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TETRAHYDROISOQUINOLINE ALKALOIDS OF THE MEXICAN COLUMNAR CACTUS *PACHYCEREUS WEBERI**

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Key Word Index—*Lemaireocereus weberi*; *Pachycereus weberi*; *Stenocereus weberi*; Cactaceae; tetrahydroisoquinoline alkaloids; lemaireocereine; weberine; weberidine; nortehuanine; tehuanine; heliamine; *N*-methylheliamine; oxymethylcorypalline; pellotine.

Abstract—Eight tetrahydroisoquinoline alkaloids have been crystallized and identified from the nonphenolic and phenolic extracts of the giant Mexican cereoid cactus, *Pachycereus weberi* (Coult.) Br. and R. The identities were established as 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (nortehuanine) **1**; 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (lemaireocereine) **2**; 7-methoxy-1,2,3,4-tetrahydroisoquinoline (weberidine) **3**; 5,6,7,8-tetramethoxy-1,2,3,4-tetrahydroisoquinoline (weberine) **4**; 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (heliamine) **5**; 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*N*-methylheliamine or oxymethylcorypalline) **6**; 2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline (tehuanine) **7**; and 1,2-dimethyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (pellotine) **8**. Compounds **1**–**4** have not been identified previously as natural compounds, while compounds **5**–**8** are previously known cactus alkaloids.

INTRODUCTION

Pachycereus weberi (Coult.) Backbg. [syn. *Lemaireocereus weberi* (Coult.) Br. and R. and *Stenocereus weberi* (Coult.) Riccob.] is the tallest Mexican columnar cactus, a native of Puebla and Oxaca where it is commonly called 'candelabro' and 'cardon'. Although there are no ethnobotanical reports of medicinal uses of this species, such reports have been made for related columnar species [1–6]. *P. weberi* has been botanically classified in the artificial genus *Lemaireocereus*, and the alkaloid and terpene contents of Mexican high columnar cacti belonging to this genus have recently attracted taxonomic attention; the presence, absence, and/or type of these constituents seem to be useful as chemotaxonomic characters [7]. Previous phytochemical work with this species by Djerassi *et al.* reported the isolation of the phenolic peyote alkaloid, anhalonidine (1-methyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline) [8].

RESULTS AND DISCUSSION

Chloroform extraction of defatted and basified plant material, followed by acid–base partitioning and ion exchange chromatography, produced two initial fractions containing the phenolic alkaloids and the nonphenolic alkaloids. Resolution of the nonphenolic fraction by a combination of column chromatography and PLC on Si gel resulted in the isolation of 6 crystalline tetrahydroisoquinoline alkaloids as their hydrochlorides (compounds **1**, **2**, **3**, **5**, **6**, and **7**) (Fig. 1). Resolution of the phenolic fraction by PLC on Si gel yielded only one crystalline alkaloid hydrochloride (**8**); traces of anhalonidine, as previously reported [8], were observed in this fraction by TLC.

A second extraction of the plant material, using ethanol followed by ion exchange chromatography and a chloroform–water partitioning of the nonphenolic fraction, yielded a nonphenolic chloroform fraction and a nonphenolic water fraction. Both of these nonphenolic fractions were purified by absorption on Celite, by elution with hydrochloric acid, and by acid–base partitioning of the acidic eluates to yield a nonphenolic extract containing the less polar alkaloids and a nonphenolic extract containing the more polar alkaloids. Resolution of the less polar alkaloids by a combination of column chromatography and PLC led to the isolation of two alkaloid hydrochlorides **4** and **7**). Fractional crystallization of the more polar alkaloids resulted in the isolation of the hydrochloride of **5**. Analytical TLC indicated the presence of additional quantities of **1**, **2**, and **6** in the less polar fraction and **3** and **5** in the more polar fraction, but attempts were not made to reisolate these compounds.

The phenolic compound **8**, which had been crystallized after fractionation of the original chloroform extract, could not be detected in the phenolic fraction of the ethanol extracts. Thus, this phenolic alkaloid

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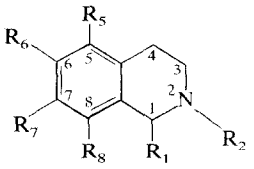

Compound	Trivial name	R_1	R_2	R_5	R_6	R_7	
1	Nortehuanine	H	H	OMe	OMe	OMe	H
2	Lemaireocereine	H	H	H	H	OMe	OMe
3	Weberidine	H	H	H	H	OMe	H
4	Weberine	H	H	OMe	OMe	OMe	OMe
5	Heliamine	H	H	H	OMe	OMe	H
6	*N*-Methylheliamine	H	Me	H	OMe	OMe	H
7	Tehuanine	H	Me	OMe	OMe	OMe	H
8	Pellotine	Me	Me	H	OMe	OMe	H

Fig. 1. Tetrahydroisoquinoline alkaloids isolated from *P. weberi*.

may be an artifact of the initial fractionation scheme; we have recently demonstrated that such is the case with the phenolic alkaloid, deglucopterocereine, which is formed from the hydrolysis of pterocereine [(−)-1-hydroxymethyl-2-methyl-5-β-*O*-glucopyranosyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline] during similar fractionation of extracts of the cactus *Pterocereus gaumeri* (Br. and R.) MacDoug and Mir [9].

The identity of nonphenolic compounds **1–7** was established by physical (mp and TLC) and spectral (UV, IR, MS, and ^{1}H NMR) analyses followed by synthesis, with the exception of **4** which was not synthesized due to the unavailability of suitably substituted starting materials.

The EI-MS of **1** revealed a M^+ at *m/e* 223 ($C_{12}H_{17}NO_3$). A strong peak at M^+-1 as well as a base peak due to the loss of a fragment of 29(CH_2=N—H), attributable to a retro Diels–Alder cleavage of the M^+ suggested the tetrahydroisoquinoline nucleus [10]; the UV spectra also supported this suggestion with characteristic bands at 210 and 263 nm, demonstrating bathochromic shifts due to substituents on the aromatic ring [11]. The ^{1}H NMR showed a one-proton singlet at δ 6.7 indicating trisubstitution on the aromatic ring, and the lack of *N*-methyl adsorption confirmed that the compound was a secondary amine, as had been indicated by the TLC reaction with fluorescamine. MS data with 6,7,8-trisubstituted tetrahydroisoquinolines showed base peaks at M^+-1, rather than from the retro Diels–Alder mode of cleavage [12]; this observation helped to rule out a 6,7,8-substitution pattern. Comparison of the IR spectra of **1** with that of the isomeric peyote alkaloid, anhalinine (6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline) showed non-identity. Thus, a 5,6,7-trisubstitution pattern was proposed, and the hydrochloride of the necessary compound was synthesized by Bobbitt's modification of the Pomeranz–Fritsch reaction [13]. The physical and spectral data of the synthesized compound were essentially identical to those of **1**, establishing its identity as 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, a new alkaloid which we have named nortehuanine.

Compound **2** exhibited a base peak in the EI-MS at *m/e* 193 corresponding to an empirical formula of $C_{11}H_{15}NO_2$ (M^+). An intense peak at *m/e* 164 (M^+-29) again implicated a retro Diels–Alder breakdown of a tetrahydroisoquinoline nucleus. The ^{1}H NMR showed two singlets at δ 3.88 and δ 3.82 for two methoxy groups attached to an aromatic system and a singlet at δ 7.08 for two aromatic protons. These data indicated an asymmetric disposition of two methoxy groups on the aromatic nucleus and ruled out a 6,7-distribution pattern in which the two methoxys would likely be chemically equivalent. Previously reported ^{1}H NMR of 5,8- and 6,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochlorides, in DMSO-d_6 and deuterated methanol, respectively, eliminated these isomers as possible structures for **2** [14]. Co-occurrence of 5,6,7-trisubstituted and 7,8-disubstituted tetrahydroisoquinolines has been reported in the giant saguaro cactus, *Carnegiea gigantea* (Engelm.) Br. and R. [15], consequently, 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride was synthesized [13] and found to be physically and spectrally identical to **2**; this new alkaloid was named lemaireocereine.

Compound **3** exhibited a M^+ at *m/e* 163 ($C_{10}H_{13}NO$) with a base peak at 134 (M^+-29, retro Diels–Alder cleavage). In the ^{1}H NMR an AB quartet was readily recognized indicating a 1,2,4-substitution pattern on benzene [16]. The downfield doublet of the AB system was centered at δ 7.23 (J_o = 8.6 Hz); the upfield doublet was split into 4 lines due to *meta* coupling of the B proton with a third proton; the upper part of the second doublet was overlapped with the absorption of the third proton giving an overall appearance of an unresolved triplet. This monosubstitution pattern on the aromatic portion could only fit two possible isomers, namely 6- or 7-methoxy-1,2,3,4-tetrahydroisoquinoline. The 6-methoxy isomer, longimammatine, has been previously isolated in our laboratory from the cactus *Dolichothele longimamma* (DC.) Br. and R. [17], and comparison of its spectral data showed non-identity with compound **3**. Subsequently unequivocal synthesis [13] of 7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride proved it to be physically and spectrally identical to **3**; this new alkaloid was named weberidine.

The EI-MS spectra of compound **4** displayed a very intense M^+ at *m/e* 267 ($C_{14}H_{21}NO_4$); again the tetrahydroisoquinoline nucleus was indicated by the intense peaks at M^+-1 and M^+-43 (retro Diels–Alder cleavage losing CH_2=N—Me) and by the near bands

at 205, 223, and 282 nm in the UV spectra. The ^{1}H NMR indicated a surprising lack of aromatic absorption, and the presence of 4 singlets was attributable to 4 methoxy groups; 3 proton absorption at δ 2.94, due to an *N*-methyl, confirmed that the compound was a tertiary amine. On the basis of these spectral data **4** was proposed to be 2-methyl-5,6,7,8-tetramethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride; this is a new compound and was named weberine; the isolation of this compound constitutes the first report of an aromatically tetrasubstituted tetrahydroisoquinoline alkaloid.

The similar EI–MS (*m/e* 193, M^+, $C_{11}H_{15}NO_2$) of compounds **5** and **2** (lemaireocereine which was identified as 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline) indicated an isomeric relationship between these two alkaloids. The ^{1}H NMR spectra of **5** displayed two one-proton singlets in the aromatic region at δ 6.9 and 6.85 and a six-proton singlet at δ 3.85 corresponding to the methoxy groups. The observed equivalence of the methoxy groups, as well as the UV spectrum which was very similar to that reported for carnegine (1,2-dimethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) [11], suggested that the 6,7-dimethoxy isomer was more plausible. Synthesis, using the Pictet–Spengler reaction [16], of 6,7-dimethoxy-1,2,3,4-tetrhydrisoisoquinoline hydrochloride provided reference material which was physically and spectrally identical to **5**. During the course of this work, isolation of the same compound from the giant cactus *Pachycereus pecten-aboriginum* (Engelm.) Br. and R. was reported, and the compound was named heliamine [4]; however, the reported ^{1}H NMR is confusing since the coupling constant reported implicated that the two signals in the aromatic region (δ 6.78 and 6.8) integrated for two protons and constituted a doublet; such would be incorrect for 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. Nevertheless, the MS reported is very similar to that observed in the current study and the structure was proven by synthesis [4].

Compound **6** had a M^+ at *m/e* 208 ($C_{12}H_{17}NO_2$) with a base peak at *m/e* 164 (M-43, retro Diels–Alder cleavage of a tertiary tetrahydroisoquinoline). The ^{1}H NMR and UV spectra strongly suggested a similar structure to **5** (heliamine). The chemical shifts of the aromatic protons were almost the same (δ 6.92 and 6.83); however, the two methoxy groups (δ3.85 and 3.84) were not quite equivalent, which could be explained by the presence of an *N*-methyl group (δ 3.04). These data permitted the postulation that **6** was 2-methyl-6,7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline hydrochloride; this compound could be named either *N*-methylheliamine or oxymethylcorypalline. It has been previously identified by mass fragmentography but not isolated in crystalline form, from the Mexican cactus *Pilosocereus guerreronis* (Backbg.) Byl. and Rowl. The identity was confirmed physically and spectrally by unequivocal synthesis again using the Pictet–Spengler reaction [20].

Compound **7** revealed a strong M^+ at *m/e* 237 ($C_{13}H_{19}NO_3$) and strong peaks at M^+-1 and M^+-43 (base peak, retro Diels–Alder cleavage of a tertiary amine tetrahydroisoquinoline). The ^{1}H NMR spectra revealed trisubstitution of the aromatic ring (3 methoxys at δ 3.8–3.9), a single aromatic proton (δ 6.4) and the expected *N*-methyl (δ 2.92). The UV spectrum as well as the EI–MS fragmentation strongly suggested a substitution pattern identical to that of **1** (nortehuanine). Thus, **7** was proposed to be 2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride. This identification was physically and spectrally verified by synthesis using Bobbitt's modification of the Pomeranz–Fritsch reaction for tertiary amines [21]. This alkaloid has been previously isolated from the Mexican cactus, *Pachycereus tehuantepecanus* MacDoug. and Bravo, and named tehuanine (Weisenborn, J., personal communication); however, the details of isolation and structure elucidation have never been published. Kapadia *et al.* briefly reported a synthesis for tehuanine but presented little or no physical and spectral data [22].

Compound **8** was suspected of being a peyote 8-hydroxytetrahydroisoquinoline due to its blood-red colour when sprayed with tetrazotized benzidine reagent on TLC plates. Comparison of the IR spectrum of the hydrochloride with that of authentic pellotine hydrochloride (1,2-dimethyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline) showed them to be identical. Pellotine has been previously isolated from the peyote cactus, *Lophophora williamsii* (Lem.) Coult. [10], and the Mexican peyotillo cactus, *Pelecyphora aselliformis* Ehren. [23]; in addition, it has been identified in *Lophophora diffusa* (Croizat) H. Bravo [24].

Monosubstituted tetrahydroisoquinolines, such as weberidine, are uncommon in cacti although the 6-methoxy compound has been reported in two Mexican *Dolichothele* species [17, 25]. The 6,7-disubstituted tetrahydroisoquinolines, such as heliamine and *N*-methylheliamine, are more common and are also known to co-occur with 7,8-disubstituted and 5,6,7-trisubstituted tetrahydroisoquinolines in the saguaro, *C. gigantea* [15]. The 6,7,8-trisubstituted tetrahydroisoquinolines, such as anhalonidine and pellotine, are well-known alkaloids from the peyote cactus, *L. williamsii* [10]. The 5,6,7-trisubstituted tetrahydroisoquinolines, such as tehuanine and nortehuanine, are relatively rare ([9, 15]; Weisenborn, J., personal communication). The 5,6,7,8-tetrasubstituted tetrahydroisoquinolines such as weberine, are completely new. Finding all 4 alkaloid types, i.e. mono-, di-, tri-, and tetrasubstituted compounds, in the same species of cactus shows a highly evolved enzyme system for ring oxidation and *O*-methylation. A current survey of closely related Mexican columnar cacti for these and other alkaloids appears to be of chemotaxonomic significance [26].

EXPERIMENTAL

Mps were determined on a capillary melting point apparatus and were uncorr. UV spectra were recorded in H_2O and IR spectra using KBr pellets. ^{1}H NMR spectra were determined at 80 MHz using $CDCl_3$ or D_2O as solvents and TMS or DDS, respectively, as int. standards. Low resolution EI–MS and CI–MS were recorded on a Dupont 21-492B mass spectrometer. Analytical TLC plates were Bakerflex IB2-F, and the solvent systems, visualization methods, and techniques used for analytical TLC and PLC were employed as previously reported [17, 27]. Separations by adsorption column chromatography employed Merck Si gel (60–200

mesh, normal, grade 950), and Amberlite IRA 401S (Mallinkrodt) in the hydroxide form was used for anion exchange chromatography [28].

Plant material. Field-dried specimens of shredded *P. weberi* were received from the Medicinal Plant Resources Laboratory, Agriculture Research Center, U.S. Department of Agriculture, Beltsville, Maryland, U.S.A., in March 1976. The plant material was collected by Edward H. Sallee near Puebla, Mexico, in November 1975. Reference specimens are being maintained at the Agriculture Research Center, and reference photographs are on file at Purdue University. Dried shredded material was ground through a 2 mm screen in a Wiley Mill.

Extraction. A total of 2.1 kg of the powdered plant material was continuously Soxhlet extracted with petrol (60–80°) for 3 days to remove lipids (6.63 g). The defatted marc was moistened with $CHCl_3$—MeOH—58% NH_4OH (2:2:1), macerated in $CHCl_3$—MeOH—58% NH_4OH (9:0.9:0.1), and extracted via percolation using *ca* 30 l. of $CHCl_3$. The $CHCl_3$ extract was concd *in vacuo* to a thick brown syrup (40 g). This material was then processed, essentially as previously reported [17], to yield fraction A (19 g, alkaloids), fraction B (non-alkaloidal material), and fraction C (10 g, H_2O soluble alkaloids). Fraction A was resolved into phenolic (1.2 g) (PA) and nonphenolic (16.9 g) (NPA) portions by use of anion exchange column chromatography as previously described [17, 28].

Resolution of nonphenolic alkaloids from fraction A (NPA). Resolution of extract NPA was performed by column adsorption chromatography with 240 g of Si gel wet packed in C_6H_6 in a 30 × 1.5 in. glass column, 8 g of the NPA extract was adsorbed to 12 g of Si gel and applied to the top of the column. Development was made with C_6H_6 (2.5 l.), C_6H_6—$CHCl_3$ (19:1) (1.25 l.), C_6H_6—$CHCl_3$ (17:3) (3 l.), C_6H_6—$CHCl_3$ (3:1) (3 l.), C_6H_6—$CHCl_3$ (3:2) (1 l.), C_6H_6—$CHCl_3$ (1:5) (3 l.), C_6H_6—$CHCl_3$ (3:17) (2.5 l.), $CHCl_3$ (3 l.), $CHCl_3$—MeOH (98.5:1.5) (3 l.). A total of 112 fractions, of 225 ml each, were collected and combined on the basis of analytical TLC. Alkaloids were eluted in fractions 67–104, as the C_6H_6—$CHCl_3$ (3:17) and subsequent solvents were being used for development.

Isolation and identification of tehuanine (**7**). Fractions 78–80 contained a mixture of two alkaloids as indicated by TLC. The lower R_f component (**7**) was major and was isolated by fractional crystallization as its hydrochloride (1.787 g, 219–221°). PLC of the mother liquor was used to isolate an additional 30 mg (mp 219°) but the minor component (**4**) failed to crystallize. Fractions 81–84 contained the same alkaloid and yielded an additional 0.4 g (mp 219–221°). Compound **7** was a single spot on TLC, produced a purple colour with iodoplatinate, and gave no reaction with fluorescamine; UV $\lambda_{max}^{H_2O}$ (log ε): 203 (4.35), 211 (3.68) *sh*, 280 (2.92), 289 (2.61) *sh*; IR ν_{max}^{KBr} cm^{-1}: 2910, 2480, 1595, 1880, 1480, 1450, 1175, 1100, 940, 890, 850, 690; ^1H NMR (80 MHz, $CDCl_3$): δ 6.4, *s*, 1H, (C=CH); 4.2, *s*, 2H, (CH_2-1); 3.9, *s*, 3H, (OCH_3); 3.8, *s*, 3H, (OMe); 3.8, *s*, 3H (OMe); centered at 3.2, two *m*, 4H, (CH_2—CH_2—3,4); CI-MS $(M+H)^+$: 238; EI-MS *m/e* (%): 237 (97), 236 (75), 222 (13), 205 (55), 194 (100), 179 (55). The above spectral data suggested that **7** was either 2-methyl-5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (tehuanine) or the 6,7,8-trimethoxy isomer. The 6,7,8-isomer (*N*-methylanhalinine HCl) was synthesized from mescaline by the Eschweiler–Clarke reaction [29, 30] and from *N*-methylmescaline by the Pictet–Spengler reaction [20] and was found to be different (IR ^1H NMR, and MS) from **7**. The 5,6,7-isomer (tehuanine hydrochloride) was synthesized from 3,4,5-trimethoxybenzaldehyde and aminocetaldehyde diethylacetal, using Bobbitt's modification of the Pomeranz–Fritsch reaction [21]; the synthesized compound (mp 221°) was spectrally identical (IR and ^1H NMR superimposable) to **7**.

Isolation and identification of oxymethylcorypalline (**6**). Fractions 85–90, as indicated by TLC analysis, contained 2 alkaloids, these were resolved by PLC. The upper band yielded 10 mg of additional tehuanine HCl, and the lower band yielded 25 mg of **6** (mp 210°). This compound also produced a purple chromophore with iodoplatinate and gave no reaction with fluorescamine; UV $\lambda_{max}^{H_2O}$ (log ε): 210 (4.4), 217 (3.6), 282 (3.4), 288 (3.3); ^1H NMR (80 MHz, D_2O): δ 6.9, *s*, 1H, (C=CH); 6.8, *s*, 1H, (C=CH); 4.3, *bs*, 2H, (CH_2); 3.85, *s*, 3H, (OMe); 3.84, *s*, 3H, (OMe); 3.6, *m*, 2H, (CH_2-3); 3.05, *m*, 2H, (CH_2-4); 3.04, *s*, 3H, (N—Me); CI-MS $(M+H)^+$: 208; EI-MS *m/e* (%): 207 (63), 206 (57), 164 (100), 149 (14), 120 (17). The spectral data suggested a 2-methyl-dimethoxy-1,2,3,4-tetrahydroisoquinoline, and the ^1H NMR and UV spectra strongly suggested the 6,7-dimethoxy rather than other alternatives such as the 7,8-dimethoxy compound. Synthesis of 2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (oxymethylcorypalline or *N*-methylheliamine) was carried out using the Pictet–Spengler reaction [20] and employing *N*-methyl-3,4-dimethoxy-β-phenethylamine and formaldehyde. The synthesized compound (mp 215°) was identical to compound **6** (IR, ^1H NMR and MS).

Isolation and identification of heliamine (**5**). TLC of fractions 93–100 revealed a major component, **5**, with traces of compounds **1** and **3**. Fractional crystallization produced 285 mg of the hydrochloride of **5** (mp 248°). Reaction with fluorescamine on TLC as well as a lack of N—Me protons in the ^1H NMR indicated a secondary amine; UV $\lambda_{H_2O}^{max}$ (log ε): 203 (4.5), 220 (3.8), 284 (3.6), 288 (3.6) *sh*; IR ν_{max}^{KBr} cm^{-1}: 2900, 2750, 1610, 1510, 1245, 1210, 1100, 1000, 840, 790; ^1H NMR (80 MHz, D_2O): δ 6, *s*, 1H, (C=CH); 6.8, *s*, 1H, (C=CH); 4.3, *s*, 2H, (CH_2-1); 3.8, *s*, 6H, (OMe); 3.5(c)*t*, 2H, (CH_2-3); 3.0(c)*t*, 2H, (CH_2-4); CI-MS $(M+H)^+$: 194; EI-MS *m/e* (%): 193 (90), 192 (57), 178 (9), 165 (17), 164 (100), 149 (14), 121 (16). The spectral data suggested that **5** was simply the *N*-demethyl analog of oxymethylcorypalline (**6**). Reference 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (heliamine) was synthesized from 3,4-dimethoxy-β-phenethylamine and formaldehyde using the Pictet–Spengler reaction [18] (mp 252°). All the spectral data (IR, ^1H NMR, and MS) were identical to that of **5** confirming its identity as heliamine.

Isolation and identification of lemaireocereine (**2**) *and nortehuanine* (**1**). On the basis of TLC analyses the mother liquors of fractions 93–100 were combined with fractions 91–92. PLC yielded 3 alkaloid hydrochlorides: **5** (heliamine) mp 248°, 40 mg) (lower band), **1** (mp 260°, 20 mg) (middle band), and **2** (mp 180°, 25 mg) (upper band). Compound **1** reacted with fluorescamine on TLC to indicate a secondary amine function; UV $\lambda_{max}^{H_2O}$ (log ε): 203 (4.4), 223 (3.7) *sh*, 281 (3.2); 292 (3.0) *sh*; IR ν_{max}^{KBr} cm^{-1}: 2920, 2770, 1585, 1480, 1100, 1115, 1040, 865, 770; ^1H NMR (80 MHz, D_2O): δ 6.7, *s*, 1H, (C=CH); 4.3, *s*, 2H, (CH_2-1); 3.88, *s*, 3H, (OMe); 3.85, *s*, 3H, (OMe); 3.85 *s* 3H, (OMe); 3.5, *t*, 2H, (CH_2-3); 297, *t*, 2H, (CH_2-4); CI-MS $(M+H)^+$ 224; EI-MS *m/e* (%): 223 (80), 222 (48), 194 (65), 192 (100), 179 (39), 156 (58). The ^1H NMR demonstrated trimethoxylation, and the UV spectrum was very similar to that of tehuanine (**7**), indicating a 5,6,7-trimethoxylation. Comparison of the

IR spectrum with that of the peyote alkaloid anhalinine hydrochloride (6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline) revealed them to be different compounds although the spectra were quite similar; a misleading observation was that with TLC anhalinine and **1** showed identical R_f values in 5 different solvent systems. The available data suggested that **1** was 5,6,7-trimethoxy-1,2,3,4-tetrahydroisoquinoline, so the hydrochloride of this compound was prepared after synthesis from 3,4,5-trimethoxybenzaldehyde and aminoacetaldehyde diethylacetal by Bobbitt's modification of the Pomeranz–Fritsch reaction [13]. The synthetic compound (mp 268°) was identical (IR, ^{1}H NMR, and MS) to the isolated **1**, thus confirming its identity as a new alkaloid nortehuanine. Compound **2** also gave a secondary amine reaction with fluorescamine on TLC; UV $\lambda_{max}^{H_2O}$ (log ε): 201 (4.5), 223 (3.9) *sh*, 278 (3.4), 286 (3.4), 293 (3.3) *sh*; IR ν_{max}^{KBr} cm^{-1}: 3035, 2720, 2600, 1580, 1495, 1280, 1250, 1095, 1000, 895, 800; ^{1}H NMR (80 MHz, D_2O): δ 7.1, *s*, 2H, (C═CH); 4.4, *s*, 2H, (CH_2-1); 3.9, s, 3H, (OMe); 3.8, *s*, 3H, (OMe) 3.4(c) *m*, 2H, (CH_2-3); 3.0(c) *m*, 2H, (CH_2-4); CI–MS $(M+H)^+$: 194; EI–MS *m/e* (%): 193 (100), 192 (46), 164 (82), 178 (14), 149 (45), 121 (11). The MS data for **2** and heliamine were nearly identical, only differing in some peak intensities. The ^{1}H NMR indicated a nonsymmetrical substitution for the two methoxy groups. Following these leads, 7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride was synthesized from 2,3-dimethoxybenzaldehyde and aminoacetaldehyde diethyl acetal by Bobbitt's modification of the Pomeranz–Fritsch reaction [13]. The synthetic compound (mp 185°) was identical (UV, IR, ^{1}H NMR) to **2**; this new alkaloid has been named lemaireocereine.

Isolation and identification of weberidine (**3**). The HCl of this compound crystallized directly from fractions 101–104 (mp. 228°, 5 mg). Fluorescamine spray on TLC indicated a secondary amine function; UV $\lambda_{max}^{H_2O}$ (log ε): 200 (4.4), 214 (3.8), 280 (3.4), 288 (3.4); IR ν_{max}^{KBr} cm^{-1}: 2910, 2830, 2780, 1590, 1240, 1160, 900; ^{1}H NMR (80 MHz, D_2O): δ centered at 7.2, *d*, 1H, $J_0 = 8.6$, (C═CH), centered at 6.9, *d*, $J_m = 2.6$ (C═CH); centered at 6.8, unresolved *t*, (C═CH); 4.3, *s*, 2H, (CH_2-1); 3.8, *s*, 3H, (OMe); 3.5, *t*, 2H, (CH_2-3); 3, *t*, 2H, (CH_2-4); CI–MS $(M+H)^+$ 164; EI–MS *m/e* (%): 163 (60), 162 (33), 135 (17), 134 (100), 119 (8), 104 (8), 91 (17). The monosubstitution pattern in the ^{1}H NMR could fit only two isomers, namely 6- or 7-methoxy-1,2,3,4-tetrahydroisoquinoline. The former is the known alkaloid, longimammatine [17], which produced nonidentical spectral data. Consequently, 7-methoxy-1,2,3,4-tetrahydroisoquinoline was synthesized from 3-methoxybenzaldehyde and aminoacetaldehyde diethyl acetal using Bobbitt's modification of the Pomeranz–Fritsch reaction [13]. The synthetic compound (mp 233°) was spectrally identical (UV, IR, ^{1}H NMR) to **3**. This new alkaloid was named weberidine.

Isolation of pellotine (**8**). PLC of 0.83 g of extract PA yielded 5 major bands, but a crystalline hydrochloride (**8**) could be obtained from the eluates of only one band (mp 240°, 10 mg). The blood-red colour produced on TLC plates by tetrazotized benzidine was characteristic for the 8-hydroxytetrahydroisoquinolines usually found in peyote [28]. Compound **8** co-chromatographed with reference pellotine (1,2-dimethyl-6,7-dimethoxy-8-hydroxy-1,2,3,4-tetrahydroisoquinoline) (obtained from Dr. A. G. Paul, The University of Michigan) in 5 TLC systems and produced an IR spectrum that was superimposable with the IR spectrum of pellotine HCl.

Ethanolic extraction and fractionation. A total 2 kg of the powdered plant material was defatted as described above (6 g of lipids). The defatted marc was then extracted via percolation using 15.5 l. of EtOH. The EtOH extract was concd to a paste under rotary vacuum evaporation (145.3 g). This residue (140 g) was then separated into phenolic (P_1) (2.5 g) and nonphenolic (NP_1) (69 g) fractions by the use of anion exchange chromatography as described above (1 kg of resin, 70 × 3.5 in. glass column). The nonphenolic fraction (NP_1) was fractionated into H_2O soluble and nonH_2O soluble compounds by partitioning between $CHCl_3$ and H_2O. The crude extract (64 g) was treated with $CHCl_3$, and the insoluble residue was dissolved in H_2O. In turn the $CHCl_3$ and H_2O extracts were partitioned with H_2O and $CHCl_3$, respectively. The resulting nonphenolic H_2O fraction and nonphenolic $CHCl_3$ fraction were then concentrated to dryness (yielding respective residues of 40 and 21 g). Each was dissolved in a minimum vol. of MeOH and adsorbed onto respective quantities of 1 kg and 620 g of Celite. Respective vol. of 2 and 3 l. of N HCl were used to elute the alkaloids from the Celite. The acid solns were each extracted with Et_2O, and the Et_2O extracts discarded. The pH of each soln was adjusted to 9.5 with 58% NH_4OH, and the basified solns were re-extracted with Et_2O and $CHCl_3$ using respective volumes of 5 l. and 8 l. each. Evaporation of the solvents produced respective residues of 1.4 g (NPA_2) (more polar alkaloids) and 10.25 g (NPA_1) (less polar alkaloids).

Resolution of NPA$_1$. NPA_1 was adsorbed from EtOH to 30 g of Si gel and chromatographed on a 60 × 1.5 in. column of Si gel (600 g). The column was developed by solvents of C_6H_6 (3 l.), C_6H_6—$CHCl_3$ (19:1) (2 l.), C_6H_6—$CHCl_3$ (17:3) (1 l.), C_6H_6—$CHCl_3$ (7:3) (1 l.), C_6H_6—$CHCl_3$ (1:1) (1 l.), C_6H_6—$CHCl_3$ (2:3) (3 l.), C_6H_6—$CHCl_3$ (3:7) (6 l.), $CHCl_3$ (4.4 l.), $CHCl_3$—MeOH (99:1) (1 l.), $CHCl_3$—MeOH (97.5:2.5) (3 l.), $CHCl_3$—MeOH (19:1) (3 l.), MeOH (4 l.). A total of 260 fractions of 100 ml each were collected and monitored by TLC, and similar fractions were combined. Alkaloids were first detected in combined fractions 212–231. Fractions 239–246 contained a mixture of tehuanine and **4**, which had failed to crystallize after PLC of the mother liquors from the original tehuanine isolation (NPA fractions 78–80). From fractions 247–250 a large amount of tehuanine HCl (2 g) was crystallized directly. Additional fractions contained alkaloids previously isolated and were not processed further. TLC of NPA_2 (more polar alkaloids) detected heliamine as the major component plus lesser quantities of previously isolated alkaloids, and 1 g of heliamine HCl was crystallized directly from this extract.

Isolation and identification of weberine (**4**). Fractions 239–246, from the column fractionation of NPA_1, were separated into two bands (tehuanine and **4**) by PLC. After trials with many solvents, the hydrochloride of **4** finally crystallized (mp 164–165°, 25 mg) from EtOAc; UV $\lambda_{max}^{H_2O}$ (log ε): 205 (4), 223 (3.5) *sh*, 282 (2.9), 292 (2.8) *sh*; IR ν_{max}^{KBr} cm^{-1}: 2830, 2540, 1415, 1360, 990, 900; ^{1}H NMR (80 MHz, $CDCl_3$): δ 4.2, *bs*, 2H, (CH_2-1); 3.9, *s*, 3H, (OMe); 3.88, *s*, 3H, (OMe); 3.86, *s*, 3H, (OMe); 3.83, *s*, 3H, (OMe); centered at 3.2, *m*, 4H, (CH_2-3,4); 2.9, *s*, 3H, (N-Me); CI–MS $(M+H)^+$: 268; EI–MS *m/e* (%): 267 (90), 266 (96), 236 (100), 224 (96), 209 (93), 181 (17).

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