ASYMMETRIC SYNTHESIS OF (*R*)-(+)-NORANICANINE

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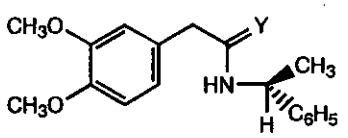
Abstract - - Optically active (*R*)-(+)-noranicanine (1) was synthesized *via* stereoselective reduction of the corresponding iminium ion possessing a chiral auxiliary by Polniaszek's method.

The 1-benzylisoquinoline alkaloid, (*R*)-(+)-noranicanine, which was isolated from *Aniba canelilla* H.B.K. (Lauraceae),[1,2] was assigned the structure, (*R*)-1-(3-hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1) on the basis of spectral evidence and synthesis of the racemate. We describe here an asymmetrical synthesis of (*R*)-(+)-noranicanine *via* stereoselective reduction of the corresponding iminium ion possessing a chiral auxiliary by Polniaszek's method.[3,4]

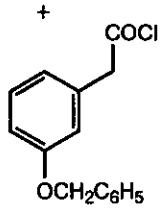
The standard Schotten-Baumann reaction of (*R*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1-phenylethylamine (3) and acid chloride (4) derived from 3-benzyloxyphenylacetic acid[5] afforded an 87.2 % yield of the amide (5), which was then transformed into the corresponding iminium ion possessing a chiral auxiliary (6) through the Bischler-Napieralski reaction. Stereoselective reduction of this compound (6) with sodium borohydride in methanol at -78°C afforded the (*R*)-*N*-substituted tetrahydroisoquinoline (7) in high yield based on the amide (5). In this reduction, the diastereoisomer of 7 was not isolated. *N*- And *O*-debenzylation by catalytic hydrogenation of 7 afforded (*R*)-(+)-noranicanine (1). All spectral data of this synthetic compound were identical with those of the naturally occurring (*R*)-(+)-noranicanine (1)[1,2] and the respective specific rotation were identified.

Consequently, the structure of (*R*)-(+)-noranicanine can be unequivocally



(2) Y = O (3) Y = H_2

+



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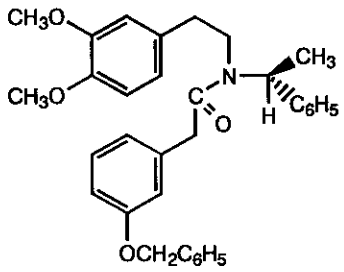

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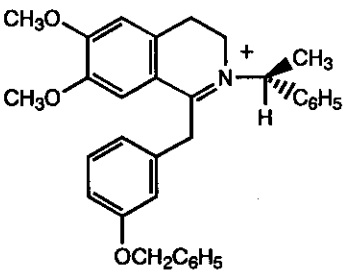

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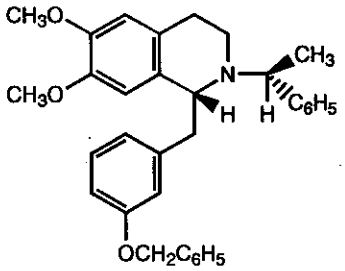

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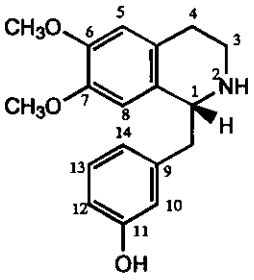

(1)

represented by formula (1). The natural base ($[\alpha]_D$ +36.0°, $CHCl_3$) was not crystallized because it was a minor product, but the synthetic compound (1) was afforded as colorless needles, mp 182°C, $[\alpha]_D$ +34.3°.
This synthetic route by Polniaszek *et al.* is proved to be one of the suitable method for obtaining optically active 1-benzylisoquinoline alkaloids.

EXPERIMENTAL

All melting points were determined using a Yanagimoto microscopic hot-stage apparatus and are uncorrected. ^{1}H-Nmr spectra were obtained on a JEOL FX-200 spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Ir and uv spectra were recorded on a Shimadzu IR-435 and Shimadzu UV-160 spectrophotometer, respectively. Ms were obtained using a JEOL JMS DX-303 EIms spectrometer. Optical rotations were measured on a JASCO DIP-360 polarimeter. All organic extracts were dried over anhydrous $MgSO_4$. Column chromatography and preparative thin layer chromatography (tlc) were carried out on Wakogel C-200 (100~200 mesh) and with silica gel $60F_{254}$ (Merck).

(*R*)-*N*-(1-Phenyl)ethyl-2-(3,4-dimethoxyphenyl)acetamide (2) An ether solution (180 ml) of 3,4-dimethoxyphenylacetyl chloride prepared from the corresponding phenylacetic acid (11.8 g, 0.06 mol) and excess thionyl chloride (30 ml, 0.42 mol) by the usual method, and 180 ml of 5% aq. Na_2CO_3 solution were alternately added dropwise to an ether solution (180 ml) of (*R*)-α-phenylethylamine (9.28 ml, 0.073 mol), with stirring at 0~5°C. Stirring was continued for 1 h at the same temperature, and the precipitate was filtered off and dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed successively with 10% aq. HCl solution, 5% aq. NaOH solution and water, and dried. Removal of the solvent by evaporation left a residue, which was recrystallized from ethanol-hexane to furnish the optical active acetamide (2), colorless needles, mp 101~102°C (17.6 g, 97.8%). $[\alpha]_D^{25}$ -17.4° (c= 0.29, $CHCl_3$); uv λ_{max}^{EtOH}nm(log ε): 204(4.71); ir $\nu_{max}^{CHCl_3}$cm^{-1}: 3400(NH), 1675(C=O); ^{1}H-nmr δ:1.40 (3H, d, CH_3, J = 7.0 Hz), 3.52 (2H, s, CH_2Ar), 3.84, 3.88 (3H×2, s, OCH_3×2), 5.13 (1H, m, CH), 5.64 (1H, br., NH), 6.75~6.86 (3H, m, arom.H×3), 7.16~7.35 (5H, m, arom.H×5); EIms $^m/_z$(rel. intensity):299(M^+,84.0), 151[M^+-$C_6H_5CH(CH_3)NHCO$,100], 105[M^+-$(CH_3O)_2$-$C_6H_3CH_2CONH$,32.3]; Anal.Calcd for $C_{18}H_{21}NO_3$: C,72.22; H,7.07; N,4.68. Found: C,72.03; H,7.15; N,4.72.

(*R*)-*N*-[2-(3,4-Dimethoxyphenyl)ethyl]-1-phenylethylamine (3) BF_3 etherate (*ca.*47%, 0.6 ml) and 1.0 M BH_3-THF solution (12.0 ml, 0.125 mol) were carefully added dropwise to a solution of the amide (2)(1.42 g, 0.0047 mol) in anhydrous THF (24.0 ml) at room temperature and the mixture was refluxed for 2.5 h under Ar. After the excess reagent was decomposed with 5 N aq. HCl solution (35 ml), most of the solvent was evaporated off *in vacuo*. The aqueous solution was adjusted to pH 13 with 10% aq. NaOH solution, and extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated. Residual oil was converted into the hydrochloride salt, which was recrystallized from MeOH-Me_2CO. Colorless needles, mp 216°C (1.12 g, 73.2%). Anal. Calcd for $C_{18}H_{23}NO_2 \cdot HCl$: C,67.17; H,7.52; N,4.35. Found: C,67.07; H, 7.64; N,4.40. The hydrochloride was treated in the usual manner to give an oily free base (3). $[\alpha]_D^{28}$ +39.5° (c=0.56, $CHCl_3$); uv λ_{max}^{EtOH}nm (log ε): 203(4.66), 279(sh, 1.71); ir $\nu_{max}^{CHCl_3}$cm^{-1}: 3280(NH); ^{1}H-nmr δ: 1.32 (3H, d, CH_3, J=6.6 Hz), 1.46 (1H, br., NH), 2.69 (4H, m, CH_2×2), 6.67~6.81 (3H, m, arom.H×3), 7.22~7.35 (5H, m, arom.H×5); EIms m/z(rel. intensity): 285(M^+, 5.2), 152[M^++1-$CH_2NHCH(CH_3)C_6H_5$, 50.1], 134[M^+-$(CH_3O)_2C_6H_4CH_2$, 71.9], 105[M^+-$(CH_3O)_2C_6H_4CH_2NH$, 100].

(*R*)-*N*-(1-Phenyl)ethyl-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-2-(3-benzyloxyphenyl)acetamide (5) An ether (100 ml) solution of acetyl chloride (4) prepared from 3-benzyloxyphenylacetic acid (4.0 g, 0.0165 mol) as noted above, and 5% aq. NaOH solution (100 ml) were added dropwise alternately to an ether solution (100 ml) of (*R*)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-1-phenylethylamine (3)(4.27 g, 0.015 mol) with stirring at 0~5°C. After further stirring at the same temperature for 2 h, the ether layer was washed with water and dried. The solvent was evaporated off to give a pale yellow oil (5) [yield 6.65 g (87.2 %)] showing a single spot on tlc. $[\alpha]_D^{24}$ +6.6° (c=0.15, $CHCl_3$); uv λ_{max}^{EtOH}nm (log ε): 203(4.59); ir $\nu_{max}^{CHCl_3}$cm^{-1}: 1650(C=O); EIms m/z(rel. intensity): 509(M^+, 20.7), 358(4.0), 197(4.4), 164(100), 134(15.9), 105 (47.3), 91(20.4).

(*R*)-1-(3-Benzyloxybenzyl)-*N*-[(1*R*)-phenylethyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (7) A mixture of the amide (5)(5.25 g, 0.01 mol) and $POCl_3$ (25.6 ml, 0.28 mol) in dry toluene (50.0 ml) was refluxed for 3.5 h. Evaporation of excess reagent and solvent left a residue, which was thoroughly washed with petroleum ether. The residual reagent was decomposed by addition of MeOH (10 ml). The solution was made alkaline with 10% aq. NH_4OH solution, and extracted with CH_2Cl_2. The extract was

washed with water, dried and evaporated, leaving the chiral iminium ion (6) (5.0 g) as a pale brown oily substance, indicating a single spot on tlc. This compound (6) was used for the following reaction without purification.

To a stirred solution of iminium ion (6) (4.9 g, 0.01 mol) in MeOH (200 ml) was gradually added $NaBH_4$ (6.70 g, 0.17 mol) at -78°C. The mixture was stirred at the same temperature for 2 h, excess $NaBH_4$ was decomposed with 10% AcOH and most of MeOH was removed by evaporation *in vacuo*. The residual solution was made alkaline with 10% aqueous NH_4OH solution and extracted with CH_2Cl_2. Usual work-up of the CH_2Cl_2 layer gave an oily residue, whose column chromatography on silica gel with hexane-CH_2Cl_2 [9:1 ($^v/_v$)] gave a pale brownish oil (7), showing a single spot on tlc[4.83 g, 95.0% from 5]. $[\alpha]_D$ -57.6° (c=0.59, $CHCl_3$); uv λ_{max}^{EtOH}nm(log ε): 204(4.73); ^{1}H-nmr δ:1.37(3H, d, CH_3, J = 6.6 Hz), 2.40~3.38(6H, m, CH_2×2), 3.04~3.81(2H, m, CH×2), 3.49, 3.83(3H×2, s, OCH_3×2), 4.93(2H, s, OCH_2), 5.87(1H, s, C-8), 6.56(1H, s, C-5), 6.53~6.58(2H, m, arom.H×2), 6.77~6.83(1H, m, arom.H×1), 7.07~7.21(6H, m, arom.H×6), 7.28~7.42(5H, m, arom.H×5); EIms $^m/_z$(rel. intensity): 493(M^+, 0.21), 388(M^+-$C_6H_5CHCH_3$, 0.30), 296(M^+-$C_6H_5OC_6H_4CH_2$, 100), 192(M^++1-$C_6H_5CHCH_3$-$C_6H_5OC_6H_4CH_2$, 68.5), 176(192+1-CH_3, 12.5), 105($C_6H_5CHCH_3$, 59.1), 91($C_6H_5CH_2$, 47.8).

(*R*)-(+)-1-(3-Hydroxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline [(*R*)-(+)-noranicanine] (1) A mixture of (7) (986 mg, 0.02 mol) and 5% Pd-C (*ca.*100 mg) in EtOH (*ca.*60 ml) containing concentrated hydrochloric acid (2 ml) was shaken at room temperature under a hydrogen atomosphere (3.0 $^{kg}/_{cm^2}$) for 32 h using a medium-pressure catalytic hydrogenator. The catalyst was removed by filtration, the filtrate was made alkaline with 10% aq. NH_4OH solution and extracted with CH_2Cl_2. Usual work-up of the extract yielded a residue which was recrystallized from Me_2CO to afford colorless needles (1), mp 182°C (448 mg, 74.9 %). $[\alpha]_D$ +34.3° (c=0.2, $CHCl_3$); uv λ_{max}^{EtOH}nm (log ε): 204(4.78), 282(3.78), $\lambda_{max}^{EtOH-KOH}$nm (log ε): 213(5.16), 287(3.74); ir $\upsilon_{max}^{CHCl_3}cm^{-1}$: 3300~3050, 1610, 1585; EIms $^m/_z$ (rel. intensity): 299(M^+,0.2), 193(16.4), 192(100), 177(3.7), 148(4.0); ^{1}H-nmr: 2.79(2H, m, C-4), 2.93(1H, dd, J = 1.5, J = 10.0 Hz, C-α), 3.01(1H, dd, J = 6.0, 12.0 Hz, C-3), 3.18(1H, dd, J = 5.3, 10.0 Hz, C-α), 3.24(1H, dd, J = 5.5, 12.0 Hz, C-3), 3.79, 3.86(3H×2, s, CH_3O×2), 4.26(1H, dd, J = 5.0, 8.5 Hz, C-1), 6.60(1H, s, C-8), 6.66(1H, s, C-5), 6.69(1H, m, C-10), 6.69(1H, m, C-12), 6,69(1H, m, C-14), 7.14(1H, dd, J = 7.0, 9.0 Hz, C-13); ^{13}C-nmr: 56.6(C-1), 40.5(C-3), 29.0(C-4), 127.0

(C-4α), 112.1(C-5), 147.3 and 147.8 (C-6 and C-7), 109.8(C-8), 129.7(C-8α), 42.4(C-α), 140.1(C-9), 116.2(C-10), 157.6(C-11), 114.4(C-12), 130.0(C-13), 121.0(C-14), 55.9 and 56.1 (2×OCH_3); Anal. Calcd for $C_{18}H_{21}NO_3$: C,72.22; H,7.07; N,4.68; Found: C,71.96; H,7.08; N,4.62.

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