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BISHORDENINYL TERPENE ALKALOIDS AND OTHER CONSTITUENTS OF *ZANTHOXYLUM CULANTRILLO* AND *Z. CORIACEUM**

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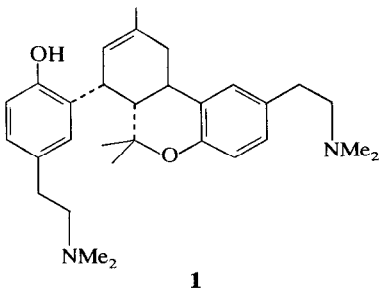
Key Word Index—*Zanthoxylum culantrillo*; *Z. coriaceum*; Rutaceae; alkaloids; bishordeninyl terpenes.

Abstract—A new alkaloid, culantraramine, has been found in *Zanthoxylum culantrillo*, and the known alkaloid, alfileramine, has been identified from *Z. coriaceum*. Both alkaloids are members of a new structural type, bishordeninyl terpenes. *Z. culantrillo* was also found to contain eudesmin, epieudesmin, hordenine, *N*-methylisocorydine, magnoflorine, candicine, skimmianine, synephrine, tembetarine and a dihydroxy-dimethoxytetrahydroprotoberberine. Isolated from *Z. coriaceum* were *N*-methylisocorydine, dihydro-chelerythrine, chelerythrine, *N*-methylcanadine and aegiline, in addition to alfileramine.

INTRODUCTION

We recently reported [1] the isolation of alfileramine (**1**) from leaves of *Zanthoxylum punctatum* Vahl. This was the first known example of what biogenetic considerations [1] lead us to call 'bishordeninyl terpene' alkaloids, after the presumed monoterpene and hordenine (**2**) precursors. The structural relationship of **1** to cannabinoids has been pointed out [1] and this relationship made the search for additional examples of considerable interest.



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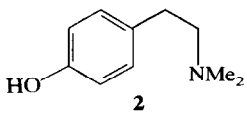

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We now wish to report that **1** also occurs in the leaves of *Z. coriaceum* A. Rich. and that a new member of this series has been identified from leaves of *Z. culantrillo* H.B.K. We have also isolated and identified a number of other constituents from these previously uninvestigated species.

Z. culantrillo is known to Honduran natives as 'Duerme Lengua' since chewed fresh bark or leaves cause a numbing sensation on the tongue. *Z. coriaceum* is common in the Bahamas where it is known as 'Harkless Club' (derived from 'Club of Hercules'). The boiled roots are used against diarrhea and as an antihemmorrahagic [2]. An extract of the leaves is used in Venezuela for earache [3]. *Z. culantrillo* also occurs in Peru. Peruvian botanical specimens in the Field Museum Of Natural History (Chicago) contain the notations: 'medicinal' (F. Woytkowski, No. 5415), "leaves put in alcohol and drunk for snake bite" (E. P. Killip, No. 2359) and "much crowded with Lepidoptera and Diptera . . . insects seem narcotized . . . very excited" (P. C. Hutchinson, No. 6539).

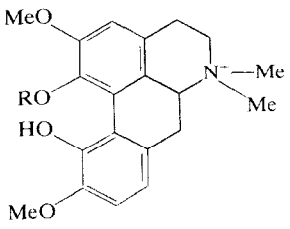
RESULTS

Zanthoxylum culantrillo. Isolated from stems and identified by NMR, UV, MS and TLC were (−)-*N*-methylisocorydine (**3**) and candicine (**4**) as their iodides, synephrine (**5**) and a trace of skimmianine (**6**). The presence of magnoflorine (**7**) and tembetarine (**8**) was indicated by TLC and UV data. A trace of one additional alkaloid was found and its MS, UV and TLC behavior indicated that it was a 2,3,10,11-dihydroxydimethoxytetrahydroprotoberberine but an exact identification could not be made.

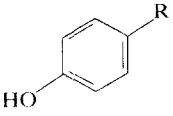
From a nonpolar (hexane extract) fraction of the leaves, we isolated and characterized (by NMR, UV, MS, mp and optical rotation) (−)-eudesmin (**9**) and (+)-epieudesmin (**10**). These lignans were recently reported for the first time from *Zanthoxylum* in 3 Asian species [4].

The alkaloid content of the leaves was low compared to that of the stems and none of the stem alkaloids were detected in the leaves. Instead, hordenine (**2**) and a new alkaloid, which we named culantraramine, was isolated. Two other alkaloids were present but could not be obtained sufficiently pure for complete identification.

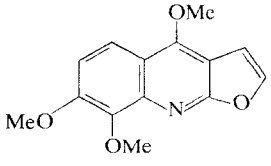
* Part 4 in the series "Constituents of *Zanthoxylum*." For Part 3, see Caolo, M. A., Anderson, O. and Stermitz, F. R. (1979) *Tetrahedron* **35**, 1493.



3 R = Me
7 R = H



4 R = $CH_2CH_2\overset{+}{N}Me_3$
5 R = $CH(OH)CH_2NHMe$



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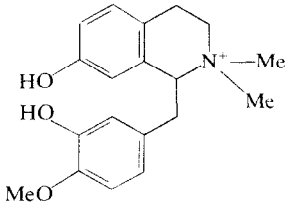

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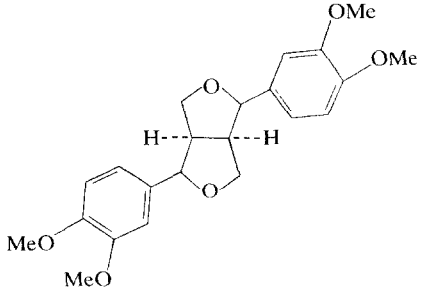
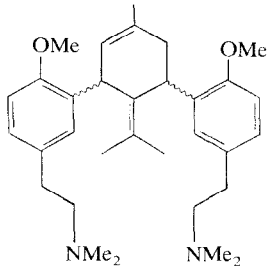


9 Aryl rings *cis*
10 Aryl rings *trans*



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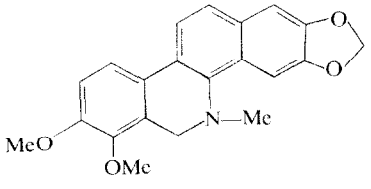
From extensive isolation and purification work, 5 mg of pure culantraramine was obtained. High resolution MS established the molecular formula as $C_{32}H_{46}N_2O_2$ (MW 490), which represented a C_2H_4 structural increment more than the formula for **1**. The presence of three C-Me, two NMe_2 groups and two trisubstituted benzene rings was evident from both the ^1H and ^{13}C NMR spectra. Culantraramine must therefore be closely related to alfileramine. The ^1H and ^{13}C NMR spectra also showed the presence of two OMe groups, which accounted for the two oxygens and the molecular formula increase (two units of CH_2) over alfileramine. The CI–MS showed a 94% relative intensity peak at *m/e* 166 which corresponds to the *O*-methylhordeninyl fragment. The ^{13}C NMR spectrum of alfileramine exhibits a resonance at 77.35 ppm which arises from the quaternary carbon next to oxygen in the benzopyran ring of **1**. This was absent in the spectrum of culantraramine. The ^{13}C NMR of culantraramine showed resonances for 16 sp^2 carbons and hence it must contain two benzene rings and two double bonds. From these data and a presumption of minimal change from **1**, we have assigned structure **11** to culantraramine. The double bond in the monoterpene portion was placed *exo* as shown because each of the C—Me groups was a singlet in the ^1H NMR, and because of the 1:2 ratio of vinyl to methine protons. A second alkaloid, named isoculantraramine, was obtained as a mixture with culantraramine. The mixed NMR spectrum indicated (by difference) that this unknown was closely related to **1** and **11** and also contained 3 C—Me and two OMe groups. A trace amount available from repeated TLC separations showed a M^+ at *m/e* 490 in the MS and a UV spectrum identical to that of **11**. As was the case with **1**, culantraramine was not completely stable in solution and, particularly on standing in $CHCl_3$ solution, showed conversion to numerous other alkaloidal materials (new TLC spots).

The stereochemical relationship of the two aryl groups in **11** is not known. Dreiding models of **11** show that the terpinolene ring is most stable in nearly an exact boat conformation, but no preference could be determined for either a *cis* or *trans* relationship of the aryl substituents. The ^1H NMR resonances for the C—Me groups on the *exo* double bond are both upfield of 'normal' positions (1.2 and 1.3 ppm vs the expected 1.6–1.8 ppm). They are clearly in the shielding area of the aryl rings in at least one conformation of each configuration.

An important property of culantraramine is that it is, unlike **1**, optically active ($[\alpha]_D$ +57°). Although **1** has 3 chiral centers, it was optically inactive as isolated from *Z. punctatum* [1] and *Z. coriaceum* (see below).

Z. coriaceum. From the roots we isolated and identified dihydrochelerythrine (**12**), (−)-*N*-methylisocorydine, (−)-*N*-methylcanadine (**13**) (as the iodide) and (±)-aegiline (**14**) by MS, NMR, UV and mp (except



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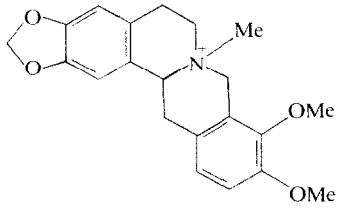

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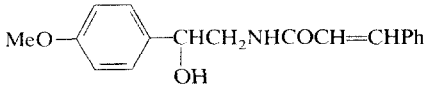

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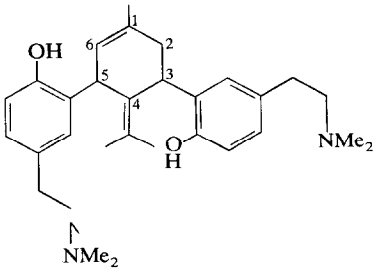
for **12**, which was an oil). Chelerythrine was found and identified by TLC and UV–visible comparison with a known sample.

The leaves of this species contain 4 major alkaloids and a number of minor ones, none of which appear to be identical to the alkaloids of the roots. Hordenine and alfileramine were isolated and identified (NMR, MS, UV, TLC). Mixture NMR spectra and TLC data indicated that the two remaining alkaloids were additional bishordeninyl terpenes. The crude alkaloid mixture was initially obtained through a procedure which involved acid and base treatment, but the total crude (mainly alfileramine and the two unknowns) showed optical rotation. When alfileramine was obtained by MeOH–Me_2CO crystallization from this mixture, it was optically inactive. An attempt was then made to isolate alfileramine without acid or base treatment. A MeOH Soxhlet extraction residue was purified by two fractionations through Sephadex columns (MeOH–$CHCl_3$) to obtain a glassy solid. The NMR of this solid in CD_3OD had C—Me and aromatic absorptions identical to alfileramine, but with N—Me and N—CH_2— resonances shifted downfield. Treatment with NH_3 converted the material to alfileramine. Unlike alfileramine, the glassy solid was soluble only in polar solvents. These data all indicated that we had isolated an acid salt of alfileramine, presumably as it occurs in the plant. Optical rotation measurements showed that the alfileramine salt was optically inactive. It seems unlikely therefore that alfileramine is being racemized during isolation procedures, but probably occurs in the plant as the racemic mixture.

DISCUSSION

The structural relationship of alfileramine and culantraramine suggests their possible genesis from a common precursor such as **15**. A close biogenetic relationship would indicate that the relative configuration of aryl substituents in **11** should be *trans* as it is in **1**. On the other hand, the usual type of mechanism for cyclization (e.g. protonation at C-4 of **15**, followed by oxygen attack at the tertiary cation center) should not yield an optically inactive alfileramine. Either an alternative scheme must be envisioned for formation of **1** or a postulation of racemization during leaf drying or Soxhlet extraction would have to be made.

A survey [5, 6] of the Rutaceae indicated that 61 *Zanthoxylum* (and *Fagara*) species had been investigated chemically through 1976. A number of additional reports have appeared since then. In none of these publications has there been a report of the occurrence of alkaloids such as **1** and **11**. Any one (or a combination) of a number of reasons may be suggested for this lack. Many investigations deal only with roots, root bark, and/or stem bark, and we have yet to find bishordeninyl terpene alkaloids in these plant parts. Probably 80% or more of the chemistry has been performed on African and Asian species. Perhaps these alkaloids are restricted to American species. If this is true, some taxonomic or phylogenetic information on the *Zanthoxylum* genus may result when a sufficient number of species have been tested for the presence of bishordeninyl terpenes. Finally, if the majority of the species contain these alkaloids in the relatively low concentrations encountered in *Z. culantrillo*, then difficulties with isolation and purification may simply have precluded their identification.



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EXPERIMENTAL

Z. culantrillo H.B.K. was collected in April 1977 by J. Stermitz and K. Pope in Dept. Morazań, Honduras (Voucher: Colorado State University Herbarium, Accession No. 2749).

Dried and ground stems (1.4 kg) were extracted in a Soxhlet for 8 hr with Skelly Solve B and then for 14 hr with EtOH. The EtOH was evapd *in vacuo* to yield 120 g of viscous residue. This was treated with 150 ml of 5% aq. HCl and extracted twice with 150 ml of $CHCl_3$. The aq. phase was made basic to pH 8 with NaOH and 1 g of KI was added. The soln was extracted with $CHCl_3$, the $CHCl_3$ dried (Na_2SO_4), filtered and evapd to yield 1.3 g of residue. The aq. layer was then extracted with BuOH and the BuOH evapd to yield 10 g of residue. The residue was dissolved in 30 ml MeOH and 60 ml Me_2CO added. This soln was passed through a short column of neutral Al_2O_3 (Activity I) and the eluent evapd to yield 4.8 g of residue. This was rechromatographed on 200 g of Al_2O_3 starting with Me_2CO–MeOH (10:1). Fraction 6 (Me_2CO–MeOH 5:1) yielded 260 mg of yellow oil from which 20 mg of (−)-*N*-methylisocorydine iodide, **3**, crystallized with Me_2CO–MeOH, mp 230–235° (lit. [7] mp 230–231°). The structure was established by UV, ^1H NMR in D_2O, TFA, CD_3OD and DMSO with added NaOD. This was done because the literature [8] ^1H NMR data showed one N—Me at 3.65 ppm (CD_3OD), whereas we found it at 3.46 ppm in the same solvent. Fraction 7 yielded 200 mg of a yellow oil which was recrystallized from MeOH to yield 40 mg of candicine iodide (**4**) mp 236–237°, UV, TLC, and ^1H NMR and ^{13}C NMR identical with a synthetic sample. Fractions 10–12 (Me_2CO–MeOH, 2:1) yielded 50 mg of a semi-solid whose UV, TLC, ^1H NMR and ^{13}C NMR spectra were identical with a commercial sample of synephrine (**5**). The 1.3 g $CHCl_3$ extract residue was dissolved in 10 ml of MeOH and 160 mg of additional (−)-*N*-methylisocorydine iodide was obtained. The mother liquor was chromatographed on Al_2O_3 as before. Fraction 1 yielded 20 mg of semi-solid identified as skimmianine, **6**, by UV, ^1H NMR and MS. Additional candicine and *N*-methylisocorydine iodides were obtained from other fractions. Traces of two other alkaloids could be seen in TLC of many of the above fractions. They were best isolated by Sephadex LH-20 column chromatography (1:1 $CHCl_3$–MeOH) directly on the EtOH extraction residue. Thus, 3 g of residue chromatographed on 50 g of Sephadex (3 ml fractions) gave alkaloids in Fractions 12–16 which were combined (800 mg). The mixture was chromatographed on Al_2O_3 (Me_2CO–MeOH, 6:1). Fractions 5 and 6 yielded *N*-methylisocorydine iodide, fractions 7–13 yielded an alkaloid whose UV spectrum and TLC

R_f in two solvents was the same as standard tembetarine (**8**), and fractions 13–24 mainly an alkaloid whose UV and TLC behavior in two solvent systems was identical with a standard sample of magnoflorine (**7**). The latter could also be obtained in larger quantities by a direct Al_2O_3 column purification on the EtOH residue.

In alkaloid work on other genera we have often used a BuOH–C_6H_6 extraction method which has provided quick, relatively pure crude alkaloid fractions. This has generally failed with *Zanthoxylum*, presumably because of the polar nature of most of the alkaloids. This procedure did, however, allow us to isolate one additional alkaloid from *Z. culantrillo*. One kg of dried and ground stems and twigs was saturated with satd Na_2CO_3 soln and allowed to stand overnight in 2.5 l. BuOH–C_6H_6 (1:1). This soln was extracted (3 × 200 ml) with 1 N H_2SO_4, back-extracted once with $CHCl_3$ and then brought to pH 11 and extracted with $CHCl_3$. The pH was adjusted to 7.5 and re-extracted with $CHCl_3$. The pH 11 extract yielded 40 mg of crude and the pH 7.5 extract 185 mg. The latter extract was chromatographed on Sephadex LH-20 and fractions 8–16 showed numerous alkaloids. MeOH was added to fraction 14, most of which dissolved, but left a trace amount of a white solid with the following characteristics. UV (EtOH): 287, 225 *sh*; with OH^- 248, 303 nm. MS (*m/e*, rel. int.): 327 (56), 326 (21), 312 (5), 178 (81), 176 (40), 151 (33), 150 (100), 135 (23). TLC: R_f 0.34 (Me_2CO–$CHCl_3$, 1:1). The UV absorption and MS clearly establish the unknown as a dihydroxydimethoxytetrahydroprotoberberine [9, 10]. By TLC it was nonidentical with any of the 4 possible and known 2,3,9,10-isomers (R_f in $CHCl_3$–Me_2CO, 1:1 = 0.52), but had the same R_f value as the 2,3,10,11-isomers (Brochmann-Hanssen, E., personal communication). The UV and UV base shift showed it not to be govadine, the 2,10-dihydroxy-3,11-dimethoxy isomer [11], but its identity with any of the other 3 possible isomers could not be established.

Leaves of *Z. culantrillo* (400 g dry wt) were extracted successively with hexane, $CHCl_3$ and MeOH. The hexane residue (20 g) was chromatographed on Si gel with hexane–EtOAc. Fractions 102–110 yielded, after recrystallization of the residue from hexane–EtOAc, 202 mg of (−)-epieudesmin (mp, optical rotation, analyt., ^{1}H NMR, MS). Fractions 118–131 yielded, after similar recrystallization of the residue, 211 mg of (+)-eudesmin (mp, optical rotation, analyt., ^{1}H NMR, MS).

The MeOH extraction soln was evapd to one third vol. and cooled. A nonalkaloidal ppt. was filtered off and the remainder evapd to a viscous liquid. This was dissolved in 5% HCl, washed with $CHCl_3$, made basic to pH 13, extracted with $CHCl_3$, adjusted to pH 8 and again extracted with $CHCl_3$. The pH 8 extract residue (526 mg) yielded mainly hordenine, **2** (TLC, ^{1}H NMR, UV comparison with known sample). The pH 13 extract residue (268 mg) was chromatographed on Al_2O_3, Activity I (Me_2CO–MeOH, 19:1 and Me_2CO–MeOH, 9:1). Fractions 3–5 were combined to yield a colorless oil (23 mg) which TLC (MeOH–H_2O–NH_4OH, 15:3:1) showed was mainly two alkaloids, R_f 0.45 and 0.5. The R_f 0.5 alkaloid, culantraramine, was obtained pure by prep-TLC or column chromatography (Si gel, MeOH–$CHCl_3$, 9:1). The R_f 0.45 alkaloid, isoculantraramine, could be obtained pure only in a trace amount by prep-TLC.

Culantraramine (**11**). MS (EI): 490.3558 (50) (Calc. for $C_{32}H_{46}N_2O_2$: 490.3557), 460 (5), 446 (8), 434 (6), 246 (14), 245 (15), 244 (13), 58 (100). MS (CI): 492 (21), 491 (68), 248 (35), 247 (20), 246 (100), 214 (17), 180 (16), 166 (94); λ_{max}^{EtOH} nm: 278, 285 *sh*; $[\alpha]_D^{25}$ −52° (EtOH; *c* 0.59); ^{1}H NMR ($CDCl_3$): δ 1.2 (*s*, 3H), 1.31 (*s*, 3H), 1.71 (*s*, 3H), 2.31 (*s*, 6H), 2.39 (*s*, 6H), 2.7–3.4 (*m*), 3.59 (*s*, 3H), 3.64 (*s*, 3H), 4.19 (*br s*?, 2H), 5.39 (*br s*?, 1H), 6.47–7.08 (*m*, 6H); ^{13}C NMR ($CDCl_3$): δ 23.23, 23.57, 29.60, 32.47, 32.71, 36.84, 39.52, 44.50, 44.64, 48.23, 54.91, 55.36, 60.85, 61.19, 109.66, 110.17, 110.53, 115.57, 123.62, 126.05, 126.71, 127.75, 129.36, 130.23, 130.79, 134.24, 144.77, 155.26, 156.59. It was not possible to obtain a useful off-resonance ^{13}C NMR spectrum. Some decomposition occurred in $CHCl_3$ soln (new TLC alkaloid spots). In some of the ^{1}H NMR spectra obtained on samples which has been re-purified or reisolated after additional chromatography, changes had occurred in the 4.09 and 5.39 peaks (broadening and/or splitting into additional broad resonances), although other absorptions remained essentially unchanged.

Isoculantraramine. MS (EI): 490.3494 (Calc. for $C_{32}H_{46}N_2O_2$: 490.3558), 267 (14), 167 (65), 151 (53), 123 (65), 58 (100); λ_{max}^{EtOH} nm: 278, 285 *sh*; ^{1}H NMR ($CDCl_3$) obtained by subtraction of culantraramine peaks from 1:1 mixture of culantraramine and isoculantraramine: δ 0.7 (*s*, 6H split into 2*s* of 3H each at 100 MHz), 1.8 (*s*, 3H), 2.35 (*s*, 6H), 2.39 (*s*, 6H), 2.4–3.0 (*m*), 3.84 (*s*, 6H), 4.2 (*br s*), 5.52 (*br s*?), 4.6–7.3 (*m*). Peak areas were not determinable for some of the above resonances due to the weakness of the signal.

Zanthocylum coriaceum A. Rich was collected by M. O. S. Russell on Long Island in the Bahamas in April 1977 (Voucher: Colorado State University Herbarium Accession Nos. 54262, 56660 and 55773).

Dried and ground roots (300 g) of *Z. coriaceum* were extracted successively in a Soxhlet with hexane, $CHCl_3$ and MeOH. The hexane was evapd to yield 4.7 g of a golden-yellow residue. Upon standing, a portion of this residue showed the presence of crystals. These were removed with Me_2CO–MeOH and recrystallized to yield (±)-aegiline, **14** (mp, ^{1}H NMR, UV, MS). The residue was chromatographed on Si gel (1plc), eluted with hexane–EtOAc (4:1) followed by 2:1, 1:1, EtOAc and EtOAc–MeOH (1:1). Fractions 58–94 were combined to yield 164 mg of nearly pure alkaloid which was purified by trituration to yield a light-yellow oil, dihydrochelerythrine, **12** (^{1}H NMR, TLC, UV, conversion to standard chelerythrine with HCl). Fractions 173–180 (EtOAc–MeOH, 1:1) yielded 40 mg of chelerythrine. Fractions 138–149 (356 mg) were mostly aegiline by NMR. TLC of the $CHCl_3$ residue (4.1 g) indicated it was similar in alkaloid content to the hexane residue. The MeOH residue (40 g) was dissolved in 5% HCl, extracted with $CHCl_3$ and made basic to pH 9. KI was added and the soln extracted with $CHCl_3$. Differential trituration and crystallization with MeOH yielded 500 mg of *N*-methylisocorydine iodide, **3** (mp, ^{1}H NMR, UV, TLC, IR comparison with a standard sample) and 400 mg of (−)-*N*-methylcanadine iodide, **13** (mp, ^{1}H and ^{13}C NMR, optical rotation, comparison with a sample synthesized from berberine by reduction and methylation).

Dried and ground leaves of *Z. coriaceum* (600 g) were extracted successively with hexane, $CHCl_3$ and MeOH. Major alkaloids were detected by TLC only in the MeOH fraction. Alkaloids were detected at R_f 0.1, 0.25, 0.4, 0.5 and 0.6. The 0.25, 0.4 and 0.5 were major. The MeOH soln was evapd to $\frac{1}{3}$ vol. and cooled. A non-alkaloidal ppt. was filtered off and the remaining MeOH evapd to leave a viscous dark liquid. One-sixth of the residue was dissolved in Me_2CO–MeOH (2:1) and chromatographed through a short column of Al_2O_3 (Activity III). Fractions 1 and 2 were mainly alkaloidal and yielded 1.6 g of crude (0.25% total

alkaloid content from leaves). A portion of the crude mixture (5 alkaloids) had $[\alpha]_D^{25} - 34°$ (*c* 0.31, EtOH). A small portion was dissolved in 1 M HCl, extracted with $CHCl_3$, made basic to pH 9 and extracted again with $CHCl_3$. The $CHCl_3$ residue was recrystallized from Me_2CO–MeOH and yielded 5 mg of (±)-afileramine, **1** (MS, ^1H NMR and ^{13}C NMR, UV, TLC comparison with known sample). Alfileramine was the R_f 0.25 alkaloid of the mixture. 10% of the original MeOH extract of the leaves was chromatographed on a 4 × 27 cm Sephadex LH-20 column ($CHCl_3$–MeOH, 1:1). Fractions 3–5 were combined (1.2 g) and triturated with Me_2CO to yield 1.2 g of a dark-brown solid. Of this, 77 mg was re-chromatographed on Sephadex. Fractions 9 and 10 were combined to yield 15 mg of a glassy-brown solid which was insoluble in Me_2CO and $CHCl_3$. The ^1H NMR spectrum in CD_3OD showed aromatics (δ 6.6-7.3), *C*-methyls (0.45, 1.65 and 1.82), CH_2NR_2 (2.9) and NMe_2 resonances (2.70, 2.78) against external TMS. The ^1H NMR spectrum of authentic alfileramine in CD_3OD showed nearly identical resonances with the exception of the CH_2NR_2 and NMe_2 peaks which were in their normal [1] upfield positions. Alfileramine is very soluble in $CHCl_3$. Treatment of the glassy solid with NH_4OH converted it to alfileramine. These data show that the solid was an acid salt of alfileramine, isolated directly from the extract without prior basification. The 15 mg sample of the glass solid had no optical rotation (*c* 0.15, EtOH). From late fractions of both Sephadex chromatographies, hordenine, **2**, could be isolated and identified (^1H NMR, TLC, comparison with authentic sample).

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