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Synthesis of optically Active Prenylamine from (—)-Norephedrine

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Optically active prenylamine was synthesized from natural (—)-norephedrine, through the aziridine derivatives. The absolute configuration of (+)-prenylamine was confirmed to have (*S*)-configuration by the synthesis. Further, the pharmacological activity was examined.

Prenylamine, N-(3,3-diphenylpropyl)-α-methylphenethylamine (I), is therapeutically an useful compound which exhibits a dilating activity on the coronary blood vessels. Many processes[2] for the preparation of I and the optical resolution[3] have hitherto been reported. However, the synthesis of optically active I has not been reported.

We wish to describe a novel synthesis of optically active prenylamine *via* the aziridine derivatives derived from natural (—)-norephedrine.

2-Methyl-3-phenylaziridine (V) was synthesized by the following two methods as shown in Chart 1.

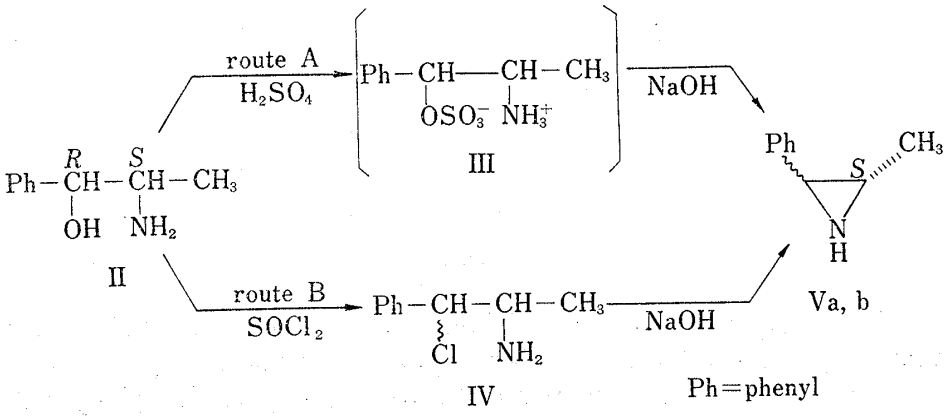

Chart 1

In route A, (—)-norephedrine (II) was treated with sulfuric acid to yield the intermediary sulfate ester (III), which was then directly cyclized to the aziridine (V) by treatment with hot aqueous sodium hydroxide, according to the Brois' procedure.[4] The resulting product (V) was a mixture of *trans* isomer (Va) and *cis* isomer (Vb) in a ratio of 95 : 5 on the basis of the nuclear magnetic resonance (NMR) spectrum. The yield of the mixture (Va, b) was 84% from II.

In route B, 2-amino-1-chloro-1-phenylpropane (IV) hydrochloride was obtained by the treatment of II with thionyl chloride by Taguchi's method.[5] The product (IV) was almost

1) Location: *16-89, Kashima-3-chome, Yodogawa-ku, Osaka, 532, Japan.*
2) G. Ehrhart, E. Linder, and H. Ott, Ger. Patent 1111642 (1958) [*C.A.*, **56**, 8630*h* (1962)]; *idem*, Ger. Patent 1100031 (1961) [*C.A.*, **56**, 3413*h* (1962)]; C. van der Stelt, U.S. Patent 3230256 (1966) [*C.A.*, **64**, 8080*f* (1966)].
3) H. Maske, E. Linder, and H. Ott, Ger. Patent 1115263 (1962) [*C.A.*, **56**, 10040*d* (1962)].
4) S. Brois, *J. Org. Chem.*, **27**, 3532 (1962).
5) T. Taguchi and M. Kojima, *Chem. Pharm. Bull.* (Tokyo), **3**, 4 (1955).

threo isomer, and the *erythro* isomer was formed only about 4%. The purified *threo* isomer of IV was treated with hot aqueous sodium hydroxide by the Kojima's procedure[6] to give a mixture of *trans* isomer (Va) and *cis* isomer (Vb) in a ratio of 6: 94 on the basis of the NMR spectrum. The yield of the mixture (Va, b) was 79.8% from IV·HCl. Specific rotations, $[\alpha]_D^{21}$, of Va and Vb are −61.9° and −67.8°, respectively.

Treatment of Va with 3,3-diphenylpropyl iodide in the presence of potassium carbonate in hot methyl ethyl ketone gave *trans* 1-(3,3-diphenylpropyl)-2-methyl-3-phenylaziridine (VIa) as a colorless oil, $[\alpha]_D^{27}$ +26.1°, in 66% yield. Under the same reaction conditions, the corresponding *cis* isomer (VIb) was obtained from Vb as colorless needles, mp 60—61°, $[\alpha]_D^{27}$ −74.9° in 90% yield. The structures of VIa and VIb were confirmed by their infrared (IR), NMR spectral data and their elemental analyses. It is presumed that the yields of the N-alkylation of Va and Vb were affected by their steric hindrance.

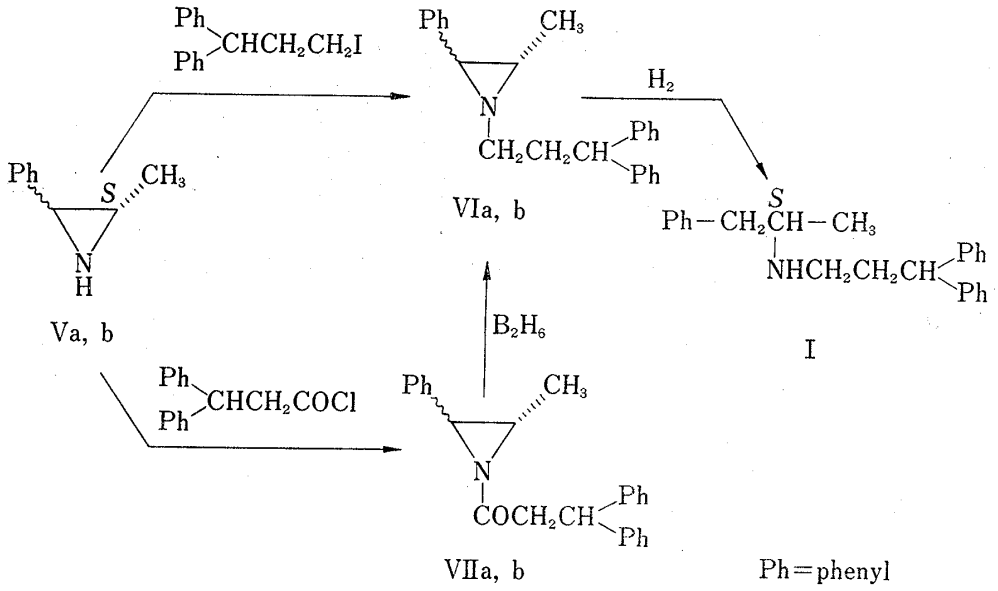

Chart 2

N-Alkylaziridine (VI) was also obtained from acylation of V, followed by reduction with diborane; *trans* 1-(3,3-diphenylpropionyl)-2-methyl-3-phenylaziridine (VIIa), a colorless oil, was prepared quantitatively by the reaction of Va with 3,3-diphenylpropionyl chloride in the presence of triethylamine in tetrahydrofuran (THF). In the same way, *cis* isomer (VIIb) was also synthesized quantitatively from Vb as a colorless oil. The structures of VIIa and VIIb were confirmed by their IR and NMR data. The *trans* N-acylaziridine (VIIa) dissolved in THF was reduced by refluxing with diborane, generated from sodium borohydride and boron trifluoride etherate in the mixture, to give a colorless oily amine-borane complex of VIa.

Then, N-alkylaziridine (VI) was hydrogenolyzed according to the Haberl's procedure;[7] VIa was reduced in ethanol under the hydrogen pressure of 3—4 kg/cm² in the presence of palladium-carbon to give (+)-prenylamine (I) as a colorless oil in 90% yield. Consequently, it was proved that (+)-I has (*S*)-configuration, because the absolute configuration of Cα of II is retained. Under the same reaction conditions, hydrogenolysis of VIb was carried out to give the same product (*S*)-(+)-I.

The amine-borane complex of VIa was also hydrogenolyzed in methanol by use of Raney Ni under the hydrogen pressure of 50 kg/cm² at 60—70° to give (*S*)-(+)-(I) in 40% yield from Va. Treatment of (*S*)-(+)-I with the various acids gave the corresponding salts: hydrochloride,

6) M. Kojima, *Yakugaku Zasshi*, **79**, 11 (1959).
7) R.H. Haberl, *Monatsh. Chem.*, **89**, 814 (1958).

mp 200—201°, $[\alpha]_D^{27}$ +12.1°; glycolate,[3] mp 128.5—129.5°, $[\alpha]_D^{27}$ +10.9°; D(−):lactate, mp 140—141°, $[\alpha]_D^{27}$ +15.1° and L-tartrate (neutral), mp 174—175°, $[\alpha]_D^{27}$ +21.3°.

The optically active I was also synthesized by the following several methods *via* the oxazoline derivative which was easily derived from the N-acylaziridine (VII).

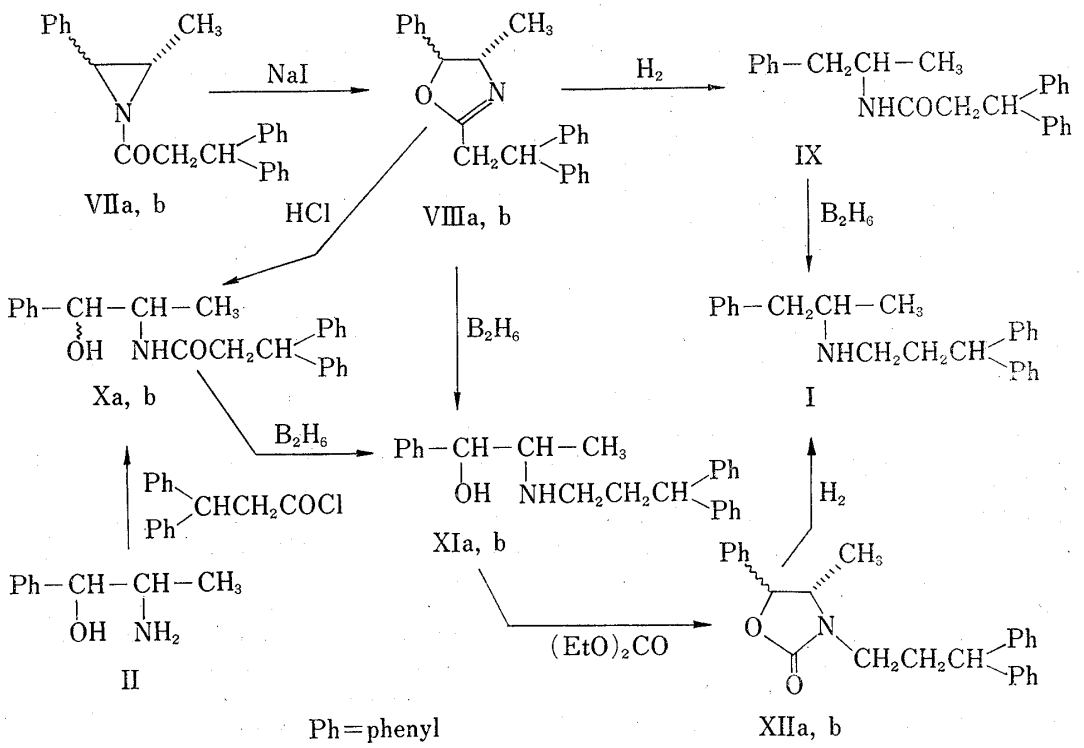

Chart 3

The conventional treatment[8] of VIIa with sodium iodide in refluxing acetone gave stereoselectively *trans* 2-(2,2-diphenylethyl)-4-methyl-5-phenyl-2-oxazoline (VIIIa), mp 89—91°, in 72% yield. On the other hand, under the same reaction conditions *cis* isomer (VIIb) gave a mixture of VIIIa and *cis* isomer (VIIIb) in a ratio of about 1:1 in 81% yield. The oxazoline (VIIIa) was hydrogenolyzed in ethanol under the hydrogen pressure of 55 kg/cm² at 60—70° over Raney Ni to give 1-phenyl-2-(3,3-diphenylpropionylamino)propane (IX), mp 108—109°, in 88% yield. Then, IX was reduced by diborane in THF to give (*S*)-(+)-(I) in 90% yield.

Further, *trans* oxazoline (VIIIa) was reduced by diborane in THF to give *threo* 1-phenyl-2-(3,3-diphenylpropylamino)-1-propanol (XIa), mp 107—108°, in nearly 40% yield. XIa was also synthesized by diborane-reduction of *threo* 1-phenyl-2-(3,3-diphenylpropionylamino)-1-propanol (Xa), mp 138—139°, which was prepared by hydrolysis of VIIIa with aqueous hydrochloric acid. Whereas, *erythro* isomer (Xb) was prepared by acylation of II with, 3,3-diphenylpropionyl chloride since the *cis* oxazoline (VIIIb) could not be isolated. In the same manner as Xa, Xb was reduced by diborane to give *erythro* 1-phenyl-2-(3,3-diphenylpropylamino)-1-propanol (XIb), mp 96—98°, in 88% yield. XIa and XIb were allowed to react with ethyl carbonate in the presence of sodium methoxide in benzene to give *trans* 3-(3,3-diphenylpropyl)-4-methyl-5-phenyl-2-oxazolidone (XIIa) and the *cis* isomer (XIIb), respectively, in good yields. (*S*)-(+)-(I) was prepared independently by the hydrogenolysis[9] of both XIIa and XIIb over palladium-carbon under the hydrogen pressure of 3.5 kg/cm² in ethanol in high yields.

8) T.A. Foglia, L.M. Gregory, and G. Maerker, *J. Org. Chem.*, **35**, 3779 (1970).
9) A.G. Georgiev, L.D. Zheliazkov, and M.G. Kazandjiev, Bulgaria Patent 11326 (1967).

Although the pharmacological activity of the gluconate of (*S*)-(+)-prenylamine was the same as that of (±)-prenylamine, these methods are new chemical conversions of natural (−)-norephedrine and further, gave a chemical elucidation of the absolute configuration of (+)-prenylamine.

Experimental[10]

***trans* 2-Methyl-3-phenylaziridine (Va)**——To a suspension of (−)-norephedrine (II) (15.1 g, 0.1 mole) in H_2O (50 ml) was added 50% H_2SO_4 (18.0 g, 0.1 mole) and the solution was concentrated to dryness *in vacuo*. Benzene was added to the residue. The mixture was refluxed to remove H_2O for 5 hr under vigorous stirring by the azeotropic method using Dean-Stark separator. The resulting crude III was collected by filtration and dissolved in 2N NaOH (200 ml) at 0°. Then the solution was slowly heated with stirring and stirring was continued for 5 hr at approximately 90°. The oily upper layer separated was extracted with benzene and dried over Na_2SO_4. Evaporation of the solvent afforded an oily residue, which was distilled under reduced pressure to give Va (11.2 g, 84.0%) as a colorless oil, bp 95—97° (10 mmHg). This distillate contained 5% *cis* isomer (Vb) on the basis of NMR spectrum. Pure Va was separated by preparative gas chromatography (Hyprose SP-80, 6 mm×3 m, 155°). $[\alpha]_D^{21}$ −61.9° (*c*=1, MeOH). IR ν_{max}^{film} cm^{-1}: 3250 (NH). NMR ($CDCl_3$) δ: 1.18 (1H, s, NH), 1.34 (3H, d, J=5.5 Hz, CH_3), 1.92—2.30 (1H, m, C<u>H</u>–CH_3), 2.62 (1H, d, J=3.5 Hz, C<u>H</u>–Ph), 7.20 (5H, s, aromatic).

***threo*-2-Amino-1-chloro-1-phenylpropane (IV)**——To a solution of II (30.2 g, 0.2 mole) in $CHCl_3$ (60 ml), $SOCl_2$ (52.4 g, 0.44 mole) was added under ice-cooling with stirring. After stirring for 4 hr at room temperature, the reaction mixture was concentrated *in vacuo*. The residual syrup was washed with ether to afford crude IV·HCl, which contained a small amount of *erythro* isomer (about 4%). Recrystallization from EtOH afforded IV·HCl (35.6 g, 86.3%) as colorless prisms, mp 173—174°. $[\alpha]_D^{20}$ +95.4° (*c*=1, MeOH). *Anal.* Calcd. for $C_9H_{13}NCl_2$: C, 52.44; H, 6.36; N, 6.80. Found: C, 52.52; H, 6.42; N, 6.90. NMR (D_2O) δ: 1.25 (3H, d, J=6 Hz, CH_3), 3.72—4.30 (1H, m, C<u>H</u>–CH_3), 5.18 (1H, d, J=9.5 Hz, C<u>H</u>–Ph), 7.53 (5H, s, aromatic).

***cis* 2-Methyl-3-phenylaziridine (Vb)**——To a solution of IV·HCl (6.18 g, 0.03 mole) in H_2O (24 ml) was added 50% NaOH (7.2 g, 0.09 mole) and the reaction mixture was refluxed for 1 hr. The reaction mixture was extracted with benzene and the extract was dried over Na_2SO_4 and evaporated. The residue was recrystallized from *n*-hexane to give Vb (2.65 g, 66.3%) as colorless needles, mp 67—68°. From the mother liquor a mixture of Va and Vb was obtained in a ratio of 1: 1.6 as a colorless oil (0.54 g, 13.5%). $[\alpha]_D^{21}$ −67.8° (*c*=1, MeOH). *Anal.* Calcd. for $C_9H_{11}N$: C, 81.16; H, 8.32; N, 10.52. Found: C, 80.82; H, 8.82; N, 10.63. IR ν_{max}^{Nujol} cm^{-1}: 3220 (NH). NMR ($CDCl_3$) δ: 0.90 (3H, d, J=6 Hz, CH_3), 1.08 (1H, s, NH), 2.15—2.60 (1H, m, C<u>H</u>–CH_3), 3.10 (1H, d, J=6 Hz, C<u>H</u>–Ph), 7.28 (5H, s, aromatic).

***trans* 1-(3,3-Diphenylpropyl)-2-methyl-3-phenylaziridine (VIa)**——To a solution of Va (3.33 g, 0.025 mole) in methyl ethyl ketone (100 ml) were added 3,3-diphenylpropyl iodide (12.1 g, 0.038 mole) and K_2CO_3 (5.2 g, 0.038 mole) and the mixture was refluxed for 24 hr. After concentration *in vacuo* the residue was extracted with benzene and the benzene extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The oily residue was chromatographed over silica gel with $CHCl_3$ to give VIa (5.4 g, 66.2%) as a colorless oil. $[\alpha]_D^{27}$ +26.1° (*c*=1, MeOH). NMR ($CDCl_3$) δ: 1.23 (3H, d, J=5 Hz, CH_3), 1.75—3.10 (6H, m, Ph–C<u>H</u>–C<u>H</u>–CH_3, N–C<u>H</u>$_2$–C<u>H</u>$_2$–CH), 4.06 (1H, t, J=8 Hz, C<u>H</u>Ph_2), 7.17 (15H, s, aromatic).

***cis* 1-(3,3-Diphenylpropyl)-2-methyl-3-phenylaziridine (VIb)**——In the same way VIb was obtained from Vb (3.33 g, 0.025 mole) as colorless crystals (7.36 g, 90%). Recrystallization from petr. ether gave colorless needles, mp 60—61°. $[\alpha]_D^{27}$ −74.9° (*c*=1, MeOH). *Anal.* Calcd. for $C_{24}H_{25}N$: C, 88.03; H, 7.70; N, 4.28. Found: C, 87.81; H, 7.78; N, 4.33. NMR ($CDCl_3$) δ: 0.89 (3H, d, J=5 Hz, CH_3), 1.67 (1H, quintet, C<u>H</u>–CH_3) 1.99—2.80 (5H, m, C<u>H</u>–Ph, N–C<u>H</u>$_2$C<u>H</u>$_2$–CH), 4.11 (1H, t, J=8 Hz, C<u>H</u>Ph_2), 6.82—7.58 (15H, m, aromatic).

***trans* 1-(3,3-Diphenylpropionyl)-2-methyl-3-phenylaziridine (VIIa)**——To a stirred solution of Va (0.27 g, 2 mmole) and triethylamine (0.2 g, 2 mmole) in THF (15 ml) was added dropwise a solution of 3,3-diphenylpropionyl chloride (0.5 g, 2 mmole) in THF (15 ml) at 0—5°. After stirring for 1 hr at room temperature, the resulting triethylamine hydrochloride was filtered off and the filtrate was concentrated *in vacuo*. To the residue benzene and H_2O were added. The benzene layer was separated, dried over Na_2SO_4 and evaporated to give the crude VIIa (0.7 g, 100%) as a colorless oil. The crude VIIa was used in the next step without further purification. IR ν_{max}^{film} cm^{-1}: 1685 (CO). NMR ($CDCl_3$) δ: 1.18 (3H, d, J=5.5 Hz, CH_3), 2.28—2.80 (1H, m, C<u>H</u>–CH_3), 2.86 (1H, d, J=2.5 Hz, C<u>H</u>–Ph), 3.04 (2H, d, J=8 Hz, CO–C<u>H</u>$_2$–CH), 4.62 (1H, t, J=8 Hz, C<u>H</u>Ph_2), 6.80—7.60 (15H, m, aromatic).

10) All melting points are uncorrected. NMR spectra were taken on a Hitachi Perkin-Elmer R-20A spectrometer with tetramethylsilane as an internal standard. Chemical shifts are given in δ (ppm) values. IR spectra were measured on a Shimadzu IR 27G spectrometer. Gas-liquid chromatograph was performed with a Shimadzu gas chromatograph Model GC 4B. Optical rotations were measured in methanol with a Perkin-Elmer Model 141 polarimeter.

***cis* 1-(3,3-Diphenylpropionyl)-2-methyl-3-phenylaziridine (VIIb)**——VIIb (7.0 g, 100%) was obtained from Vb (2.66 g, 0.02 mole), triethylamine (2.0 g, 0.02 mole) and 3,3-diphenylpropionyl chloride (4.9 g, 0.02 mole) as a colorless oil in a similar manner described above. IR ν_{max}^{film} cm^{-1}: 1695 (CO). NMR ($CDCl_3$) δ: 0.86 (3H, d, J=6 Hz, CH_3), 2.47 (1H, quintet, C<u>H</u>–CH_3), 3.05 (1H, d, J=6 Hz, C<u>H</u>–Ph), 3.15 (2H, d, J=8 Hz, CO<u>CH$_2$</u>–CH), 4.65 (1H, t, J=8 Hz, C<u>H</u>Ph$_2$), 6.80—7.68 (15H, m, aromatic).

***trans* 2-(2,2-Diphenylethyl)-4-methyl-5-phenyl-2-oxazoline (VIIIa)**——A mixture of VIIa (0.56 g, 1.65 mmole) and sodium iodide (1.24 g, 8.3 mmole) in acetone (30 ml) was heated at reflux for 24 hr. The solvent was removed *in vacuo*, and the residue was extracted with benzene. The benzene extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The oily residue was chromatographed over silica gel with $CHCl_3$ to give VIIIa (0.4 g, 71.5%). Recrystallization from isopropyl ether gave colorless needles, mp 89—91°. $[\alpha]_D^{27}$ −2.0° (c=1, MeOH). *Anal.* Calcd. for $C_{24}H_{24}ON$: C, 84.42; H, 6.79; N, 4.10. Found: C, 84.09; H, 6.89; N, 4.32. IR ν_{max}^{Nujol} cm^{-1}: 1660 (C=N). NMR ($CDCl_3$) δ: 1.18 (3H, d, J=7 Hz, CH_3) 3.13 (2H, d, J=8 Hz, C<u>H$_2$</u>CHPh$_2$), 3.80 (1H, quintet, C<u>H</u>–CH_3), 4.55 (1H, t, J=8 Hz, C<u>H</u>Ph$_2$), 4.71 (1H, d, J=8 Hz, C<u>H</u>–Ph), 6.60—7.62 (15H, m, aromatic).

***cis* 2-(2,2-Diphenylethyl)-4-methyl-5-phenyl-2-oxazoline (VIIIb)**——A mixture of VIIb (6.83 g, 0.019 mole), sodium iodide (14.9 g, 0.093 mole) and acetone (70 ml) was treated in the similar manner described above to give the semi-solid product (5.2 g, 81%), which was a mixture of VIIIa and VIIIb in a ratio of 1:1 on the basis of NMR spectrum. Separation of VIIIb from the mixture by means of column chromatography was unsuccessful.

1-Phenyl-2-(3,3-diphenylpropionylamino)propane (IX)——A mixture of VIIIa (4.1 g. 0.012 mole), Raney Ni catalyst (2 ml) and EtOH (150 ml) was shaken at 60—70° under the hydrogen pressure of 55 kg/cm^2 for 1 hr. The catalyst was removed by filtration and the filtrate was evaporated. The residue was recrystallized from benzene–ether to give IX (3.6 g, 87.3%) as colorless needles, mp 108—109°. $[\alpha]_D^{27}$ −5.0° (c=1, MeOH). *Anal.* Calcd. for $C_{24}H_{25}ON$: C, 83.92; H, 7.34; N, 4.08. Found: C, 83.93; H, 7.39; N, 4.07. IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH), 1635 (CO). NMR ($CDCl_3$) δ: 0.85 (3H, d, J=7 Hz, CH_3), 2.40—2.66 (2H, m, C<u>H$_2$</u>–Ph), 2.81 (2H, d, J=8 Hz, CO–C<u>H$_2$</u>–CH), 3.84—4.40 (1H, m, C<u>H</u>–CH_3), 4.54 (1H, t, J=8 Hz, C<u>H</u>Ph$_2$), 5.13 (1H, d, J=9 Hz, NH), 6.82—7.52 (15H, m, aromatic).

***threo* 1-Phenyl-2-(3,3-diphenylpropionylamino)-1-propanol (Xa)**——A mixture of VIIIa (0.5 g, 1.5 mmole), $CHCl_3$ (5 ml) and 2% HCl (10 ml) was stirred at room temperature for 1 hr. The resulting precipitate was collected by filtration. To a suspension of the precipitate in benzene (10 ml) was added 10% Na_2CO_3 (5 ml). The mixture was stirred at room temperature for 1 hr. The benzene layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene to give Xa (0.1 g, 19%) as colorless needles, mp 138—139°. $[\alpha]_D^{27}$ −30.2° (c=1, MeOH). *Anal.* Calcd. for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.07; H, 7.04; N, 4.25. IR ν_{max}^{Nujol} cm^{-1}: 3300 (NH), 1740 (CO). NMR ($CDCl_3$) δ: 0.82 (3H, d, J=7 Hz, CH_3), 2.82 (2H, d, J=8 Hz, CO–C<u>H$_2$</u>–CH), 3.64 (1H, d, J=3 Hz, OH), 3.79—4.23 (1H, m, C<u>H</u>–CH_3), 4.23—4.73 (2H, m, C<u>H</u>–Ph, C<u>H</u>Ph$_2$), 5.73 (1H, d, J=7 Hz, NH). 7.23 (15H, s, aromatic).

***erythro* 1-Phenyl-2-(3,3-diphenylpropionylamino)-1-propanol (Xb)**——To a stirred solution of II (1.0 g, 6.6 mmole) in $CHCl_3$ (5 ml) were added dropwise a solution of 3,3-diphenylpropionyl chloride (1.52 g, 6.2 mmole) in $CHCl_3$ (5 ml) and 10% NaOH (2.67 g, 6.7 mmole) simultaneously at 0—5°. After stirring at room temperature for 1 hr, the $CHCl_3$ layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from benzene to give Xb (1.55 g, 65.2%) as colorless needles, mp 120—121°. $[\alpha]_D^{27}$ −28.2° (c=1, MeOH). *Anal.* Calcd. for $C_{24}H_{25}O_2N$: C, 80.19; H, 7.01; N, 3.90. Found: C, 80.06; H, 7.11; N, 4.13. IR ν_{max}^{Nujol} cm^{-1}: 3400, (OH), 3320, (NH), 1630, (CO). NMR ($CDCl_3$) δ: 0.73 (3H, d, J=7 Hz, CH_3), 2.86 (2H, d, J=7.5 Hz, CO–C<u>H$_2$</u>–CH), 3.22 (1H, s, OH), 3.80—4.30 (1H, m, C<u>H</u>–CH_3), 4.30—4.85 (2H, m, C<u>H</u>–Ph, C<u>H</u>Ph$_2$), 5.65 (1H, d, J=7.5 Hz, NH), 7.23 (15H, s, aromatic).

***threo* 1-Phenyl-2-(3,3-diphenylpropylamino)-1-propanol (XIa)**——To a solution of VIIIa (4.1 g, 0.012 mole) in THF (80 ml) was added $NaBH_4$ (0.85 g, 0.0225 mole) and then dropwise a solution of BF_3·ether (4.3 g, 0.03 mole) in THF (20 ml) at 0—5° with stirring. The reaction mixture was stirred at room temperature for 1 hr and then refluxed 2 hr. After cooling, dil. NaOH and AcOEt were added to the mixture and the AcOEt layer was separated, washed with H_2O, dried over Na_2SO_4 and then evaporated. The oily residue was chromatographed over silica gel with benzene–AcOEt (4:1) to recover the starting material (VIIIa, 0.8 g, 19.5%). Then the elution with benzene–AcOEt–EtOH (7:2:1) gave XIa (1.65 g, 39.7%). Recrystallization from benzene petr. ether afforded colorless needles, mp 107—108°. $[\alpha]_D^{27}$ +41.0° (c=1, MeOH). *Anal.* Calcd. for $C_{24}H_{27}ON$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.20; H, 7.92; N, 4.18. IR ν_{max}^{Nujol} cm^{-1}: 3300 (OH), 3180 (NH). NMR ($CDCl_3$) δ: 0.85 (3H, d, J=7 Hz, CH_3), 1.90—3.02 (7H, m, C<u>H</u>–CH_3, N<u>H</u>–C<u>H$_2$</u>–C<u>H$_2$</u>, OH), 3.78—4.25 (2H, m, C<u>H</u>-Ph, C<u>H</u>Ph$_2$), 7.22 (10H, s, aromatic), 7.28 (5H, s, aromatic).

***erythro*-1-Phenyl-2-(3,3-diphenylpropylamino)-1-propanol (XIb)**——To a solution of Xb (1.20 g, 3.3 mmol) in THF (50 ml) was added $NaBH_4$ (0.76 g, 20 mmole) and then dropwise a solution of BF_3·ether (3.8 g, 27 mmole) in THF (10 ml) at 0—5° with stirring. The reaction mixture was treated in the same manner described above to give crude XIb (1.0 g, 87.7%). Recrystallization from benzene–*n*-hexane gave colorless needles, mp 96—98°. $[\alpha]_D^{21}$ +4.4° (c=1, MeOH). *Anal.* Calcd. for $C_{24}H_{27}ON$: C, 83.44; H, 7.88; N, 4.05. Found: C, 82.71; H, 7.93; N, 4.08. IR ν_{max}^{Nujol} cm^{-1}: 3150 (NH). NMR ($CDCl_3$) δ: 0.75 (3H, d, J=7 Hz, CH_3),

1.88—3.08 (7H, m, C<u>H</u>-CH_3, $NHC\underline{H}_2C\underline{H}_2$, OH), 4.00 (1H, t, J=7.5 Hz, $C\underline{H}Ph_2$), 4.60 (1H, d, J=4 Hz, C<u>H</u>-Ph), 7.22 (15H, s, aromatic). Similarly Xa was reduced to give XIa in good yield.

***trans*-3-(3,3-Diphenylpropyl)-4-methyl-5-phenyl-2-oxazolidone (XIIa)**——To a solution of XIa (1.0 g, 2.9 mmole) in benzene (10 ml) were added ethyl carbonate (0.37 g, 3.1 mmole) and sodium methoxide (0.18 g, 3.4 mmole) at room temperature with stirring. After stirring for 1.5 hr, the reaction mixture was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was recrystallized from EtOH to give XIIa (0.96 g, 89.3%) as colorless needles, mp 88—89°. $[\alpha]_D^{27}$ −0.8° (c=1, MeOH). *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.64; H, 6.84; N, 4.08. IR ν_{max}^{Nujol} cm^{-1}: 1750 (CO). NMR ($CDCl_3$) δ: 1.21 (3H, d, J=6 Hz, CH_3), 2.28 (2H, q, J=8 Hz, CH_2-$C\underline{H}_2$-CH), 2.70—4.10 (4H, m, C<u>H</u>-CH_3, $NC\underline{H}_2$-CH_2, $C\underline{H}Ph_2$), 4.85 (1H, d, J=7 Hz, C<u>H</u>-Ph), 7.20 (10H, s, aromatic), 7.32 (5H, s, aromatic).

***cis*-3-(3,3-Diphenylpropyl)-4-methyl-5-phenyl-2-oxazolidone (XIIb)**——In a similar manner as described above, the reaction of XIb (1.73 g, 5 mmole), ethyl carbonate (0.65 g, 5.5 mmole), sodium methoxide (0.32 g, 6 mmole) and benzene 20 ml gave XIIb (1.74 g, 93.5%) as colorless needles (EtOH), mp 124—125°. $[\alpha]_D^{21}$ −13.9° (c=1, MeOH). *Anal.* Calcd. for $C_{25}H_{25}O_2N$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.54; H, 6.81; N, 3.89. IR ν_{max}^{Nujol} cm^{-1}: 1725 (CO). NMR ($CDCl_3$) δ: 0.63 (3H, d, J=6 Hz, CH_3), 2.36 (2H, q, J=8 Hz, $CH_2C\underline{H}_2CH$), 2.64—4.20 (4H, m, C<u>H</u>-CH_3, N-$C\underline{H}_2$-CH_2-$C\underline{H}Ph_2$), 5.30 (1H, d, J=8 Hz, PhC<u>H</u>) 7.24 (15H, s, aromatic).

1-Phenyl-2-(3,3-Diphenylpropylamino)propane (Prenylamine) (I)——a) Catalytic Hydrogenolysis of VIa: A mixture of VIa (2.62 g, 8 mmole), 10% Pd-C (0.64 g) and EtOH (100 ml) was shaken at room temperature under the hydrogen pressure of 3.5 kg/cm² for 2 hr. The catalyst was removed by filtration and the filtrate was evaporated to give I (2.43 g, 92.0%) as a colorless oil. A solution of I (0.86 g, 2.6 mmole) in ether was mixed with a solution of D(−)-lactic acid (0.23 g, 2.6 mmole) in ether and the resulting precipitate was collected by filtration. The precipitate was washed with ether to afford the crude I-lactate (0.96 g, 88.1%), which was recrystallized from acetone to give colorless needles, mp 140—141°. $[\alpha]_D^{27}$ +15.1° (c=1, MeOH). *Anal.* Calcd. for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; N, 3.43. Found: C, 77.26; H, 7.94; N, 3.58.

b) Catalytic Hydrogenolysis of VIb: A mixture of VIb (1.0 g, 3 mmole), 10% Pd-C (0.3 g) and EtOH (80 ml) was shaken under the same reaction conditions described above to give I as a colorless oil. The oil was treated with EtOH–HCl to yield I-hydrochloride (0.98 g, 87.0%) which was recrystallized from EtOH to give colorless needles, mp 200—201°. $[\alpha]_D^{27}$ +12.1° (c=1, MeOH). *Anal.* Calcd. for $C_{24}H_{28}NCl$: C, 78.77; H, 7.71; N, 3.83. Found: C, 78.90; H, 7.77; N, 3.60. I-free base was obtained as a colorless oil from I-hydrochloride and NaOH in the usual way. $[\alpha]_D^{27}$ +18.8° (c=1, MeOH) [lit.[3] $[\alpha]_D^{20}$ +16° (MeOH)]. IR ν_{max}^{film} cm^{-1}: 3100 (NH). NMR ($CDCl_3$) δ: 0.96 (3H, d, J=7 Hz, CH_3), 1.35 (1H, s, NH), 1.90—3.00 (7H, m, Ph-$C\underline{H}_2$-C<u>H</u>, N-$C\underline{H}_2C\underline{H}_2$), 3.88 (1H, t, J=7 Hz, $C\underline{H}Ph_2$), 6.70—7.60 (15H, m, aromatic).

c) Acylation followed by Reduction with Dibrorane and Catalytic Hydrogenolysis of Va: To a stirred solution of Va (3.33 g, 0.025 mole) and triethylamine (2.53 g, 0.025 mole) in THF (20 ml) was added dropwise a solution of 3,3-diphenylpropionyl chloride (6.13 g, 0.025 mole) in THF (13 ml) under cooling. The reaction mixture was stirred at room temperature for 1 hr, and then separated triethylamine hydrochloride was filetred off. To the filtrate was added $NaBH_4$ (1.42 g, 0.038 mole) and then dropwise a solution of BF_3·ether (5.9 g, 0.042 mole) in THF (13 ml) at 0—5° with stirring. The reaction mixture was stirred for 1 hr at room temperature and then refluxed for 2.5 hr. After concentration *in vacuo*, dil.NaOH and benzene were added to the residue and the benzene layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated to give the crude amine-borane of VIa as a colorless oil. A mixture of the amine-borane Raney Ni catalyst (5 ml) and MeOH (50 ml) was shaken at 60—70° under hydrogen pressure of 55 kg/cm² for about 6 hr. The catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give crude I as a colorless oil. Through the solution of crude I in ether was bubbled dry HCl to afford I-hydrochloride (3.6 g, 39.5% from Va), mp 200—201°, which was identified with I-hydrochloride obtained at b) by the IR spectral comparison and mixed melting point determination.

d) Reduction of IX with Diborane: To a solution of IX (2.75 g, 8 mmole) in THF (50 ml) was added $NaBH_4$ (2.3 g, 60 mmole) and then dropwise a solution of BF_3·ether (11.4 g, 80 mmole) in THF (20 ml) at 0—5° with stirring. The reaction mixture was stirred at room temperature for 30 min and then refluxed for 3 hr. After cooling, 10% HCl was added to the reaction mixture and the whole was refluxed for 30 min and concentrated to remove THF. The resulting aqueous solution was made strongly basic to litmus with 10% NaOH and extracted with benzene. The benzene extract was washed with H_2O, dried over Na_2SO_4 and evaporated. The residue was treated in the same way described above to afford I-hydrochloride (2.65 g, 90.5%), mp 200—201°, which was identified with the authentic sample by comparison of IR and NMR spectra.

e) Catalytic Reduction of XII: A mixture of XIIa (0.56 g, 1.5 mmole), 10% Pd-C (0.06 g), HCl–EtOH (18%, 1 ml) and EtOH (50 ml) was shaken at room temperature under hydrogen pressure of 3.5 kg/cm² for 5 hr. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOH to give I-hydrochloride (0.50 g, 90.5%), mp 200—201°. *cis* Isomer (XIIb) was treated in the same way to give I-hydrochloride.

I-Glycolate: Colorless needles (AcOEt). mp 128.5—129.5° $[\alpha]_D^{27}$ +10.9° (c=1, MeOH) [lit.[3] mp 125°, $[\alpha]_D^{20}$ +7° (MeOH)]. *Anal.* Calcd. for $C_{26}H_{31}O_3N$: C, 77.00, H, 7.71, N, 3.45. Found: C, 76.97; H, 7.79; N, 3.81.

I-L-Tartrate: Colorless prisms (EtOH). mp 174—175°. $[\alpha]_D^{27}$ +21.3° (c=1, MeOH). *Anal.* Calcd. for $C_{26}H_{30}O_3N$: C, 77.20; H, 7.48; N, 3.46. Found: C, 76.70; H, 7.47; N, 3.46.

I-Gluconate: Colorless amorphous powder.

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