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Synthesis of 7,8-Dimethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepin-1-ol

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The *trans* (IVa) and *cis* (IVb) isomers of 7,8-dimethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepin-1-ol were stereospecifically synthesized.

Rhoeadine (involved the *cis* hydrogens shown in I) and alpinine (involved the *trans* hydrogens shown in II)[2] are the representatives of a small group of alkaloid, which have been found only in the genus *Papaver*, and the striking structural feature of this series of alkaloids is that these alkaloids contain a 3-benzazepine skeleton possessing an oxygen function and a phenyl group at C_1 and C_2, respectively. The first synthesis of this type alkaloid was recently reported by Irie, *et al.*[3] who synthesized rhoeadine (I) from the spiro-isoquinoline intermediate (III) applying a Wagner-Meerwein rearrangement which resulted in the ring enlargement of the six membered hetero ring.

The object of our present investigation is to explore the general synthetic route of the 3-benzazepine skeleton in connection with the synthesis of rhoeadine type alkaloids and the structure proof of a new alkaloid, the investigation of which is currently under way. The present paper is concerned with the stereospecific synthesis of the *trans* (IVa) and *cis* (IVb) isomers of 7,8-dimethoxy-N-methyl-2-phenyl-1,2,4,5-tetrahydro-3H-3-benzazepin-1-ol.

Gardent, *et al.*[4] has already reported the synthesis of a 3-benzazepin-1-one derivative (VI), which has no phenyl group at C_2, in a 65% yield by the Bischler-Napieralski ring closure of the glycine anilide derivative (V). After the manner of this synthesis, the cyclization reaction of the anilide derivative (VIII) derived from α-homoveratrylaminophenylacetic acid (VIIa) *via* (VIIb) was attempted but, in the present case, the diimino compound (IX), which resulted from detosylation and cyclization of the substrate, was obtained in a 40% yield. In order to selectively hydrolyze the exocyclic imino function, the compound (IX) was subjected to hydrolysis under various reaction conditions. All attempts, however, were unsuccessful and the resulting product was a 1-benzoylisoquinoline derivative (X), which assumed to be formed by hydrolysis of both imino functions and subsequent recyclization of the hydrolysis product. The synthetic route by way of this type cyclization, therefore, was abandoned and we directed our attention to another synthetic pathway.

It has been reported that the desylamine derivatives (XI) having the different kinds of substituents on each benzene ring are generally synthesized from the desoxybenzoin derivatives obtained by the Friedel-Crafts acylation *via* bromination and subsequent replacement of the bromine atom by an amino group.[5] On the other hand, Zalukaev, *et al.*[6] stated that reduction of the nitro compound (XII) with Zn-AcOH under refluxing afforded a 1,4-isoquinoline dione derivative (XIII). We, therefore, attempted to synthesize first the compound

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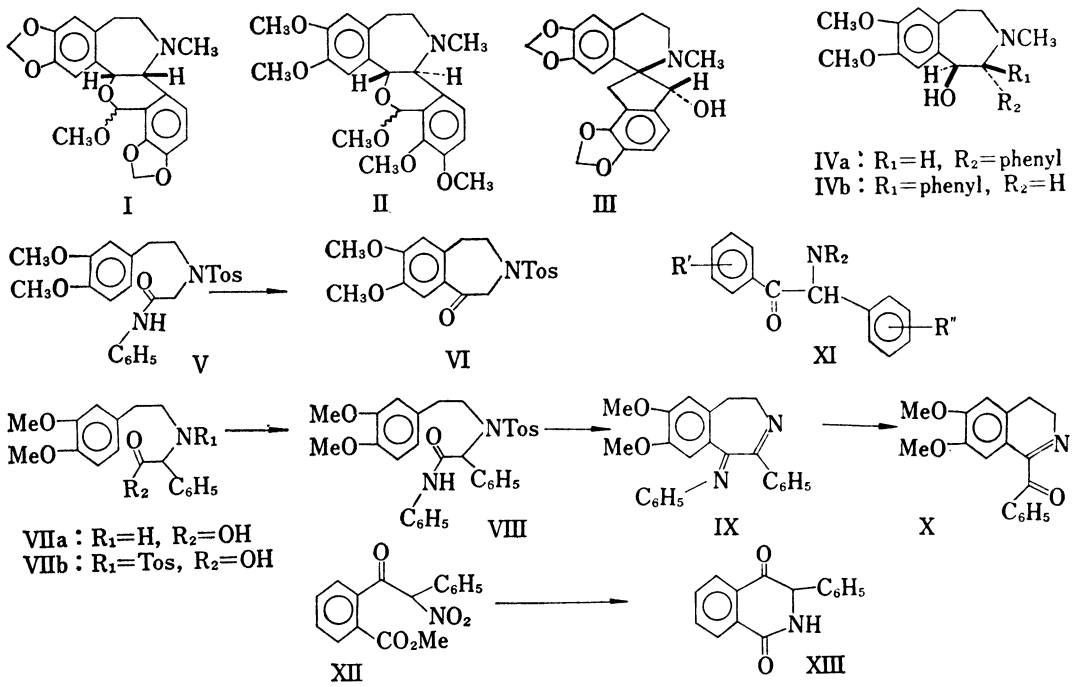

Chart 1

(XIVa) from easily accessible materials and the amino ester compound (XIVc) was then expected to afford the 7-membered lactam ring by the cyclization reaction.

The compound (XIVa) has been prepared by Bentley, *et al.*[7] from methyl 3,4-dimethoxy-homoveratrate and phenylacetyl chloride in a 32% yield applying the Friedel-Crafts acylation under the presence of $AlCl_3$ as a catalyst. After examination of the reaction conditions, it was noted that good yeilds, a 67% yield in the optimum result, were formed provided that $ZrCl_4$ catalyst is used. Bromination of the compound (XIVa) with bromine furnished the desyl-bromide (XIVb), mp 137—138°, $C_{19}H_{19}O_5Br$, in a 98% yield, the infrared (IR) spectrum of which showed absorption bands at 1735 (ester) and 1690 (ketonic function) cm^{-1}. Next, substitution of the bromine atom in XIVb by monomethylamine afforded the desylamine hydrobromide (XIVc), mp 213—215°, $C_{20}H_{23}O_5N$-HBr, in a 84% yield. Reduction of the compound (XIVc) with $NaBH_4$ gave unexpectedly the lactam alcohol A (XV), mp 211—213°, $C_{19}H_{21}O_4N$-1/3H_2O, in a 98% yield, which occurred from reduction of the ketonic function and lactam cyclization in one operation. The IR spectrum of the compound (XV) showed a band at 1630 cm^{-1} (lactam) and the nuclear magnetic resonance (NMR) spectrum revealed signals at 4.41 (1H, d, J=8 Hz, >C<u>H</u>-C_6H_5), and 5.17 δ (1H, d, J=8 Hz, >C<u>H</u>-OH). The NMR spectrum of the crude reduction product does not show any extra singals corresponding to the diastereoisomer (XVII, *vide infra*), suggesting that reduction with $NaBH_4$ proceeded stereospecifically. This stereospecific reduction can be rationalized by the Cram's rule as shown in Fig. 1. Thus, the reagent preferentially approaches the carbonyl gorup from the side of the smallest group H, and the resulted alcohol is cyclized to give the lactam alcohol A (XV) having the *trans* hydrogens at C_1 and C_2. Oxidation of the lactam alcohol A (XV) with Collins' reagent[8] afforded the keto lactam (XVI), mp 137° (M^+ 325) in a 85% yield, which was also obtained by heating the desylamine hydrobromide (XIVc) in AcOH even through

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8) J.C. Collins, W.W. Hess and F.J. Frank, *Tetrahedron Letters*, **1968**, 3363.

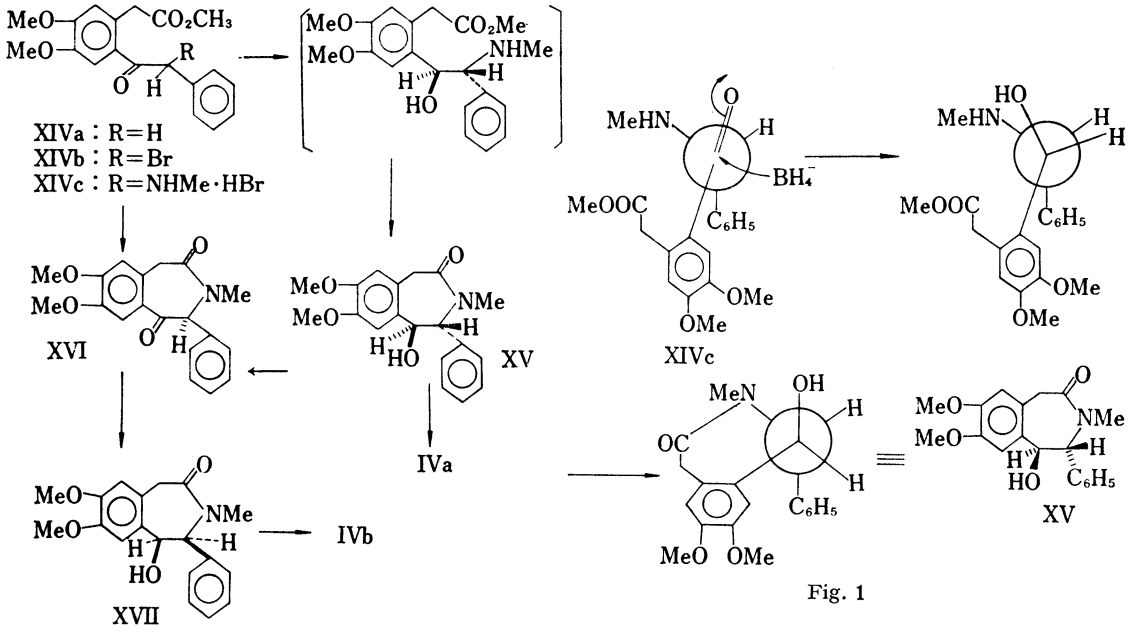

Chart 2

Fig. 1

the yield was very poor. Reduction of the keto lactam (XVI) in methanol with $NaBH_4$ furnished the lactam alcohol B (XVII), mp 175—177° (M^+ 327) in a 87% yield, the NMR spectrum of which exhibited signals at 4.87 (1H, d, J=3 Hz, >C<u>H</u>-C_6H_5) and 5.52 δ (1H, d, J=3 Hz, >C<u>H</u>–OH). Since any extra singnals corresponding to the diastereoisomer (XV) were not observed in the NMR spectrum of the crude reduction product, $NaBH_4$ reduction of the carbonyl group in XVI was also stereospecific. Reduction of the lactam alcohol A (XV) and B (XVII) with $LiAlH_4$ gave the amino alcohol A (IVa), an oil, (M^+ 313) and B (IVb), an oil, (M^+ 313), respectively. The NMR spectrum of the amino alcohol A (IVa) showed signals at 3.68 (1H, d, J=7 Hz, >C<u>H</u>-C_6H_5) and 4.82 δ (1H, d, J=7 Hz, >C<u>H</u>–OH), and that of the amino alcohol B (IVb) exhibited signals at 3.43 (1H, d, J=1.5 Hz, >C<u>H</u>-C_6H_5) and 4.66 δ (1H, d, J=1.5 Hz, >C<u>H</u>–OH). By comparing the coupling constants of two signals corresponding to >C<u>H</u>-C_6H_5 and >C<u>H</u>–OH in two pairs of compounds, thus, the lactam alcohol A (XV) and B (XVII), and the amino alcohol A (IVa) and B (IVb), respectively, the configurational relationship at C_1 and C_2 was estimated to be *trans* in XV (J=8 Hz), IVa (J=7 Hz), and *cis* in XVII (J=3 Hz) and IVb (J=1.5 Hz). These configurational assignments were also supported by the IR spectral observation. Thus, a hydroxyl band assingned to intramolecularly bonded hydroxyl streching appeared only in the spectrum of the compound (IVb) (at 3370 cm^{-1} in a diluted solution), which possesses the *cis* hydrogens, and is possible to form a hydrogen bonding between the hydroxy and amino group.

It is noteworthy in connection with the synthesis of rhoeadine (I, *cis*) and alpinine (II, *trans*) that the *cis* (IVb) and *trans* (IVa) isomers could be stereospecifically synthesized through the present synthetic route in the relatively high yield.

Experimental

Melting points were determined with a microscopic hot-stage and are uncorrected. The IR spectra were measured for solutions in $CHCl_3$ with a Hitachi EPI spectrometer, unless otherwise stated, and the NMR spectra were recorded at a Varian A-60 instrument, using $CDCl_3$ as the solvent: the line positions or centers of multiplets are given in the δ ppm scale with reference to TMS as the internal standard. Un-

less specified otherwise, the mass spectral determinations were performed with a Hitachi RMU-6D mass spectrometer with a direct heated inlet system.

N-Tosyl-α-homoveratrylaminophenylacetic Acid (VIIb)——To a solution of 7.7 g of tosyl chloride in 40 ml of ether was added a solution of 6.3 g of α-homoveratrylaminophenylacetic acid (VIIa)[9] in 40 ml of aq. 1N NaOH solution. To this mixture was added in several portions 50 ml of 1N NaOH solution under vigorous stirring for 2 hr. The aqueous layer was separated, acidified with HCl and extracted with ether. The ether extracts were dried over anhyd. $MgSO_4$ and evaporated to give 4.57 g of crystals (yield, 48%), which were recrystallized from EtOH. mp 160—162°. IR ν_{max} cm^{-1}: 1720 (COOH). *Anal.* Calcd. for $C_{25}H_{27}O_6NS$: C, 63.95; H, 5.80. Found: C, 63.77; H, 5.95.

N-Tosyl-α-homoveratrylaminophenylacetanilide (VIII)——A mixture of 2.13 g of N-tosyl-α-veratrylaminophenylacetic acid (VIIb), 4 g of $SOCl_2$ and 50 ml of benzene was refluxed for 30 min on a water bath. The solvent and excess $SOCl_2$ were evaporated under reduced pressure, and the residue was dissolved in ether. To this solution was added a solution of 2 ml of aniline in 20 ml of ether under stirring. After 10 ml of aq. 10% Na_2CO_3 solution was added, stirring was allowed to continue for further 30 min. The precipitated crystals were then collected by filtration, successively washed with 1N Na_2CO_3, water and ether, and recrystallized from a mixture of ethanol and acetone to give 2.31 g of the compound (VIII), mp 199—202°, (yield 93%). *Anal.* Calcd. for $C_{31}H_{32}O_5N_2S$: C, 68.37; H, 5.92. Found: C, 68.53; H, 5.90.

The Compound (IX)——To a solution of 1 g of the anilide (VIII) in 6 ml of $CHCl_3$ were added 40 ml of benzene and 2 ml of $POCl_3$ hydrolyzed in the following manner.[4] To 30 g of $POCl_3$ was gradually added 2.2 ml of water under ice cooling and the mixture was kept on standing for a week in a flask equipped with a $CaCl_2$ tube. The reaction mixture above was refluxed for 2 hr and poured into 20 ml of aq. 10% NaOH solution containing ice pieces. The organic layer was separated from the aqueous layer and evaporated *in vacuo*. When triturated with a mixture of ethanol and ether, the residue was crystallized, and recrystallization from ether gave 271 mg of the compound (IX), (yield 40%), mp 161—163°. IR ν_{max} cm^{-1}: 1625 (>C=N-). *Anal.* Calcd. for $C_{24}H_{22}O_2N_2$: C, 77.81; H, 5.99. Found: C, 77.97; H, 5.88.

Hydrolysis of the Compound (IX): 1-Benzoyl-6,7-dimethoxy-3,4-dihydroisoquinoline (X)——To a solution of 200 mg of the diimine (IX) in 20 ml of acetone was added 4 ml of 0.2N HCl solution. The mixture was allowed to stand at room temperature for 3 min. The organic solvent was evaporated under diminished pressure and the residue was made basic with 10% Na_2CO_3 solution and extracted with CH_2Cl_2. The extract was dried over anhyd. K_2CO_3, and evaporated to leave 185 mg of an oil. IR ν_{max} cm^{-1}: 1670 (>C=O). This compound (X) was characterized as its picrate, mp 172—174°. *Anal.* Calcd. for $C_{24}H_{20}O_{10}N_4$: C, 54.90; H, 3.84. Found: C, 54.76; H, 3.80. This picrate was then identified with the picrate of the compound which was synthesized through the established synthetic route. Thus, 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline[10] was derived from N-(3,4-dimethoxyphenethyl)phenylacetamide[11] after the manner reported.[10] Oxidation of the 3,4-dihydroisoquinoline above with active MnO_2 in $CHCl_3$ gave an oil, the picrate of which was identical with that of the hydrolysis product from the diimine (IX).

Methyl 4,5-Dimethoxy-2-phenylacetylphenyl Acetate (XIVa)——A solution of 3 g of phenylacetic acid and 4.5 g of PCl_5 in 40 ml of CH_2Cl_2 was stirred for 1 hr. To this solution was added 3 g of $ZrCl_4$ under ice cooling and stirring was continued for 30 min. Then, 2.1 g of methyl homoveratrate was added to this mixture and the mixture was stirred for 24 hr at room temperature, poured into ice water, made alkaline with aq. Na_2CO_3 solution and extracted with CH_2Cl_2. The extract was dried over K_2CO_3 and evaporated to leave an oil. Trituration of the oil with ether afforded 2.2 g of crystals (yeild 67%), which were recrystallized from ether. mp 95—96°. IR ν_{max} cm^{-1}: 1670 (ketone) and 1730 (ester). NMR: 3.67, 3.83, and 3.90 (each 3H, s), 3.89 and 4.21 (each 2H, s), 6.72 (1H, s), 7.27 (5H, s) and 7.38 (1H, s). This compound has been synthesized by Bentley, *et al.*[7] using $AlCl_3$ as a catalyst. The physical data of our sample were quite identical with those of the compound reported.

2′-Carbomethoxymethyl-4′,5′-dimethoxydesylbromide (XIVb)——A solution of 3.28 g of the compound (XIVa) in 15 ml of $CHCl_3$ was diluted with 10 ml of ether. To this solution was gradually added a solution of 2 g of bromine in 5 ml of ether at room temperature under stirring. The reaction was followed by TLC. When the spot due to the starting material had not been perceived on the TLC plate, the reaction mixture was diluted with 10 ml of ether and allowed to stand for a while. The precipitated crystals were collected by filtration. Additional crystals were obtained from the filtrate. Thus, the filtrate was washed with aq. $NaHCO_3$ solution, dried over $MgSO_4$ and evaporated to leave the residue, which on trituration with ether crystallized. Total weight of crystals was 4.0 g (yield 98%). For analysis, a sample was recrystallized from ether. mp 137—138°, IR ν_{max} cm^{-1}: 1690 (ketone) and 1735 (ester). *Anal.* Calcd. for $C_{19}H_{19}O_5Br$: C, 56.03; H, 4.70. Found: C, 56.22; H, 4.78. NMR: 3.69, 3.79, and 3.90 (each 3H, s), 3.88 (2H, s), 6.28 and 6.75 (each 1H, s), 7.25—7.65 (6H, m).

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10) S. Yamada and A.M.E. Omar, *Chem. Pharm. Bull.* (Tokyo), **12**, 249 (1964).
11) T. Kametani, K. Wakisaka and K. Fukumoto, *Yakugaku Zasshi*, **85**, 956 (1965).

N-Methyl-2′-carbomethoxymethyl-4′,5′-dimethoxydesylamine Hydrobromide (XIVc)——To a solution of 1 g of the desylbromide (XIVb) in 40 ml of benzene was added a solution of NHMe (1.2 equivalents) in benzene under N_2 atmosphere. The mixture was allowed to stand for 2 days. Then, several drops of 48% HBr solution were added. After the precipitated NHMe·HBr was removed, the solvent was evaporated to leave the residue which on trituration with acetone gave crystals. For analysis, a sample was recrystallized from acetone, mp 213—215°, IR ν_{max} cm^{-1}: 2300—2800 (>N^+-H), 1730 (ester), and 1675 (ketone). *Anal.* Calcd. for $C_{20}H_{23}O_5N \cdot HBr$: C, 54.80; H, 5.52. Found: C, 54.89; H, 5.53. The free base was found to be labile.

The Lactam Alcohol A (XV: *trans* Isomer)——To a solution of 240 mg of the desylamine hydrobromide (XIVc) in 12 ml of methanol was added gradually a large excess of $NaBH_4$. After the reaction mixture was kept on standing for 3 hr, the solvent was evaporated to leave the residue which was mixed with water and extracted with CH_2Cl_2. After dried over anhyd. K_2CO_3, the extract was evaporated to give 175 mg of crystals (yield 98%). For analysis, a sample was recrystallized from methanol, mp 211—213°. IR ν_{max} cm^{-1}: 3400 and 3600 (OH) and 1630 (lactam). *Anal.* Calcd. for $C_{19}H_{21}O_4N \cdot 1/3H_2O$: C, 68.45; H, 6.65. Found: C, 68.48; H, 6.51. NMR: 2.73 (3H, s), 3.77 (2H, s), 3.83 (6H, s), 4.41 (1H, d, J=8 Hz), 5.17 (1H, d, J=8 Hz), 6.67 (1H, s), 7.0 (1H, s) and 7.31 (5H, br, s).

The Keto Lactam (XVI)——To a solution of 164 mg of the compound (XV) in 20 ml of CH_2Cl_2 was added CrO_3-pyridine complex (900 mg) and the mixture was stirred for 2 hr at room temperature. The reaction mixture was filtered and the filtrate was washed with a diluted HCl solution, dried over anhyd. K_2CO_3 and evaporated to leave an oil, which on trituration with ether crystallized. For analysis, a sample was recrystallized from ether. mp 132—137°. IR ν_{max} cm^{-1}: 1660 (lactam and ketone). Mass Spectrum m/e: 325 (M^+), 178, 150, and 120. NMR: 3.32, 3.92, and 3.97 (each 3H, s), 5.46 (1H, s), 6.62 (1H, s), 7.34 (5H, br, s) and 7.77 (1H, s). The keto lactam (XVI) was also obtained from the compound (XIVc). A solution of 200 mg of the compound (XIVc) in 20 ml of AcOH was refluxed in a sealed tube under N_2 atmosphere for 2 days. Acetic acid was removed by distillation to leave an oil, which in $CHCl_3$ was chromatographed on silica gel column. Yield, 12 mg. The NMR spectrum of this oil was superimposable with that of the compound obtained above .

The Lactam Alcohol B (XVII: *cis* Isomer)——To a solution of 100 mg of the keto lactam (XVI) in 20 ml of methanol was added 100 mg of $NaBH_4$ in portions. The reaction mixture was allowed to stand for 2 hr and the solvent was distilled off. The residue was mixed with 20 ml of water and extracted with CH_2Cl_2. The extract was dried over K_2CO_3 and evaporated to leave an oil (87 mg). Trituration with ether gave crystals which were recrystallized from ether. Yield, 87%, mp 175—177°. IR ν_{max} cm^{-1}: 3400, 3600 (OH), 1620 (lactam). NMR: 2.73, 3.67, and 3.86 (each 3H, s), 4.87 (1H, d, J=3 Hz), 5.52 (1H, d, J=3 Hz), 6.50 (1H, s), 6.70 (1H, s) and 6.9—7.5 (5H, m). Mass Spectrum m/e: 327 (M^+), 180, 179, 151 and 120.

The Amino Alcohol A (IVa: *trans* Isomer)——To a solution of 62 mg of the lactam alcohol (XV) in 6 ml of tetrahydrofuran was added 200 mg of $LiAlH_4$ and the reaction mixture was refluxed for 15 hr. After excess $LiAlH_4$ was decomposed with water, the reaction mixture was filtered. The filtrate was concentrated and digested with 3% aq. AcOH. The acidic solution was made basic with ammonia and extracted with CH_2Cl_2. The extract was dried over K_2CO_3 and evaporated to leave an oil (40 mg), Yield 68%. IR ν_{max} cm^{-1}: 3600 and 3430 (OH). NMR: 2.18, 3.81 and 3.91 (each 3H, s), 3.68 (1H, d, J=7 Hz), 4.82 (1H, d, J=7 Hz), 6.7 (1H, s), 6.90 (1H, s) and 7.0—7.4 (5H, m). Mass Spectrum m/e: 313 (M^+), 194, 193, 134, 120, 91.

The Amino Alcohol B (IVb: *cis* Isomer)——To a solution of 87 mg of the compound (XVII) in 3 ml of tetrahydrofuran was added a solution of 200 mg of $LiAlH_4$ in ether and the reaction mixture was refluxed for 15 hr. The reaction mixture was treated as described previously and an oil (16 mg) was obtained. IR ν_{max} cm^{-1}: 3370 (in a diluted CCl_4 solution). NMR: 2.13, 3.80, and 3.86 (each 3H, s), 3.43 (1H, d, J=1.5 Hz), 4.66 (1H, d, J=1.5 Hz), 6.63 (1H, s), 6.67 (1H, s), and 7.30 (5H, s). Mass Spectrum (A sample was vaporized in an oven at 160°): m/e: 313, 134, 120 and 91.