopropyl-1,3-oxazolidines (**2a**, **2b**), were synthesized in quantitative yields by the condensation of (*S*)-valinol (**1**) and cyclohexyl- or 3-cyclohexenylcarbaldehyde according to a procedure similar to that used for

(2*S*, 4*S*)-2-aryl-4-isopropyl-*N*-methyl-1,3-oxazolidines.[3] These compounds were colorless oils and were confirmed to consist of one isomer by the observation of their proton nuclear magnetic resonance (^{1}H-NMR) spectra; the structures were established by means of infrared (IR), mass, and ^{1}H-NMR spectral analysis. Compound **2b** is a diastereomeric mixture of (2*S*, 4*S*, 1′*S*)- and (2*S*, 4*S*, 1′*R*)-2-(3′-cyclohexenyl)-4-isopropyl-1,3-oxazolidines as shown in Chart 2. However, these two isomers were indistinguishable by spectral analysis.



(2*S*, 4*S*, 1′*S*)-**2b** (2*S*, 4*S*, 1′*R*)-**2b** (1*S*, 1′*S*, 1″*S*)-**3b** (1*S*, 1′*S*, 1″*R*)-**3b**

Chart 2

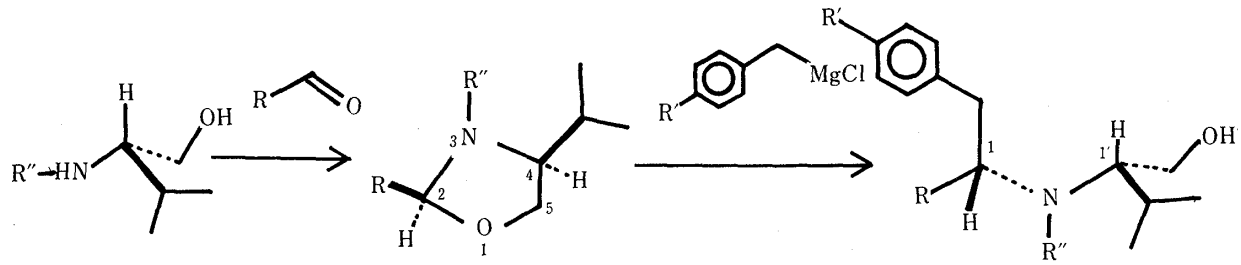
Asymmetric reactions of the chiral oxazolidines (**2a**, **2b**) with benzyl- or 4-methoxybenzylmagnesium chloride were carried out. The products were column-chromatographed on silica gel in order to remove 1,2-diarylethane, and (1*S*, 1′*S*)-1-cycloalkyl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenyl- and 2-(4-methoxyphenyl)ethylamines (**3a**—**d**) were obtained. These products were expected to consist of two isomers having (1*S*, 1′*S*) and (1*R*, 1′*S*) configurations due to a diastereotopos-differentiating reaction. However, no other diastereomer was detected by ^{1}H-NMR spectroscopy in any case.[4] This result indicated that the asymmetric reaction occurred with an extremely high diastereomeric specificity. These chiral amines (**3a**—**d**) were colorless liquids, and their structures were confirmed by means of IR, mass, and ^{1}H-NMR spectral analysis. The configurations at the 3-cyclohexenyl group of **3b** and **3d** could not be identified by spectral analysis even though the compounds were diastereomeric mixtures of (1*S*, 1′*S*, 1″*S*)- and (1*S*, 1′*S*, 1″*R*)-2-aryl-1-3″-cyclohexenyl-*N*-2′-hydroxy-1′-(isopropylethyl)ethylamines as shown in Chart 2.

The free amines were treated with hydrogen chloride methanol solution to yield colorless crystals of the hydrochlorides. The experimental data are summarized in Table I.

On the other hand, (1*R*, 1′*R*)-1-cycloalkyl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamines (**3e**—**h**) were obtained from the (2*R*, 4*R*)-oxazolidines (**2c**, **2d**) in a manner similar to that described for the *S*-isomers. The IR, mass, and ^{1}H-NMR spectra of **3e**—**h** were indistinguishable from those of the corresponding *S*-isomers. These amines were converted to the hydrochlorides. The experimental data are summarized in Table I.

(2*S*, 4*S*)-2-Cycloalkyl-4-isopropyl-*N*-methyl-1,3-oxazolidines (**5a**, **5b**) were obtained by condensation of (*S*)-*N*-methylvalinol (**4**) with cycloalkylcarbaldehyde, and the structures were confirmed by IR, mass, and ^{1}H-NMR spectral analysis. (1*S*, 1′*S*)-1-Cycloalkyl-*N*-2′-hydroxy-1′-isopropylethyl-*N*-methyl-2-phenylethylamines (**3i**, **3j**) were prepared from **5a** and **5b** by treatment with Grignard reagnet. The free bases were converted to the hydrochlorides and the experimental data are summarized in Table I.

The absolute configuration of the newly created chiral center was confirmed by X-ray analysis. The hydrochloride of **3f** was recrystallized from aqueous solution to give (1*R*, 1′*R*, 1″*R*)-1-3″-cyclohexenyl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamine hydrochloride (**3f′**·HCl) as colorless columns. The atomic numbering of **3f′**·HCl is shown in Fig. 1, and the crystal data are listed in Table II. The positional and thermal parameters with their standard deviations are listed in Table III. The intramolecular bond distances, bond angles, and torsion angles for nonhydrogen atoms are given in Tables IV and V. Stereoscopic



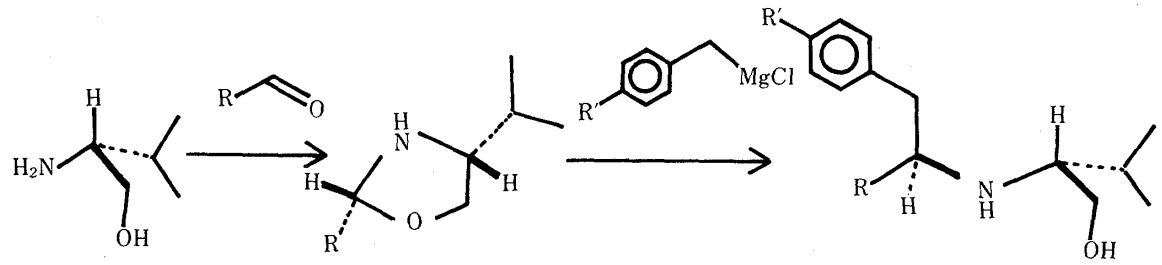


Chart 3

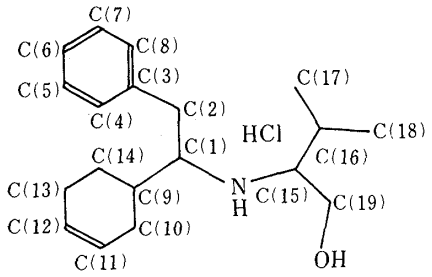


Fig. 1. Atomic Numbering of **3f'**·HCl

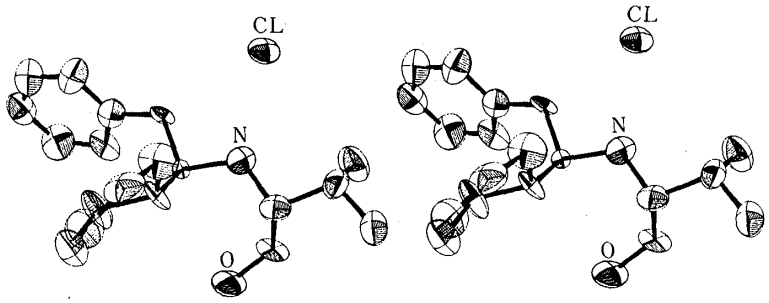


Fig. 2. Stereoscopic Drawings of the Structure of **3f'**·HCl

drawings of the molecular structure are shown in Fig. 2. The sign and magnitude of the specific rotation of **3f'**·HCl were compared with those of **3a**—**e** and **3g**—**j**, and the absolute configurations of these compounds could readily be deduced.

Pharmacology and Discussion

(1) Analgesic Activity

The hydrochlorides of **3a**—**j** were evaluated for analgesic activity in mice by using the

TABLE I. (*S*)- and (*R*)-1-Cycloalkyl-2-phenylethylamine Hydrochlorides (**3a—j**)

Compd. No.	R	R′	R″	Absolute configuration	mp (°C)	$[\alpha]_D^{20}$ [a]	Yield[b] (%)	Recrystn. solvent[c]	Formula	Analysis (%) Calcd (Found)		
										C	H	N
3a	Cyclohexyl	H	H	*S*	168—169	−28.9	83	B	$C_{19}H_{31}NO \cdot HCl$	70.02	9.90	4.30
										(70.20	10.17	4.34)
3b	3-Cyclohexenyl	H	H	*S*	171—173	−57.5	77	B	$C_{19}H_{29}NO \cdot HCl$	70.45	9.34	4.32
										(70.65	9.56	4.32)
3c	Cyclohexyl	OCH_3	H	*S*	162—164	−30.4	78	BE	$C_{20}H_{33}NO_2 \cdot HCl$	67.48	9.63	3.94
										(67.75	9.89	3.65)
3d	3-Cyclohexenyl	OCH_3	H	*S*	114—118	−49.1	71	BE	$C_{20}H_{31}NO_2 \cdot HCl$	67.87	9.11	3.96
										(67.77	9.35	3.63)
3e	Cyclohexyl	H	H	*R*	161—162	+29.2	86	B	$C_{19}H_{31}NO \cdot HCl$	70.02	9.90	4.30
										(69.87	10.13	4.11)
3f	3-Cyclohexenyl	H	H	*R*	170—172	+55.6	78	B	$C_{19}H_{29}NO \cdot HCl$	70.45	9.34	4.32
										(70.46	9.54	4.09)
3g	Cyclohexyl	OCH_3	H	*R*	158—161	+29.8	72	BE	$C_{20}H_{33}NO_2 \cdot HCl$	67.48	9.63	3.94
										(67.77	9.93	3.74)
3h	3-Cyclohexenyl	OCH_3	H	*R*	118—120	+47.9	69	BE	$C_{20}H_{31}NO_2 \cdot HCl$	67.87	9.11	3.96
										(67.57	9.26	3.60)
3i	Cyclohexyl	H	CH_3	*S*	166—167	−15.5	79	B	$C_{20}H_{33}NO \cdot HCl$	70.66	10.08	4.12
										(70.51	9.89	4.02)
3j	3-Cyclohexenyl	H	CH_3	*S*	170—172	−19.7	76	B	$C_{20}H_{31}NO \cdot HCl$	71.08	9.55	4.15
										(70.92	9.60	4.00)

a) Concentration, 0.4% in 95% ethanol. *b*) The yields are for isolated purified products.
c) B = benzene; BE = benzene–ethanol.

TABLE II. Crystal Data

Chemical formula	$C_{19}H_{29}NO \cdot HCl$
Formula weight	323.91
Crystal system	Orthorhombic
Cell dimensions (Å)	$a=$ 9.942 (2)
	$b=$25.078 (7)
	$c=$ 7.652 (2)
Cell volume (Å^3)	1907.8 (3)
Space group	$P2_12_12$
Z	4
D_c (g cm^{-3})	1.13
μ (MoK_α) (cm^{-1})	2.0

TABLE III. Positional ($\times 10^4$) and Thermal Parameters of **3f**′·HCl for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

Atom	X	Y	Z	B_{eq} (Å^2)[a]
Cl	3452 (14)	7466 (5)	6524 (20)	3.8
O	5713 (16)	7794 (6)	−868 (18)	5.9
N	5209 (15)	7648 (6)	3157 (21)	4.0
C(1)	5434 (0)	8252 (0)	2916 (0)	1.7
C(2)	5879 (19)	8421 (7)	4729 (22)	2.9
C(3)	6609 (23)	8945 (8)	4866 (27)	4.2
C(4)	6187 (24)	9327 (9)	6135 (36)	6.1
C(5)	6911 (26)	9800 (9)	6193 (36)	6.3
C(6)	8017 (25)	9922 (10)	5198 (31)	5.7
C(7)	8421 (27)	9540 (10)	4001 (36)	6.9
C(8)	7742 (19)	9026 (9)	3829 (31)	4.7
C(9)	4225 (19)	8522 (8)	2119 (26)	3.6
C(10)	2968 (22)	8515 (10)	3185 (32)	5.9
C(11)	1800 (26)	8844 (10)	2406 (30)	6.2
C(12)	2030 (28)	9218 (10)	1261 (37)	7.5
C(13)	3485 (27)	9361 (9)	612 (32)	6.2
C(14)	4586 (23)	9114 (9)	1721 (35)	6.1
C(15)	4711 (19)	7342 (8)	1598 (26)	4.0
C(16)	4366 (23)	6754 (8)	2326 (27)	4.5
C(17)	5684 (25)	6472 (9)	2941 (33)	6.0
C(18)	3681 (22)	6441 (8)	933 (29)	4.7
C(19)	5790 (20)	7330 (8)	174 (25)	4.2

a) $B_{eq}=(4/3)\sum_i\sum_j \beta_{ij} \boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

acetic acid writhing method. The test compounds were dissolved in saline and the solutions were administered subcutaneously (*s.c.*) to the animals.

The fifty percent inhibition dose (ID_{50}) of each compound was determined, *i.e.*, the amount required to decrease by 50% the number of writhings 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.[5] The ID_{50} values of the hydrochlorides of **3a—j** are summarized in Table VI. The results for the hydrochlorides of (−)-pentazocine and (−)-morphine are included for the purpose of comparison.

Some of these compounds were also evaluated for analgesic activity by intraperitoneal (*i.p.*) administration using the acetic acid writhing method, and the ID_{50} values and the 95%

TABLE IV. Bond Distances (Å) and Bond Angles (°) of **3f′**·HCl for Nonhydrogen Atoms with Their Standard Deviations in Parentheses

O–C(19)	1.417 (24)	C(1)–N–C(15)	117.0 (13)
N–C(1)	1.541 (16)	N–C(1)–C(2)	101.9 (9)
N–C(15)	1.503 (25)	N–C(1)–C(9)	111.9 (9)
C(1)–C(2)	1.516 (17)	C(2)–C(1)–C(9)	118.5 (10)
C(1)–C(9)	1.508 (19)	C(1)–C(2)–C(3)	116.6 (14)
C(2)–C(3)	1.505 (28)	C(2)–C(3)–C(4)	119.5 (19)
C(3)–C(4)	1.427 (33)	C(2)–C(3)–C(8)	118.5 (18)
C(3)–C(8)	1.392 (30)	C(4)–C(3)–C(8)	121.9 (20)
C(4)–C(5)	1.389 (33)	C(3)–C(4)–C(5)	116.3 (23)
C(5)–C(6)	1.371 (36)	C(4)–C(5)–C(6)	126.0 (24)
C(6)–C(7)	1.385 (36)	C(5)–C(6)–C(7)	116.5 (23)
C(7)–C(8)	1.461 (32)	C(6)–C(7)–C(8)	123.4 (23)
C(9)–C(10)	1.492 (29)	C(3)–C(8)–C(7)	116.8 (20)
C(9)–C(14)	1.559 (30)	C(1)–C(9)–C(10)	116.2 (16)
C(10)–C(11)	1.545 (34)	C(1)–C(9)–C(14)	108.8 (14)
C(11)–C(12)	1.303 (36)	C(10)–C(9)–C(14)	108.1 (18)
C(12)–C(13)	1.570 (39)	C(9)–C(10)–C(11)	114.3 (19)
C(13)–C(14)	1.516 (35)	C(10)–C(11)–C(12)	120.8 (24)
C(15)–C(16)	1.613 (29)	C(11)–C(12)–C(13)	122.5 (24)
C(15)–C(19)	1.529 (27)	C(12)–C(13)–C(14)	113.3 (20)
C(16)–C(17)	1.563 (33)	C(13)–C(14)–C(9)	109.3 (18)
C(16)–C(18)	1.489 (30)	N–C(15)–C(16)	105.2 (15)
		N–C(15)–C(19)	110.2 (15)
		C(16)–C(15)–C(19)	112.2 (16)
		C(15)–C(16)–C(17)	109.9 (17)
		C(15)–C(16)–C(18)	109.4 (17)
		C(17)–C(16)–C(18)	111.1 (18)
		O–C(19)–C(15)	105.6 (16)

TABLE V. Torsion Angles (°) of **3f′**·HCl with Their Standard Deviations in Parentheses

Atom 1	Atom 2	Atom 3	Atom 4[a]		Atom 1	Atom 2	Atom 3	Atom 4[a]	
C(15)	– N	– C(1)	– C(2)	178.3 (14)	C(4)	– C(5)	– C(6)	– C(7)	1.6 (39)
C(15)	– N	– C(1)	– C(9)	50.7 (16)	C(5)	– C(6)	– C(7)	– C(8)	−1.9 (37)
C(1)	– N	– C(15)	– C(16)	−171.7 (13)	C(6)	– C(7)	– C(8)	– C(3)	3.5 (35)
C(1)	– N	– C(15)	– C(19)	67.1 (18)	C(1)	– C(9)	– C(10)	– C(11)	174.0 (16)
N	– C(1)	– C(2)	– C(3)	160.9 (15)	C(14)	– C(9)	– C(10)	– C(11)	51.4 (24)
C(9)	– C(1)	– C(2)	– C(3)	−75.8 (18)	C(1)	– C(9)	– C(14)	– C(13)	169.2 (16)
N	– C(1)	– C(9)	– C(10)	64.1 (18)	C(10)	– C(9)	– C(14)	– C(13)	−63.7 (23)
N	– C(1)	– C(9)	– C(14)	−173.6 (14)	C(9)	– C(10)	– C(11)	– C(12)	−20.3 (33)
C(2)	– C(1)	– C(9)	– C(10)	−54.1 (19)	C(10)	– C(11)	– C(12)	– C(13)	0.5 (39)
C(2)	– C(1)	– C(9)	– C(14)	68.2 (17)	C(11)	– C(12)	– C(13)	– C(14)	−12.8 (36)
C(1)	– C(2)	– C(3)	– C(4)	130.3 (19)	C(12)	– C(13)	– C(14)	– C(9)	44.1 (26)
C(1)	– C(2)	– C(3)	– C(8)	−54.3 (24)	N	– C(15)	– C(16)	– C(17)	−65.7 (20)
C(2)	– C(3)	– C(4)	– C(5)	179.7 (20)	N	– C(15)	– C(16)	– C(18)	172.0 (16)
C(8)	– C(3)	– C(4)	– C(5)	4.5 (34)	C(19)	– C(15)	– C(16)	– C(17)	54.1 (22)
C(2)	– C(3)	– C(8)	– C(7)	180.0 (20)	C(19)	– C(15)	– C(16)	– C(18)	−68.2 (21)
C(4)	– C(3)	– C(8)	– C(7)	−4.9 (32)	N	– C(15)	– C(19)	– O	−85.3 (19)
C(3)	– C(4)	– C(5)	– C(6)	2.8 (39)	C(16)	– C(15)	– C(19)	– O	157.8 (16)

a) Looking from atom 2 to atom 3. The clockwise rotation of bond 3—4 with reference to bond 2—1 is given.

TABLE VI. Analgesic Activities of (*S*)- and (*R*)-1-Cycloalkyl-2-phenylethylamine Hydrochlorides

Compd. No.	The acetic acid writhing method in mice		The bradykinin-induced flexor reflex method in rats	Naloxone antagonism[b]
	ID_{50},[a] μmol/kg, *s.c.* (95% CL)	ID_{50},[a] μmol/kg, *i.p.* (95% CL)	ED_{50}, μmol/kg, *i.v.* (95% CL)	Ratio[c]
3a	483 (333—700)			0.25
3b	209 (145—301)	27 (21—34)	12.7 (10.7—19.3)	0.65
3c	247 (178—343)			0.43
3d	488 (313—762)			1.00
3e	312 (231—421)			0.57
3f	267 (194—374)	85 (60—121)	19.5 (16.4—29.7)	0.76
3g	370 (251—546)			0.32
3h	758 (467—1230)			0.88
3i	164 (125—215)		8.0 (6.5—9.9)	
3j	158 (106—220)		23.5 (17.4—32.0)	
Pentazocine HCl	23.3 (18.6—29.1)	71 (50—101)	3.9 (1.7—5.5)	
Morphine HCl	0.71 (0.2—2.8)	5.8 (4.1—8.2)		0.18

a) ID_{50} represents a dose producing 50% inhibition of writhing induced by 0.7% acetic acid.
b) Naloxone antagonism of analgesic activity was determined using the acetic acid writhing method.
c) Ratio=(number of writhings after test compound treatment)/(number of writhings after treatment with the test compound plus naloxone HCl).

CL were determined. These results are summarized in Table VI. In *s.c.* administration of the hydrochlorides of **3a**—**j**, the ID_{50} values were higher than that of pentazocine hydrochloride. However, in *i.p.* administration, the ID_{50} value of **3b** was low, and that of **3f** was similar to that of pentazocine.

The bradykinin-induced flexor reflex of rat hind-limb method[6] was used for evaluating analgesic activity of the hydrochlorides of **3b**, **3f**, **3i**, **3j**, and pentazocine. The test compounds were dissolved in saline and the solutions were administered intravenously (*i.v.*) to rats. The fifty percent effective dose (ED_{50}) of each compound was determined, *i.e.*, the amount required to reduce by 50% the bradykinin-induced flexor reflex of rat hind-limb. The ED_{50} values and the 95% CL were estimated by the method of Litchfield and Wilcoxon,[5] and the results are summarized in Table VI.

The analgesic activities of the *R*-isomers (**3e**—**h**), which have the same absolute configuration as at the chiral center at the 9-position of (−)-morphine, were compared with those of **3a**—**d**, **3i** and **3j** having the opposite absolute configuration (*S*-form). The *S*-isomers tended to show more potent activity than the *R*-isomers.

(2) Naloxone Antagonism of Analgesic Activity

These hydrochlorides of **3a**—**h** were tested for antagonistic activity against naloxone, using the acetic acid writhing method.[7] (−)-Naloxone hydrochloride (5 mg/kg) was administered *s.c.* to mice after injection of each compound. The naloxone antagonism was estimated from the ratio of the inhibition percent of the test compounds together with naloxone to those without naloxone. These results are summarized in Table VI. The analgesic activities of **3a**, **3c** and **3g** were antagonized by naloxone, while those of **3d**, **3f** and **3h** were not.

(3) Discussion

X-Ray crystallographic studies have been performed on (−)-morphine[8] and related compounds.[9] However, the phenethylamine framework in the morphinane skeleton has received little attention. In this work, the relationships between the analgesic activity and the

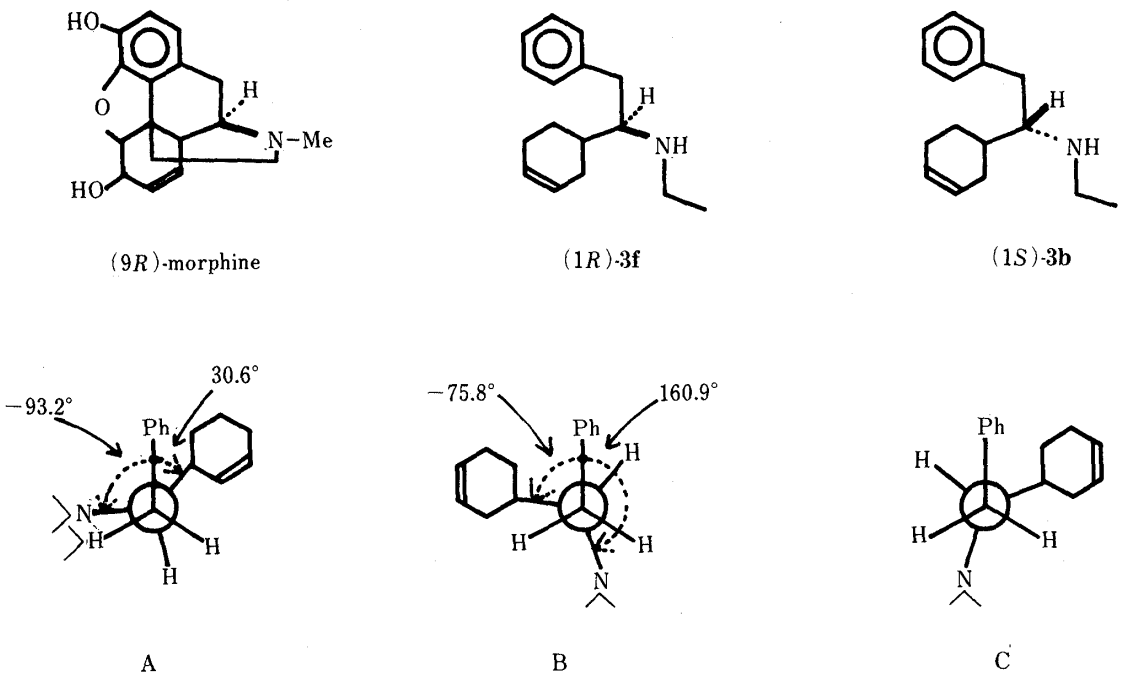


Fig. 3. Conformations at the 9—10 Bond of (−)-Morphine and 1—2 Bond of the Chiral Amines (**3f** and **3b**)

conformation of the 1—2 bond in **3a—j** were investigated in relation to the conformation of the 9—10 bond of morphinanes.

The conformations of the 9—10 bond in the Newman projection are such that the cyclohexenyl ring consisting of C(14, 13, 5, 6, 7, 8) is +clinal and the amino group is −clinal to the aromatic nucleus as shown in Fig. 3(A), *i.e.*, the torsion angles of C(11)–C(10)–C(9)–C(14) and C(11)–C(10)–C(9)–N are +30.6 and −93.2°, respectively.[10] The X-ray analysis showed that the conformation of the 1—2 bond of **3f'**·HCl was such that the cyclohexenyl ring was −clinal and the nitrogen moiety was nearly periplanar as shown in Fig. 3(B). The torsion angles of **3f'**·HCl were −75.8 and +160.9° for C(9)–C(1)–C(2)–C(3) and N–C(1)–C(2)–C(3), respectively, as shown in Table V. The conformation of **3d**, *i.e.*, the enantiomer of **3f**, may be assumed to have the cyclohexenyl ring +clinal and the nitrogen moiety periplanar (Fig. 3(C)). It was considered that the clinal conformation of the cycloalkyl ring to the aromatic nucleus in morphinane compounds might be one of the factors favoring analgesic activity. Then, α-substituted phenethylamines (**3a—j**) were synthesized and it was confirmed that the cycloalkyl ring of these compounds is similarly clinal to the aromatic nucleus. However, the −clinal isomers (**3e—h**) of these compounds were as potent as the corresponding +clinal isomers (**3a—d**), although the morphinane compounds are more potent when the conformation is +clinal. At present, there is insufficient information to evaluate the significance of these results.

Experimental

The IR spectra were recorded with a Hitachi 260-10 spectrometer and the ^{1}H-NMR spectra were obtained with a JEOL FX100 spectrometer. The mass spectra (MS) were recorded with a JEOL JMS-D300 spectrometer by using the CI (CH_4) method. 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.

(2*S*,4*S*)- and (2*R*,4*S*)-2-Cycloalkyl-4-isopropyl-1,3-oxazolidines (2a—d)——A solution of cyclohexyl- or 3-cyclohexenylcarbaldehyde (10 mmol) in ether (20 ml) was slowly added to a stirred solution of (*S*)- or (*R*)-**1** (1.0 g, 10 mmol) in ether (30 ml) with vigorous stirring on an ice-cold bath. The mixture was stirred in the presence of $MgSO_4$

(3 g) at 0—5 °C for 1 h. After removal of the solid, the mixture was concentrated to give the corresponding oxazolidine (**2a—d**) as a colorless oil in quantitative yield. These compounds were unstable and were used for the following reactions without any purification.

2a, **2c**: IR (film): 3300 (NH) cm^{-1}. MS *m/z*: 198 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.05 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 4.18 (1H, d, J=5.0 Hz, NCH–O).

2b, **2d**: IR (film): 3300 (NH) cm^{-1}. MS *m/z*: 196 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 1.05 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 4.22 (1H, d, J=4.9 Hz, NCH–O), 5.68 (2H, s, CH=CH).

(1*S*, 1′*S*)- and (1*R*, 1′*R*)-1-Cycloalkyl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamines (3a, 3b, 3e, 3f)——A suspension of benzylmagnesium chloride (50 mmol in 50 ml of THF) was slowly added, drop by drop, to a stirred solution of a chiral oxazolidine (**2a—d**) (10 mmol) in THF (50 ml) under a nitrogen atmosphere. After being stirred at room temperature for 4—5 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, 1,2-diphenylethane was removed, and the corresponding chiral amine (**3a**, **3b**, **3e**, **3f**) was obtained as a colorless oil.

3a, **3e**: IR (film): 3450 (OH) cm^{-1}. MS *m/z*: 290 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.92 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.16 (1H, dd, J=5.1, 11.0 Hz, OCH_2), 3.30 (1H, dd, J=4.4, 11.0 Hz, OCH_2).

3b, **3f**: IR (film): 3400 (OH) cm^{-1}. MS *m/z*: 288 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.92 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.16 (1H, dd, J=5.4, 11.0 Hz, OCH_2), 3.34 (1H, dd, J=4.4, 11.0 Hz, OCH_2), 5.69 (2H, s, CH=CH).

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

(1*S*, 1′*S*)- and (1*R*, 1′*R*)-1-Cycloalkyl-*N*-2′-hydroxy-1′-isopropylethyl-2-(4-methoxyphenyl)ethylamines (3c, 3d, 3g, 3h)——A suspension of 4-methoxybenzylmagnesium chloride (50 mmol in 50 ml of THF) was slowly added, drop by drop, to a solution of a chiral oxazolidine (**2a—d**) (10 mmol) in THF (50 ml) under a nitrogen atmosphere, and stirring was continued at 40—45 °C for 5 h. The reaction mixture was worked up as described above to give the corresponding chiral amine (**3c**, **3d**, **3g**, **3h**) as a colorless oil.

3c, **3g**: IR (film): 3400 (OH) cm^{-1}. MS *m/z*: 320 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.93 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.14 (1H, dd, J=5.4, 10.7 Hz, OCH_2), 3.31 (1H, dd, J=4.5, 10.7 Hz, OCH_2), 3.74 (3H, s, OCH_3).

3d, **3h**: IR (film): 3450 (OH) cm^{-1}. MS *m/z*: 318 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 0.92 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 3.18 (1H, dd, J=5.4, 11.0 Hz, OCH_2), 3.34 (1H, dd, J=4.4, 11.0 Hz, OCH_2), 3.76 (3H, s, OCH_3), 5.68 (2H, s, CH=CH).

The free bases were treated with hydrogen chloride methanol solution to give the hydrochlorides. The experimental data are summarized in Table I.

(1*R*, 1′*S*)-1-Cyclohexyl-*N*-2′-hydroxy-1′-isopropylethyl-2-phenylethylamine (3a′)——A mixture of (*S*)-**1** (1.0 g, 10 mmol) and 1-cyclohexyl-2-phenylethanone (2.0 g, 10 mmol) in toluene (30 ml) was refluxed for 24 h using a Dean-Stark trap. After removal of the solvent, an oily product (2.6 g) was obtained.

A solution of this product (2.0 g) in methanol (10 ml) was added dropwise to a stirred solution of $NaBH_4$ (0.26 g, 7 mmol) in methanol (50 ml), and the mixture was stirred at room temperature for 3 h. After removal of the solvent, H_2O (50 ml) was added and the whole was extracted with CH_2Cl_2. The solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was obtained as a colorless oil (1.7 g) and confirmed to consist of a mixture of two diastereomers [(1*S*, 1′*S*)-**3a** and (1*R*, 1′*S*)-**3a′**] by analysis of the ^{1}H-NMR spectrum. (1*R*, 1′*S*)-**3a′** was isolated by preparative thin-layer chromatography on silica gel with CH_2Cl_2–methanol (97:3). MS *m/z*: 290 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.42 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.70 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 3.15 (1H, dd, J=7.1, 10.3 Hz, OCH_2), 3.46 (1H, dd, J=4.6, 10.3 Hz, OCH_2).

(2*S*, 4*S*)-2-Cycloalkyl-4-isopropyl-*N*-methyl-1,3-oxazolidine (5a, 5b)——A solution of cycloalkylcarbaldehyde (10 mmol) in ether (20 ml) was added dropwise to a solution of (*S*)-**4** (1.17 g, 10 mmol) in ether (20 ml) with vigorous stirring on an ice-cold bath, then anhydrous $MgSO_4$ (3 g) was added, and the mixture was stirred for 1 h. After removal of the solid, the mixture was concentrated to give **5a** and **5b** as a colorless oil in quantitative yield.

5a: MS *m/z*: 212 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 0.91 (3H, d, J=6.6 Hz, $CHC\underline{H}_3$), 2.27 (3H, s, NCH_3).

5b: MS *m/z*: 210 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6.3 Hz, $CHC\underline{H}_3$), 0.93 (3H, d, J=6.3 Hz, $CHC\underline{H}_3$), 2.30 (3H, s, NCH_3), 5.67 (2H, s, CH=CH).

(1*S*, 1′*S*)-1-Cycloalkyl-*N*-2′-hydroxy-1′-isopropylethyl-*N*-methyl-2-phenylethylamine (3i, 3j)——A THF solution of benzylmagnesium chloride (50 mmol in 50 ml of THF) was added, drop by drop, to a stirred solution of *N*-methyl-1,3-oxazolidine (**5a**, **5b**, 10 mmol) in THF (50 ml) at 0—5 °C under a nitrogen atmosphere. The mixture was stirred at room temperature for 4—5 h, then H_2O (2 ml) was added and stirring was continued for 1 h. The solid was filtered off, the filtrate was dried over anhydrous $MgSO_4$ and the solvent was evaporated off. The residue was column-chromatographed on silica gel with CH_2Cl_2, and 1,2-diphenylethane was removed. The chiral amines (**3i**, **3j**) were obtained as a colorless oil.

3i: IR (film): 3400 (OH) cm^{-1}. MS *m/z*: 304 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, d, J=6.8 Hz, $CHCH_3$), 0.85 (3H, d, J=6.8 Hz, $CHCH_3$), 2.39 (3H, s, NCH_3), 3.28 (2H, d, J=6.8 Hz, OCH_2CH).

3j: IR (film): 3450 (OH) cm^{-1}. MS *m/z*: 302 ($M \cdot H^+$). ^{1}H-NMR ($CDCl_3$) δ: 0.81 (3H, d, J=6.6 Hz, $CHCH_3$), 0.85 (3H, d, J=6.8 Hz, $CHCH_3$), 2.41 (3H, s, NCH_3), 3.30 (2H, d, J=6.4 Hz, OCH_2CH), 5.68 (2H, s, CH=CH).

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

Acetic Acid Writhing Assay with *s.c.* and *i.p.*——Male ddY mice (18—22 g) were used in groups of 8 mice. The test compounds were dissolved in saline and the solutions were administered *s.c.* or *i.p.* to animals. Thirty minutes later, writhing was induced by the *i.p.* 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 ID_{50} value and the 95% CL of each compound were estimated by the method of Litchfield and Wilcoxon.[5]

Bradykinin-Induced Flexor Reflex Assay in Rats——Male Sprague-Dawley rats (300—400 g) under light ether anesthesia had a polyethylene cannula (0.6 mm o.d.) inserted retrogradely into the left femoral artery so that the tip was in the left common iliac artery just distal to the bifurcation of the abdominal aorta. Solutions injected through the cannula flowed into the contralateral (right) common iliac artery, in which a normal blood flow was maintained. Another cannula inserted into the left femoral vein was used for drugs. Immediately after anesthesia ended, the animal was suspended horizontally in a sleeve of cloth with slits through which the four limbs, tail and cannula were exposed, all but the right hind-limb and tail being loosely restrained. The right limb was linked to a force displacement transducer (Nihon Kohden, SB-1T) with a thread for recording flexor reflexes.

At least 2 h after the rat had recovered from anesthesia, 0.2 ml of 0.9% NaCl was injected, and if this did not produce any movement of the right hind-limb, 2 μg of bradykinin (Wako Pure Chemical Industries, Ltd.) in 0.2 ml saline was injected within 1 s at intervals of 10—15 min.

When, after administration of a drug, the reflex disappeared during more than two successive bradykinin injections and subsequently recovered to the control level, the effect of the drug was regarded as being inhibitory, that is analgesic. Each rat was given only one dose of a drug. The ED_{50} values and the 95% CL were estimated by the Litchfield–Wilcoxon method.[5]

Naloxone Antagonism of Analgesic Activities——Male ddY mice (18—22 g) were used in groups of 8 mice. 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. Twenty minuts 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.

X-Ray Analysis of 3f′·HCl——The crystal used in this study was a colorless column with dimensions of 0.3×0.3×0.2 mm, obtained from aqueous solution. All the measurements were performed on a Rigaku AFC-5 diffractometer using graphitemonochromated Mo $K\alpha$ radiation. The unit cell dimensions were determined by least-squares calculation with 20 high-angle reflections.

Intensity data were collected by using the $2\theta/\omega$ scan technique for $2\theta < 50.48°$ with an average scan rate of 4°/min. In total, 2008 independent reflections with $0 < 2\theta < 50.48°$ were collected, and 776 satisfying the condition $F_0 \geqq 2\sigma(F)$ were used for calculations.

The structure was solved by the direct method using MULTAN[11] and the Rigaku crystallographic package RASA-II. The structure was refined by the block-diagonal least-squares method with anisotropic temperature factors. The R factor value was 0.108 (for nonhydrogen atoms only).

References and Notes

1) H. Takahashi, Y. Chida, T. Suzuki, S. Yanaura, Y. Suzuki, and C. Masuda, *Chem. Pharm. Bull.*, **31**, 1659 (1983).
2) H. Nakamura, K. Ishii, Y. Yokoyama, S. Motoyoshi, K. Natsuka, and M. Shimizu, *J. Pharm. Pharmacol.*, **32**, 635 (1980).
3) H. Takahashi, Y. Suzuki, and T. Kametani, *Heterocycles*, **20**, 607 (1983).
4) The ^{1}H-NMR spectrum of the optically pure amine (**3a**) was compared with that of the mixture of diastereomers [(1*S*,1′*S*)-**3a** and (1*R*,1′*S*)-**3a**′] which was obtained by condensation of (*S*)-valinol with 1-cyclohexyl-2-phenylethanone, followed by the reduction with sodium borohydride.
5) J. T. Litchfield and F. A. Wilcoxon, *J. Pharmacol. Exp. Ther.*, **96**, 99 (1949).
6) M. Satoh, S. Kawajiri, K. Shishido, M. Yamamoto, and H. Takagi, *J. Pharm. Pharmacol.*, **31**, 184 (1979).
7) K. L. McGilliard and A. E. Takemori, *J. Pharmacol. Exp. Ther.*, **207**, 497 (1978).
8) L. Gylbert, *Acta Crystallogr., Sect. B*, **29**, 1630 (1973).
9) I. L. Karle, *Acta Crystallogr., Sect. B*, **30**, 1682 (1974); R. J. Sime, M. Dobler, and R. L. Sime, *ibid., Sect. B*, **32**, 2937 (1976); S. D. Darling, V. M. Kolb, G. S. Mandel, and N. S. Mandel, *J. Pharm. Sci.*, **71**, 763 (1982).
10) E. Bye, *Acta Chem. Scand., Ser. B.*, **30**, 549 (1976).
11) P. Main, M. M. Woolfson, and G. Germin, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).