

# Studies on Morphine-like Compounds. V.<sup>1</sup> Absolute Configuration and Conformations of Optically Active 1,2-Diphenylethylamine Derivatives

TADASHI SASAKI, KEN KANEMATSU,

*Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Nagoya, Japan*

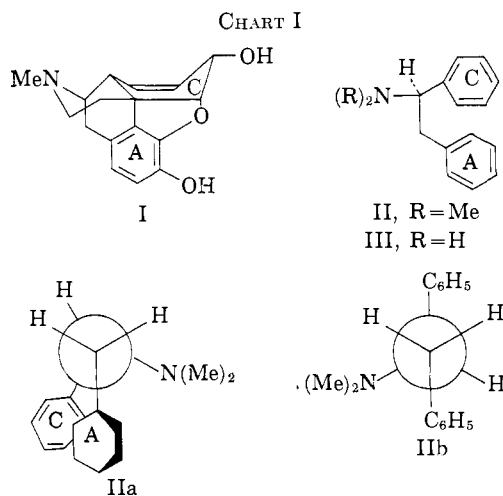
YOJIRO TSUZUKI, AND KATSUMI TANAKA

*Department of Chemistry, Tokyo College of Science, Tokyo, Japan*

Received February 18, 1966

The analgetically active (–)-N,N-dimethyl-1,2-diphenylethylamine (II), 0.33–0.5 times as potent as (–)-morphine, has been assigned the (*R*) configuration by optical rotatory dispersion measurements. Close stereochemical resemblance to (–)-morphine is indicated. Nuclear magnetic resonance data showed an eclipsed conformation for II to an extent of about 22%, which might be expected to favor its approach to some reactive surface of the nervous system.

In terms of drug–receptor interaction, the significance of stereospecificity in drug action becomes established only when the more active isomers of enantiomorphic pairs are shown to possess identical configurations.<sup>2</sup> Recently, Nakazaki, *et al.*,<sup>3</sup> concluded that (–)-1,2-diphenylethylamine (III) has the (*R*) configuration from the degradation of its (+)-N-acetyl derivative to D-aspartic acid; this is the same configuration as (–)-morphine at the analogous (C-9) asymmetric center. Nakazaki<sup>3</sup> also assumed from its activity that II is in eclipsed conformation (IIa, Chart I) rather than as IIb, perhaps the energetically favorable conformation. No experimental support of this assumption was advanced.



In the present work, the authors studied the stereochemistry and the structure–activity relationship of optically active 1,2-diphenylethylamine derivatives, whose conformational aspects in drug action are discussed.

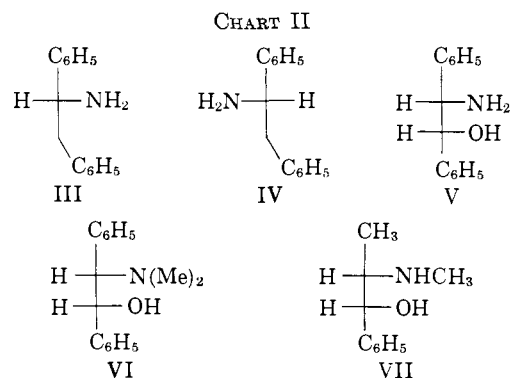
## Results and Discussion

In 1960, Lyle<sup>4</sup> suggested the (*R*) configuration for (+)-1,2-diphenylethylamine (IV, an antipode of III),

(1) Paper IV: T. Sasaki, K. Kanematsu, Y. Tsuzuki, and K. Tanaka, *Chem. Pharm. Bull.* (Tokyo), in press.

(2) A. H. Beckett and A. F. Casy in "Progress in Medicinal Chemistry," Vol. 4, G. P. Ellis and G. B. West, Ed., Butterworth and Co. (Publishers) Ltd., 1965, p 171.

because its positive-plain rotatory dispersion curve was very close to a summation curve of (*R*)-(+)- $\alpha$ -methylbenzylamine and (*S*)-(+)-amphetamine, considered to be components of IV (Chart II). Further-



more, she suggested that the portion of the above curve in the visible spectrum could be fitted to the one-term Drude equation, and the slopes thus obtained were shown to be an intrinsic property of the asymmetric center and additive. This assignment was opposite to that of Nakazaki<sup>5</sup> who suggested that the reason must be sought in Lyle's failure to take account of phenyl–phenyl interaction and hydrogen bonding between phenyl and amino groups. The above-mentioned assignment based on optical rotatory dispersion curves was doubted, and it seemed desirable to try to resolve the disagreement. In this respect, III, IV, D-(–)-*erythro*-1,2-diphenyl-2-hydroxyethylamine (1*S*, 2*R*, V), and its dimethyl compound (VI) were examined in order to establish a basis for the correlation of the absolute configuration of III with the optical rotatory dispersion curves; the results are shown in Figure 1. A values of III–VI were calculated from the one-term Drude equation and these results are shown in Table I.

When a molecule possesses more than one asymmetric center, its rotation has been assumed to be a summation of the rotations of the individual asymmetric centers. In the examination of D-(–)-*erythro*-

(3) M. Nakazaki, *et al.*, *Bull. Chem. Soc. Japan*, **36**, 161 (1963).

(4) G. G. Lyle, *J. Org. Chem.*, **25**, 1779 (1960).

(5) M. Nakazaki, *Bull. Chem. Soc. Japan*, **36**, 1204 (1963).

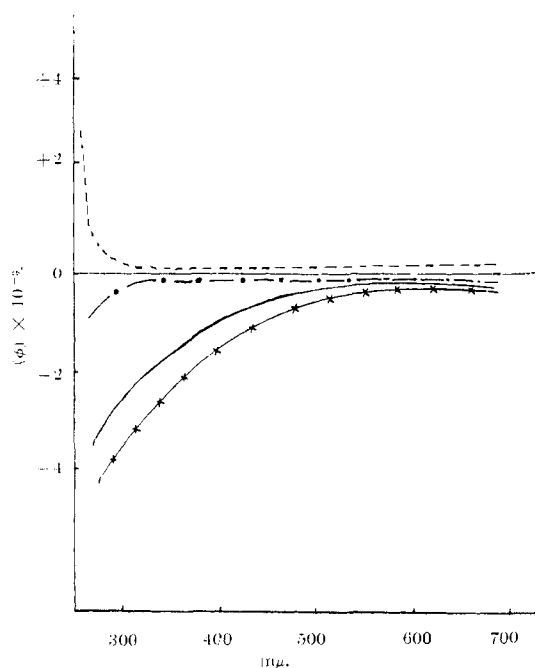


Figure 1.—Optical rotatory dispersion curves of III-VI in EtOH: —, III·HCl; ·····, IV·HCl; - · - ·, V; ····x···, VI·HCl.

TABLE I

Compound	-A value <sup>a</sup>		$\lambda_0$ , m $\mu$	$[\alpha]_{25}^{25}$ , deg (EtOH)	$M_{10}$ , °C
	Base	Salt			
III		-83.0	232	-125.5	258-260 <sup>b</sup>
IV	+26.3	+86.7	234	+128.0	259-260 <sup>b</sup>
V	-4.4	-132.0	235	-7.0	142-143
VI		-124.0	241	-158.0	255 <sup>b</sup>

<sup>a</sup>  $[\phi] = A/(\lambda^2 - \lambda_0^2)$  where  $[\phi]$  represents the molecular rotation at a given wavelength  $\lambda$  (expressed in  $\mu$ ), and  $A$  and  $\lambda_0$  are characteristic constants of a compound. <sup>b</sup> HCl salt.

1,2-diphenyl-2-hydroxyethylamine hydrochloride (V) of known absolute configuration,<sup>5</sup> the  $A$  value was -132 as shown in Table I. On the other hand, Lyle<sup>4</sup> reported that (-)-ephedrine (VII) sulfate gave negative Cotton-effect curves, the  $A$  value being -20.9 and that the C- $\alpha$  partial contribution would be -30.8. In the case of (-)-1,2-diphenylethylamine (III) hydrochloride, the slope as determined from the Drude equation was -83. This value is in close agreement with that calculated from the  $A$  values of the individual components, that is,  $V - VII = -132 - (-30.8) = -101.2$ . Thus, III has been assigned the (*R*) and IV the (*S*) configuration. This result is in agreement with the conclusion of Nakazaki<sup>3</sup> based on degradative studies.

In order to determine the preferred conformation, high-resolution nmr spectra were obtained for II and IV. The three most probable rotamers of (*S*)-(+)-1,2-diphenylethylamine hydrochloride are shown in Chart III. As shown in Figure 2, the observed

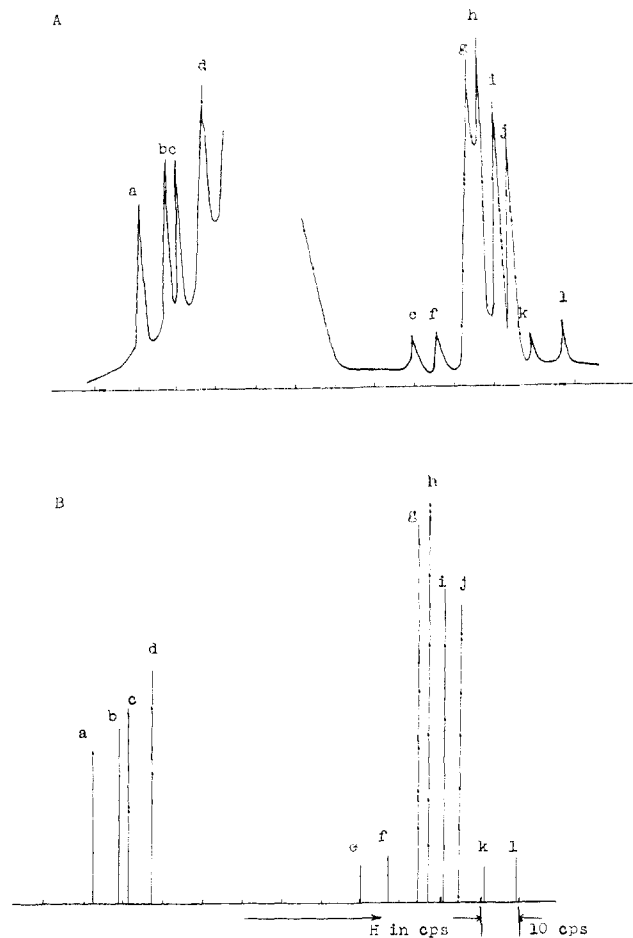
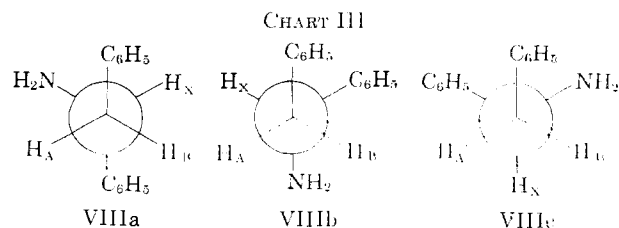


Figure 2.—A: Observed spectrum of IV in D<sub>2</sub>O at 80°. B: Calculated spectrum of IV in D<sub>2</sub>O at 80°.

spectra of IV consisted of twelve resonances (typical ABX pattern). This means that the central ethane linkage rotates freely. However, it is apparent that the methylene protons are not magnetically equivalent. Nair and Roberts<sup>6</sup> have pointed out that generally in such a compound as IV, the shifts of protons are not necessarily averaged by rapid rotation unless the residence times in each of three rotamers are equal. In order to obtain the molecular constants (chemical shifts and spin-coupling constants), all spectra were measured at 80°. In the authors' experiments, the signals of proton H<sub>X</sub> of IV were overlapped with the signal of DHO at 30°. Spectra of IV did not show any temperature dependence at 30 and 80°, indicating that the conformation of IV at 80° was similar to that at 30°. Observed and calculated molecular constants are listed in Table II.

If the proton H<sub>X</sub> in conformational isomer VIIIc were situated symmetrically with respect to two protons, H<sub>A</sub> and H<sub>B</sub>,  $J_{AX}$  would be equal to  $J_{BX}$ . The observed values, however, were not equivalent and it might be expected that among the possible conformational isomers, VIIIa and VIIIb are predominant at the investigated temperature on the basis of nmr data alone. The contribution of VIIIc should be very small, since it has all bulky groups in a skew relationship. The conformational isomer VIIIc cannot be excluded completely because of the possibility of free rotation. Thus the observed coupling constants are

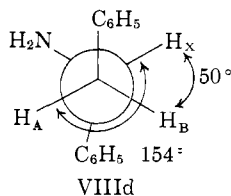
(6) P. M. Nair and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 4565 (1957).

TABLE II  
OBSERVED AND CALCULATED SPECTRA OF IV IN D<sub>2</sub>O AT 80°<sup>a</sup>

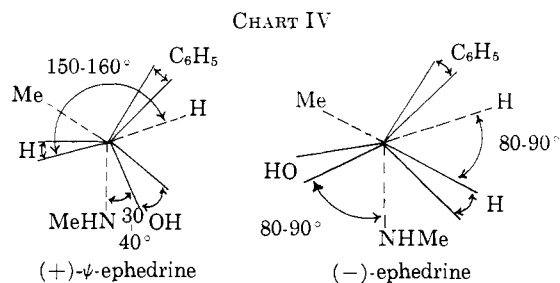
	Line position		Rel Intensity	
	Obsd	Calcd	Obsd	Calcd
a	2.1	2.15	0.824	0.824
b	8.3	8.50	0.878	0.959
c	10.7	10.76	0.914	1.008
d	17.1	17.12	1.140	1.201
e	71.4	69.95	0.135	0.184
f	76.6	76.30	0.135	0.222
g	84.9	83.70	1.813	1.980
h	86.9	86.20	1.894	2.016
i	89.9	90.06	1.623	1.614
j	95.2	94.87	1.559	1.576
k	100.0	100.02	0.197	0.195
l	108.9	108.64	0.197	0.210

<sup>a</sup>  $|J_{AB}| = 13.80$ ,  $|J_{BX}| = 6.10$ ,  $|J_{AX}| = 8.90$  cps.  $\nu_A - \nu_X = 10.50$ ,  $\nu_B - \nu_X = 73.30$  cps.  $J_{AB}$  has signs opposite to those of  $J_{AX}$  and  $J_{BX}$ ; see R. H. Bible, "Interpretation of N.M.R. Spectra," Plenum Press, New York, N. Y., 1965, pp 86-91.

averaged values contributed by each of the isomers. As only an ABX pattern was observed, a conformation such as VIIIId was estimated from the averaged values of the coupling constants on three isomers. The dihedral angles calculated from the modified Karplus equation<sup>7</sup> with  $J$  values of IV were as follows:  $\phi$  was 154° for  $J_{AX} = 8.9$  cps and 50° for  $J_{BX} = 6.1$  cps, respectively. The nmr spectral evidence suggested that the apparent preferred conformations were off-staggered forms shown in VIIIId.



Recently, Hyne<sup>8</sup> gave an account of an nmr study on the biologically active ephedrine bases; he suggested the preferred residence conformations for the bases as shown in Chart IV based upon chemical shifts, anisotropy effects, spin-coupling constants, and hydrogen-bonding phenomena.



While the interpretation offered above accommodates the experimental facts on the basis of a distribution of population among "off-staggered" conformers with preferred residence conformations, an alternative interpretation is also possible based on a population distribution among "pure staggered" conformers of the type in VIIIa, VIIIb, or VIIIc. This may be seen readily if, for convenience, we call the coupling

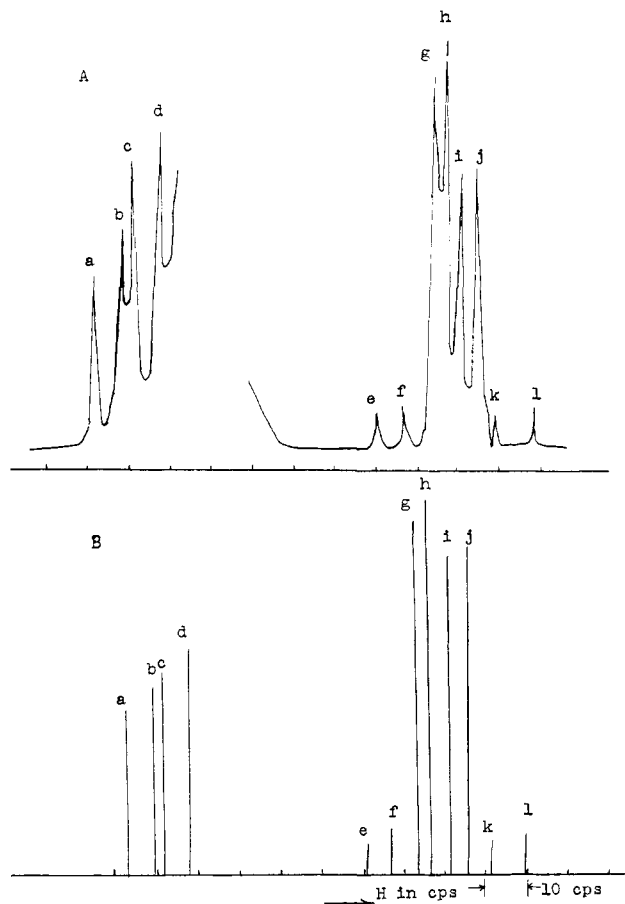


Figure 3.—A: Observed spectrum of II in D<sub>2</sub>O at 80°. B: Calculated spectrum of II in D<sub>2</sub>O at 80°.

constant between two hydrogens in *trans* configuration (*i.e.*, with a dihedral angle of 180°)  $J_T$  and that between two hydrogens in *gauche* configuration (*i.e.*, with a dihedral angle of 60°)  $J_G$ . In order to estimate the  $J_T$  and  $J_G$ , we applied the modified Karplus equation.<sup>7</sup> When a dihedral angle  $\phi$  of 180° was inserted into this equation,  $J_T$  was given as 11.0, and with  $\phi = 60^\circ$   $J_G = 3.5$  cps. Bothner-By and Naar-Colin<sup>9</sup> reported for the methine protons in 2,3-diphenylbutane,  $J_T = 13$  and  $J_G = 3$  cps as being reasonable. Anet<sup>10</sup> also reported that in *meso*- and *dl*-2,3-dibromobutane  $J_T$  and  $J_G$  are 10-12 and 1-3 cps, respectively.

The average values of  $J_{H_A H_X}$  and  $J_{H_B H_X}$  over configurations VIIIa, VIIIb, and VIIIc are then, respectively,  $J_{AX} = P_T J_T + P_G J_G + P_G' J_G$ ,  $J_{BX} = P_T J_G + P_G J_T + P_G' J_G$ , and  $P_T + P_G + P_G' = 1$ , where  $P_G$ ,  $P_G'$ , and  $P_T$  are the fractional populations. Therefore

$$P_T = \frac{J_T - J_{BX}}{J_T - J_G} = 0.65, P_G = \frac{J_T - J_{AX}}{J_T - J_G} = 0.28, \text{ and}$$

$$P_G' = 0.07$$

From the above, the most probable conformation of (*S*)-(+)-1,2-diphenylethylamine hydrochloride (IV) is the off-staggered form. The preferred conformations of (*R*)-(-)-N,N-dimethyl-1,2-diphenylethylamine hydrochloride (II) may be considered to resemble those of IV by the same analogy with shapes of pattern and spin-coupling constants. The molecular constants

(7) R. U. Lemieux, *et al.*, *Tetrahedron Letters*, 1229 (1963).

(8) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961).

(9) A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, **84**, 743 (1962).

(10) F. A. L. Anet, *ibid.*, **84**, 747 (1962).

TABLE III  
OBSERVED AND CALCULATED SPECTRA OF II IN D<sub>2</sub>O AT 80°<sup>a</sup>

	---Line position---		---Rel intensity---	
	Obsd	Calcd	Obsd	Calcd
a	1.8	1.77	0.818	0.818
b	8.2	8.44	0.898	0.957
c	10.7	10.77	0.946	1.008
d	17.5	17.48	1.251	1.208
e	70.8	70.83	0.180	0.169
f	77.3	77.50	0.209	0.210
g	84.7	84.69	1.923	2.000
h	86.8	86.96	1.962	2.038
i	91.2	91.39	1.722	1.620
j	96.1	95.95	1.674	1.580
k	100.7	100.82	0.177	0.180
l	109.9	109.82	0.193	0.180

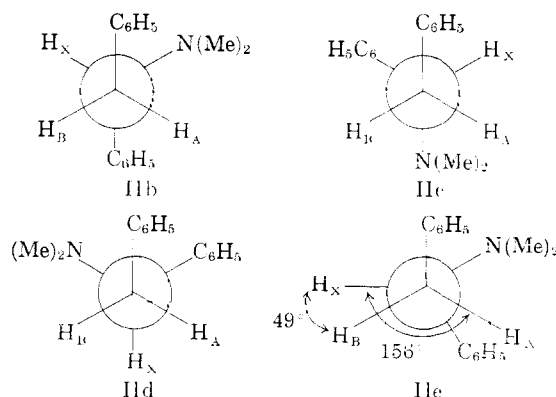
<sup>a</sup>  $J_{AB} = 13.90$ ,  $J_{BX} = 6.40$ ,  $J_{AX} = 9.30$  cps.  $\nu_A - \nu_B = 10.10$ ,  $\nu_B - \nu_X = 74.50$  cps. See footnote a, Table II.

of II are listed in Table III, and spectra are shown in Figure 3.

The shapes of spectra and spin-coupling constants of II were very similar to those of IV; the resonance lines attributed to H<sub>X</sub> were partially overlapped with a signal of DHO at 30° and thus the spectrum was also measured at 80°. The obtained molecular constants and spin-coupling constants were similar to those of IV. As listed in Table III,  $J_{AX}$  and  $J_{BX}$  have a spacing of 9.3 and 6.4 cps, respectively. The dihedral angles calculated from the modified Karplus equation<sup>7</sup> with  $J$  values of II were as follows:  $\phi$  was 49° for  $J_{BX}$  and 156° for  $J_{AX}$ . The uncertainty in  $\phi$  calculated in II might be due to *trans* and *gauche* relations of phenyl-phenyl groups.

From these nmr data it was calculated that the population distribution of conformers of IIb, IIc, and

CHART V



IId was 61, 22, and 17%, respectively. This could be interpreted as indicating internal rotation about a central C-C bond to a conformation (IIc) averaged over the three isomers.

In summary, the analgetic activity of II is consistent with its stereochemical resemblance (as determined by ORD measurements which confirm the assignments made initially by Nakazaki<sup>3</sup>) to (-)-morphine. Furthermore, the existence of II in 22% eclipsed conformation (nmr data) might explain its potency in terms of favoring its approach to some reactive surface in the nervous system.

## Experimental Section

**Nmr Spectra.**—All nmr spectra were obtained by means of a Varian A-60 spectrometer operating at fixed radiofrequency of 60 Mc/sec. Measurements were performed with approximately a 15% (w/v) solution in deuterium oxide which had a purity of 99.75% at 30 and 80°. In order to obtain the line positions used for analysis, at least nine determinations were made on each compound at 80°. Trial and error methods were used for the analysis of these spectra and calculations were carried out by the IBM-1620 Monitor System electric computer. The results are summarized in Figures 2 and 3 and Tables II and III.

**Optical Rotatory Dispersion Spectra.**—All measurements of rotations were made on a Rudolph spectropolarimeter, with measurements beginning at 700 m $\mu$ . The concentrations were not varied over the region investigated, but the pathlength ranged from 0.1-1.0 dm. The solvent was ethanol, and the temperature was essentially constant at 22-25°; see Figure 1 and Table I.

(*R*)-(-)-**N,N-Dimethyl-1,2-diphenylethylamine hydrochloride (II)** was prepared by the method of Ogin, *et al.*,<sup>11</sup> mp 218-219°,  $[\alpha]^{20}_D = -91.7^\circ$  (*c* 2.0, H<sub>2</sub>O).

(*R*)-(-)-**1,2-Diphenylethylamine hydrochloride (III)** was prepared by the method of Ogin, *et al.*,<sup>11</sup> mp 259-260°,  $[\alpha]^{25}_D = -125.5 \pm 2^\circ$  (*c* 0.97, EtOH).

(*S*)-(+)-**1,2-Diphenylethylamine hydrochloride (IV)** was prepared by the method of Ogin, *et al.*,<sup>11</sup> mp 259-260°,  $[\alpha]^{20}_D = +128.0^\circ$  (*c* 0.99, EtOH).

D-(+)-**erythro-1,2-Diphenyl-2-hydroxyethylamine (V)** was prepared by Nakazaki,<sup>3</sup> mp 142-143°,  $[\alpha]^{25}_D = -7.0 \pm 2^\circ$  (*c* 0.98, EtOH); hydrochloride, mp 213-214°,  $[\alpha]^{20}_D = -69.3^\circ$  (*c* 1.0, H<sub>2</sub>O).

D-(+)-**erythro-N,N-Dimethyl-1,2-diphenyl-2-hydroxyethylamine hydrochloride (VI)** was prepared by the method of Yamakawa,<sup>12</sup> mp 255°,  $[\alpha]^{25}_D = -158.2 \pm 2^\circ$  (*c* 1.02, EtOH).

**Acknowledgments.**—The authors are grateful to Dr. K. Kuriyama of the Shionogi Research Laboratory and Dr. H. Fujimura of the Faculty of Medicine, Gifu University, for their helpful guidance and discussion.

(11) K. Ogin, H. Fujimura, and Y. Yamakawa, *Yakugaku Zasshi*, **80**, 283 (1960).

(12) Y. Yamakawa, *ibid.*, **80**, 205 (1960).