CHARACTERIZATION OF SWEETININE, A CONSTITUENT OF *SWEETIA ELEGANS*, AS THE *ORMOSIA* ALKALOID, (±)-6-EPIPODOPETALINE[1]

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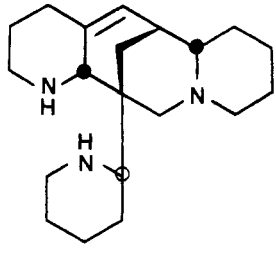
Sweetinine is an alkaloid first isolated from the bark of *Sweetia panamensis* Benth. (Leguminosae) by Beal and coworkers (1). This group established the molecular formula of the compound as $C_{20}H_{33}N_3$ and demonstrated the presence of one tertiary and two secondary amino groups in the molecule (1). Although complete structural details of sweetinine were not determined at the time of its original isolation, it was suggested that the compound may be an *Ormosia*-type quinolizidine alkaloid (1).



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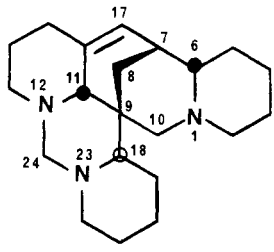

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During a screening program for legume alkaloids, several closely related *Ormosia* alkaloids were detected by gc/ms in an extract of the stem bark of *S. elegans* (Vog.) Benth. One of the major components of this alkaloidal mixture has been shown by us previously to be identical to sweetinine by chromatographic and spectral comparison with an authentic sample[3] (2). We now wish to report further spectral data for sweetinine and its formaldehyde adduct, homosweetinine. In addition, primarily on the basis of the interpretation of the pmr spectra of these two compounds, we have identified sweetinine as (±)-6-epipodopetaline (**1**).[4]

The pmr spectrum of sweetinine showed the presence of an olefinic proton, and its mass spectral fragmentation pattern indicated that the compound is a monounsaturated pentacyclic *Ormosia* alkaloid of the podopetaline[5] type (3, 4). Ir spectra of sweetinine in both KBr (1) and in solution ($CDCl_3$) exhibited a strong *trans*-band at 2760 cm^{-1}, indicating that the compound is a *trans*-quinolizidine alkaloid with H-6 *cis* to the

[1]Part of this work was presented at the 20th Annual Meeting of the American Society of Pharmacognosy, held at Purdue University, West Lafayette, Indiana, July 29-August 3, 1979.

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[3]A generous sample of sweetinine was kindly provided by Prof. J. L. Beal.

[4]Structures **1** and **2** represent only one of the enantiomers of (±)-6-epipodopetaline (sweetinine) and (±)-homo-6-epipodopetaline (homo-sweetinine), respectively.

[5]We are grateful to Dr. J. A. Lamberton for a sample of (−)-podopetaline.

C-7, C-9 methylene bridge (5, 6). The relative stereochemistry of the protons at C-11 and C-18 was deduced by examination of the pmr spectra of homo-sweetinine in several solvents. The two C-24 aminal protons of this compound appeared at δ 3.43 as a 2H singlet in $CDCl_3$ and remained unresolved even at 270 MHz. In acetone-d_6, these protons exhibited an AB pattern (δ_A 3.34, δ_B 3.43, $^2J_{AB} = -7.9$). These data suggest that H-11 and H-18 are *anti* in homo-sweetinine since analysis of the pmr spectra of model aminal compounds indicates that an AX pattern would be expected for the C-24 protons if H-11 and H-18 were *syn* (7).

Further details of the relative stereochemistry of H-6, H-11 and H-18 in homo-sweetinine were obtained in the following manner. A 1H doublet of doublets centered at δ 3.95 ($^2J_{10e,10a} = -11.4$, $^4J_{10e,8} = 1.9$) in the pmr spectrum of this compound in $CDCl_3$ was assigned to H-10eq, which in the proposed structure, **2**, is deshielded not only by N-1, but also by the *syn*-diaxial electron lone pairs ("rabbit ears") (8) of N-12 and N-23. For such an effect to be observed, H-11 must be *cis* to the C-7, C-9 bridge in homo-sweetinine. In support of this argument it was observed that in the pmr spectrum of homo-sweetinine in pyridine-d_5 the H-10eq doublet of doublets was shifted downfield to δ 4.43, possibly due to solute-solvent complexation involving the aminal nitrogen lone pairs. Thus the structure of homo-sweetinine was deduced to be **2**, and, by analogy, the structure of sweetinine is **1**.

Structure **1** corresponds to 6-epipodopetaline, an alkaloid isolated from *Podopetalum ormondii* F. Muell. (Leguminosae), whose structure was determined by X-ray crystallography (9). Confirmation of the identification of sweetinine as 6-epipodopetaline (**1**), and homo-sweetinine as homo-6-epipodopetaline (**2**), was obtained by direct spectroscopic and chromatographic comparison of the compounds.[6] However, it should be pointed out that Beal's sweetinine and the homo-sweetinine isolated in this work from *S. elegans* are racemic, while the material isolated from *P. ormondii* is levorotatory. These observations explain the discrepancies in mp determinations for sweetinine (mp, 174–175°) (1) and (−)-6-epipodopetaline (mp, 118–119°) (9). To avoid the unnecessary proliferation of trivial nomenclature in the literature, we propose the designation of sweetinine as (±)-6-epipodopetaline (**1**).

The root bark of *S. elegans* was formerly an official drug in Brazil (10), and extracts of this plant have been patented under its synonym *Leptolobium elegans* for their reputed sedative, antispasmodic and analgesic effects (11). Since certain *Ormosia* alkaloids have been claimed to possess hypnotic and analgesic ("morphine-like") properties (12), we are currently evaluating (±)-6-epipodopetaline (**1**) and related isolates for these pharmacological activities.

EXPERIMENTAL[7]

PLANT MATERIAL.—The stem bark of

[6]We are grateful to Dr. S. McLean for a sample of (−)-6-epipodopetaline.

[7]Melting points were determined using a Kofler hot-stage instrument and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Uv spectra were obtained on a Cary 118 UV-Visible spectrophotometer. Ir spectra were obtained with a Perkin-Elmer model 337 and a Beckman model IR-18A spectrophotometers, with polystyrene calibration at 1601 cm^{-1}. Pmr spectra were recorded on a Varian T-60A instrument operating at 60 MHz with a Nicolet model TT-7 Fourier Transform attachment and a Bruker 270 MHz instrument. Tetramethylsilane was used as internal standard and chemical shifts are reported on the δ (ppm) scale. Low resolution mass spectra were obtained on a Varian MAT 112S double focusing mass spectrometer operating at 70 eV.

Sweetia elegans (Vog.) Benth. (Leguminosae), collected in Brazil in February, 1972, was supplied through the Drug Research and Development Program (Natural Products Branch) of the National Cancer Institute, Bethesda, Maryland. A voucher specimen representing this collection is deposited at the Herbarium of the National Arboretum, U.S. Department of Agriculture, Washington, D.C.

CHARACTERIZATION OF SWEETINIINE.—Sweetinine [(±)-6-epipodopetaline, **1**], kindly donated by Prof. J. L. Beal, exhibited the following data: mp, 174–175°; $[\alpha]_\lambda^{23}$, λ = 589, 578, 546, 436 and 365 nm, 0.0° (c 0.41, EtOH); uv, apparent λ max (cyclohexane) 193 (log ε 4.20) and 210 nm (log ε 3.86); ir, ν max ($CDCl_3$) 3170 (NH), 2800, 2760 cm^{-1} (*trans*-bands); pmr (60 MHz, $CDCl_3$) δ 3.17 (1H, bs, H-11) and 5.43 (1H, d, $^3J_{17,7}$ = 6.1, H-17); ms, *m/z* 315 (M^+, 23%), 257 (3), 243 (3), 231 (28), 217 (8), 189 (5), 149 (26), 122 (15), 98 (48), 97 (21), 96 (16), 84 (100), 56 (14) and 41 (10). Mass measurement: Found, 315.26766, Calcd. for $C_{20}H_{33}N_3$, 315.26744.

PREPARATION OF HOMO-SWEETINIINE (**2**) FROM **1**.—Homo-sweetinine [(±)-homo-6-epipodopetaline, **2**] was quantitatively prepared from **1** (20 mg) by treatment with formaldehyde according to published procedures (1, 13, 14). The product (21 mg) was purified by preparative tlc on silica gel GHLF[5] in methylene chloride-methanol-28% ammonium hydroxide solution (85:15:1) (R_f, 0.58) and recrystallization from acetone. This compound exhibited the following data: mp, 148–151° (lit. 149–151°) (1); $[\alpha]_\lambda^{23}$, λ = 589, 578, 546, 436 and 365 nm, 0.0° (c 0.38, EtOH); ir, ν max ($CDCl_3$) 2800, 2760 cm^{-1} (*trans*-bands); pmr (270 MHz, 2760 cm^{-1} (*trans*-bands); pmr (270 MHz, $^2J_{10e,10a}$ = −11.4, $^4J_{10e,8}$ = 1.9, H-10eq), 5.27 (bd, $^3J_{17,7}$ = 6.0, H-17); (60 MHz, acetone-d_6) δ 3.34 (1H, d, $^2J_{24a,24e}$ = −7.9, H-24ax), 3.43 (1H, d, $^2J_{24e,24a}$ = −7.9, H-24eq), 4.00 (1H, dd, $^2J_{10e,10a}$ = −11.0, $^4J_{10e,8}$ = 1.8, H-10eq), 5.25 (1H, bd, $^3J_{17,7}$ = 5.7, H-17); (60 MHz, C_5D_5N) δ 3.33 (2H, s, H_2-24), 4.43 (1H, dd, $^2J_{10e,10a}$ = −11.0, $^4J_{10e,8}$ = 1.9, H-10eq), 5.36 (1H, bd, $^3J_{17,7}$ = 6.1, H-17); ms, *m/z* 327 (M^+, 68%), 312 (11), 284 (9), 244 (23), 243 (28), 229 (55), 161 (15), 134 (14), 122 (35), 98 (100), 97 (22), 96 (26), 84 (32) and 41 (20).

ISOLATION OF SWEETINIINE [(±)-6-EPIPODOPETALINE, **1**] AS ITS HOMO DERIVATIVE (**2**) FROM S. ELEGANS.—The dried, milled stem bark of *S. elegans* (680 g) was exhaustively extracted with hot methanol, and this extract was concentrated to dryness *in vacuo* at 40°, leaving a residue (93 g) which was taken up in 200 ml of 5% aqueous HCl and filtered. This solution was made basic (*p*H 9) by the addition of concentrated NH_4OH and was extracted 7 times with 300 ml portions of chloroform. The organic extracts were collected, dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent *in vacuo* left a reddish-brown gum (7.1 g) which was taken up in 150 ml of 5% aqueous HCl. This aqueous solution was washed with several portions of diethyl ether, alkalinized (*p*H 9) with concentrated NH_4OH and extracted with diethyl ether (10×50 ml). The combined diethyl ether extracts were dried, filtered and reduced to a volume of 40 ml. On standing for several hours, the solution deposited a colorless crystalline material (99 mg) which was recrystallized several times from acetone. Gc/ms showed this material to be a mixture of several C_{20} *Ormosia*-type quinolizidine alkaloids, one of the main components of which was identical (tlc, gc/ms) to an authentic sample of sweetinine[3] (2).

The problem of separating sweetinine [(±)-6-epipodopetaline, **1**] from the other alkaloids in the crystalline mixture obtained from *S. elegans* stem bark was overcome by preparation of the homo derivative by reaction with formaldehyde and subsequent purification as described above. Pure (±)-homo-6-epipodopetaline (**2**) (12 mg) derived from *S. elegans* was identical (mp, $[\alpha]_\lambda$, pmr, ms, tlc) to the homo derivative of an authentic sample of sweetinine from *S. panamensis*.[3]

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