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4-Hydroxycrebanine, a New 4-Hydroxyaporphine Alkaloid, and (*R*)-Roemeroline from *Stephania sasakii* Hayata[1]

Jun-ichi Kunitomo,* Megumi Oshikata, and Yoshiko Murakami

Faculty of Pharmaceutical Sciences, Mukogawa Women's University, 4-16, Edagawa-cho, Nishinomiya, 663, Japan

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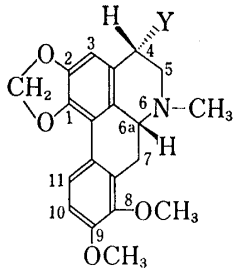
The structures of two unknown alkaloids (tentatively named Base A and Base D in a previous paper[2]) from *Stephania sasakii* Hayata (Menispermaceae) were established as 4-hydroxycrebanine (1), a new 4-hydroxyaporphine alkaloid, and (*R*)-roemeroline (3), respectively.

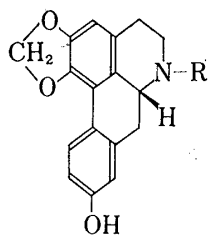
Keywords——*Stephania sasakii* Hayata; Menispermaceae; 4-hydroxyaporphine alkaloid; 4-hydroxycrebanine; aporphine alkaloid; (*R*)-roemeroline

In part XI,[2] we reported the isolation of four unknown alkaloids together with several alkaloids from *Stephania sasakii* Hayata (Menispermaceae) collected in Formosa. This paper describes the characterization and structural establishment of two alkaloids (tentatively named Base A and Base D) out of the four unknown alkaloids.

4-Hydroxycrebanine (1) (Base A), forms colorless needles from acetone, mp 191—192 °C, $[\alpha]_D$ −90.2 ° (in $CHCl_3$), and the elemental analyses and mass spectrum (MS) established the formula as $C_{20}H_{21}NO_5$ (m.w., 355.38). Its ultraviolet spectrum (UV) [λ_{max}^{EtOH} nm (log ε): 218.5 (4.53), 245 (sh., 4.17), 281 (4.34) and 320 (sh., 3.58), no bathochromic shifts upon addition of alkali] was very similar to that of crebanine (2).[3] The infrared spectrum (IR) (in $CHCl_3$) showed an alcoholic hydroxyl group at 3500 cm^{-1}. The proton magnetic resonance data (PMR) also support this substitution pattern in view of the presence of a low-field *ortho*-coupling aromatic proton at C_{11}–H (δ 7.84, d., J=9.0 Hz), which indicates that the two methoxys (δ 3.85, 3.92) must be located at C-8 and C-9.[4] The unusual downfield position of the signal of the C_3–H (δ 6.81) [C_3–H of crebanine (2) appears at δ 6.55] and the presence of one triplet proton (δ 4.47) ascribable to a hydrogen geminal to an alcoholic hydroxyl group suggested that this hydroxyl group must be located at C-4 in a peri relation with C_3–H. The MS shows a fragment ion at m/z 312 (14.5%, $M^+-CH_2=NCH_3$), which could be explained as being derived from the m/z 355 fragment ion (3.0%, M^+) by retro-Diels-Alder type fragmentation. These results suggest that this alkaloid is a 4-hydroxyl derivative (1) of crebanine (2), the main alkaloid of this plant. Even when a hydroxyl group is substituted at the C-4 position of an aporphine-type alkaloid and a new chiral center is formed, this does not affect the chiral center of the biphenyl system of aporphine.[5] Also, the optical rotatory dispersion curve (ORD) of Base A shows a negative Cotton effect between 235—245 nm, which proves that C-6a has the (*R*)-configuration, as in the corresponding aporphine.[4,6] This view is also supported by the circular dichroism curve (CD).[7] As for the configuration at C-4, the PMR spectrum of this base shows a triplet at δ 4.47 with J=2.5 Hz which indicates that C_4–H has one of two types of pseudoequatorial conformation.[8,9] After consideration of the facts that intermolecular hydrogen bonding (N·····HO) was not observed in the IR spectrum[8] and that the C_4–H signal at δ 4.47 in the PMR spectrum showed a *cis* relationship between C_4–H and C_{6a}–H,[10] it was concluded that C_4–H must have the (*S*)-configuration.[11] Finally, stereoselective hydroxylation at C-4[12] of crebanine (2) with vanadium oxytrifluoride in trifluoroacetic acid gave 4-hydroxylated crebanine, which was identical with the natural product Base A as judged by direct comparison (UV, IR, PMR and mass spectra, TLC, specific rotation and mixed melting point).



1 : Y=OH
2 : Y=H



3 : R=CH_3
4 : R=H

Chart 1

(*R*)-Roemeroline (3) (Base D) forms colorless needles, $C_{18}H_{17}NO_3$, mp 218—220 °C (sint., 133—135 °C), $[\alpha]_D$ −32.1 ° (in $CHCl_3$). All its data (UV, IR, PMR ans MS; see experimental section) are consistent with a 1,2,9-substituted aporphine having a methylenedioxy, an N-methyl and a hydroxyl group, which indicated that Base D might be N-methylanolobine. Treatment of anolobine (**4**)[13] with formaldehyde and $NaBH_4$ afforded the N-methyl derivative as colorless needles, $[\alpha]_D$ −31.3 ° (in $CHCl_3$); this compound was identical with Base D, thus proving that the structure of this alkaloid is N-methylanolobine (3). Also, as anolobine (**4**) is of the (*R*)-configuration, this alkaloid should have the same configuration, and its ORD and CD data (see experimental section) supported this assumption.[4,7] An alkaloid having this formula has been isolated from *Roemeria refracta* and named "roemeroline".[14] Unfortunately, no detailed data, especially on specific rotation, exist for roemeroline and direct comparison could not be done as an authentic sample was not available.[15] However, in order to avoid confusion, Base D was named (*R*)-roemeroline.

Experimental

All melting points are uncorrected. PMR spectra were recorded on a 60 MHz spectrometer in $CDCl_3$ with TMS as an internal standard. MS were recorded on a direct inlet system at 70 eV using a Hitachi RMU-6E spectrometer. Specific rotation, ORD and CD were determined using JASCO DIP-4 digital and J-20 spectrometer, respectively.

4-Hydroxycrebanine (1) (Base A)——Recrystallized from Me_2CO as colorless needles, mp 191—192°C, $[\alpha]_D$ −90.2° (c=0.266, $CHCl_3$). ORD ($c=1.12\times10^{-3}$, MeOH) [M] (nm): −98258.9° (245) (trough), +136294.6° (227) (peak), −36450.9° (205) (trough). CD ($c=1.12\times10^{-3}$, MeOH) [θ] (nm): +30111.6° (277), −150558.0° (237) (negative maximum), +50714.3° (218) (positive maximum). UV λ_{max}^{EtOH} nm (log ε): 218.5 (4.53), 245 (sh., 4.17), 281 (4.34), 320 (sh., 3.58), no bathochromic shifts upon the addition of alkali. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3500 (OH). PMR (in $CDCl_3$) δ: 2.60 (3H, s., NCH_3), 3.12 (1H, broad, OH), 3.85, 3.92 (3H×2, s., $OCH_3\times2$), 4.47 (1H, t., -C<u>H</u>(OH)), 6.00 (2H, d.d., J=1.5, 11.0 Hz, OCH_2O), 6.81 (1H, s., C_3-H), 6.89 (1H, d., J=9.0 Hz, C_{10}-H), 7.84 (1H, d., J=9.0 Hz, C_{11}-H). MS m/z (%): 355 (M^+, 3.0), 336 (M^+-1-H_2O, 28.1), 335 (100), 321 (336−Me, 45.3), 320 (335−Me, 78.6), 312 (M^+-CH_2=NCH_3, 14.5), 306 (336−CH_2O, 11.0), 291 (11.7), 277 (30.6). *Anal.* Calcd for $C_{20}H_{21}NO_5$ (m.w., 355.38): C, 67.59; H, 5.96; N, 3.94. Found: C, 67.80; H, 6.05; N, 3.95.

Stereoselective Hydroxylation of Crebanine (2) with Vanadium Oxytrifluoride——Crebanine (2) (1.0 g) was dissolved in trifluoroacetic acid (TFA) (18 ml), and a solution of vanadium oxytrifluoride (0.7 g) in TFA (45 ml) was added at −15°C to −10°C over a period of 2 h with stirring. The mixture was stirred at room temperature for 1 hr, then poured into ice-water (80 ml), made alkaline with aqueous 10% NH_4OH, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed, dried over $MgSO_4$ and evaporated to dryness leaving a crude oily residue. This residue was subjected to silica gel column chromatography, eluting with CH_2Cl_2. Recrystallization from Me_2CO gave colorless needles in 38.5% yield, mp 182—184°C, $[\alpha]_D$ −90.3° (c=0.288, $CHCl_3$), which were characterized by direct comparison [IR (in $CHCl_3$), PMR and mass spectra, TLC and specific rotation] with natural 4-hydroxycrebanine (1). From another fraction, two other compounds were obtained in low yields and are presently being investigated.

(*R*)-Roemeroline (3) (Base D)——Recrystallized from MeOH as colorless needles, mp 218—220°C (sint., 133—135°C), $[\alpha]_D$ −32.1° (c=0.437, $CHCl_3$) (lit.,[14] mp 228—231°C, $[\alpha]_D$ 0±30° (MeOH). ORD ($c=9.0\times10^{-4}$, MeOH) [M] (nm): −80305.6° (239) (trough), +63916.7° (217) (peak). CD ($c=9.0\times10^{-4}$, MeOH) [θ] (nm):

+27861.1° (277), −144222.2° (233) (negative maximum), +90138.9° (215) (positive maximum). UV λ_{max}^{EtOH} nm (log ε): 240 (sh., 3.78), 281 (3.95), 320 (sh., 3.31). IR ν_{max}^{KBr} cm^{-1}: 3500 (OH). PMR (in $CDCl_3$) δ: 2.54 (3H, s., NCH_3), 3.50 (1H, s., OH), 5.92, 6.05 (2H, d., J=1.5 Hz, OCH_2O), 6.50 (1H, s., C_3–H), 6.69 (1H, d., J=2.5 Hz, C_8–H), 6.75 (1H, d.d., J=2.5, 8.5 Hz, C_{10}–H), 7.93 (1H, d., J=8.5 Hz, C_{11}–H). MS m/z (%): 295 (M^+, 17.2), 294 (M^+-1, 21.5), 252 (M^+-CH_2=NCH_3, 11.6). *Anal.* Calcd for $C_{18}H_{17}NO_3 \cdot CH_3OH$: C, 69.70; H, 6.47; N, 4.28. Found: C, 69.59; H, 6.53; N, 4.06. This alkaloid was identified by direct comparison (UV, IR, PMR, TLC and mixed melting point) with an authentic sample of **3**.

N-Methylation of Anolobine (4)——To a solution of anolobine (**4**) (43 mg) in MeOH (10 ml), 10% formaldehyde methanol solution (0.3 ml) was added slowly with stirring. After 30 min, the mixture was cooled at 0—5°C and treated with excess $NaBH_4$ (43 mg). One hour later, the excess reagent was decomposed with aqueous 10% AcOH. The solution was washed once with Et_2O, made alkaline with aqueous 10% NH_4-OH and extracted with Et_2O. The Et_2O layer was washed, dried and concentrated. The residue was recrystallized from MeOH and afforded colorless needles, mp 218—220°C (sint., 133—135°C), $[\alpha]_D$ −31.3° (c=0.320, $CHCl_3$). Yield, quantitative.

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References and Notes

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