N-Methyldecahydroquinolines: An Unexpected Class of Alkaloids from Amazonian Poison Frogs (Dendrobatidae)

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The dominant alkaloids previously identified in skin extracts of Amazonian dendrobatid frogs of the genus *Ameerega* are histrionicotoxins and 2,5-disubstituted decahydroquinolines. Analysis of alkaloids in skin extracts of *Ameerega picta* from Bolivia revealed that the alkaloid **257A**, previously reported as a 2,5-disubstituted decahydroquinoline, is an *N*-methyl-2,5-disubstituted decahydroquinoline. We characterized alkaloids of another 12 of the more than 25 species recently assigned to the genus *Ameerega*, and five additional *N*-methyldecahydroquinolines were identified. In some cases, the relative configuration of the *N*-methyldecahydroquinolines was determined by comparison with the *N*-methylated products prepared from the corresponding 2,5-disubstituted decahydroquinolines of known relative configuration. A dietary source for *N*-methyldecahydroquinolines is unknown; however, myrmicine ants are the likely source for the 2,5-disubstituted decahydroquinolines. The alkaloids in skin extracts of three species of another genus of Amazonian poison frog, *Adelphobates*, were also characterized, but *N*-methyldecahydroquinolines were not detected.

Alkaloids characterized from skin extracts of poison frogs of the neotropical family Dendrobatidae now number nearly 500 and represent over 20 structural classes.[1] All alkaloids found in dendrobatid frogs are thought to have a dietary origin. However, research has shown that pumiliotoxin **251D** is hydroxylated in dendrobatid frogs of the genera *Adelphobates* and *Dendrobates* to the more toxic allopumiliotoxin **267A**.[2]

Recently, a major taxonomic revision for dendrobatids was proposed;[3] consequently reanalysis of the taxonomic and geographic distribution of alkaloids found in the skin of dendrobatid frogs is underway. The tabulation of alkaloid profiles for 36 species of dendrobatid frogs[4] in 1987 will need to be revised in view of the current taxonomy of these frogs. This work has begun with the recent report of the alkaloid profiles for 53 populations of the Central American dendrobatid poison frog *Oophaga pumilio*.[5] In the context of this reorganization, herein we present alkaloid profiles for 16 species of two Amazonian dendrobatid poison frog genera (*Ameerega* and *Adelphobates*; composed of species previously referred to the genera *Epipedobates* and *Dendrobates*, respectively[3]). Unexpectedly, six alkaloids were found to be *N*-methyl-2,5-disubstituted decahydroquinolines, and their structural characterization is described here (structures are presented in Figure 1). *N*-Methylpiperidines have been reported from myrmicine ants,[6,7] but to our knowledge *N*-methyldecahydroquinolines are unprecedented in Nature.

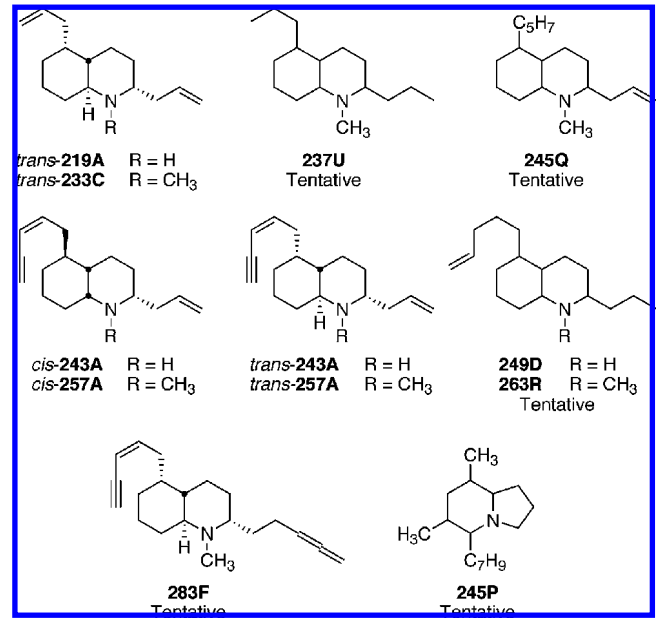

Figure 1. Structures of *N*-methyldecahydroquinolines, decahydroquinolines, and a 5,6,8-trisubstituted indolizidine. The relative configurations of *trans*-**233C**, *cis*-**257A**, and *trans*-**257A** were established by comparison to the *N*-methyl derivatives of the corresponding decahydroquinolines. The relative configurations of the other alkaloids have not been established.

Results and Discussion

Analysis of the alkaloids from three skins of *Ameerega picta* from Bolivia revealed that all of the major/minor alkaloids were histrionicotoxins and decahydroquinolines, as expected from prior analyses of other Amazonian species of *Ameerega* from Colombia, Ecuador, Peru, and Suriname.[4] The tabulation of the major, minor, and trace alkaloids identified in *A. picta* is provided in Table 1. Mass spectrometric analyses provided identification, empirical formulas, and exchange data. Surprisingly, one decahydroquinoline, **257A**, showed no exchange of an N-*H* hydrogen, suggesting that this alkaloid is *N*-substituted. The lack of a H-exchange is in contrast to data collected from a decade ago that suggested one exchangeable hydrogen from this alkaloid in other extracts (data not shown). On the basis of MS fragmentation, decahydroquinoline **257A** was indeed now characterized as having an *N*-methyl substituent. The structure was confirmed by GC-MS comparison with the *N*-methyl derivatives prepared from *cis*- and *trans*-decahydroquinolines **243A** of well-defined structures,[8,9] where **257A** proved to be identical with the *N*-methyl derivative of *trans*-**243A**. The *N*-methylations of *trans*-**243A** and other known decahydroquinolines were performed "on-column" with formaldehyde/formic acid as described in the Experimental Section. The GC-MS and GC-FTIR spectra

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Table 1. Alkaloids in Skin Extract of the Dendrobatid Frog *Ameerega picta*[a]

Ameerega species location (source)	collection date number skins abundance		HTX; PTX; aPTX; DHQ; *N*-MeDHQ; 5,8-I; 5,6,8-I; Tri; Unclass
A. picta	Dec 1987	major	HTX **259A**, **283A**, **285C**; DHQ *trans*-**243A**
Río Beni, Bolivia	3 skins		
(D. Mebs)	++		
		minor	HTX **239H**, **261A**, **285A**; DHQ **269AB**; *N*-MeDHQ *trans*-**257A**
		trace	HTX **235A**, **265E**, **287D**, **291A**; PTX **251D**, **323A**; aPTX **267A**, **341A**; DHQ *cis*-**223F**, *trans*-**223F**, 5-epi-*trans*-**223F**, *cis*-**243A**, 5-epi-*trans*-**243A**, **267L**, **269B**; 5,8-I **219J**, **231C**, **259B**; 5,6,8-I **223X**, **245P**; Tri **235M**; Unclass **191C** (an *N*,*N*-dimethyltoluamide)

[a] Abbreviations: HTX, histrionicotoxins; PTX, pumiliotoxins; aPTX, allopumiliotoxins; DHQ, decahydroquinolines; *N*-MeDHQ, *N*-methyldecahydroquinolines; 5,8-I, 5,8-disubstituted indolizidines; 5,6,8-I, 5,6,8-trisubstituted indolizidines; Tri, tricyclics; Unclass, unclassified as to structure. Major alkaloids (>50 μg/100 mg skin); minor alkaloids (>5 μg/100 mg skin); trace alkaloids (<5 μg/100 mg skin). For profiles of other *Ameerega* species, see Table S1, Supporting Information, and for *Adelphobates* species, see Table S2, Supporting Information. Abundance is defined as +++ having alkaloids >200 μg/100 mg skin, ++ having alkaloids >50 μg/100 mg skin, and + having alkaloids less than 50 μg/100 mg skin.

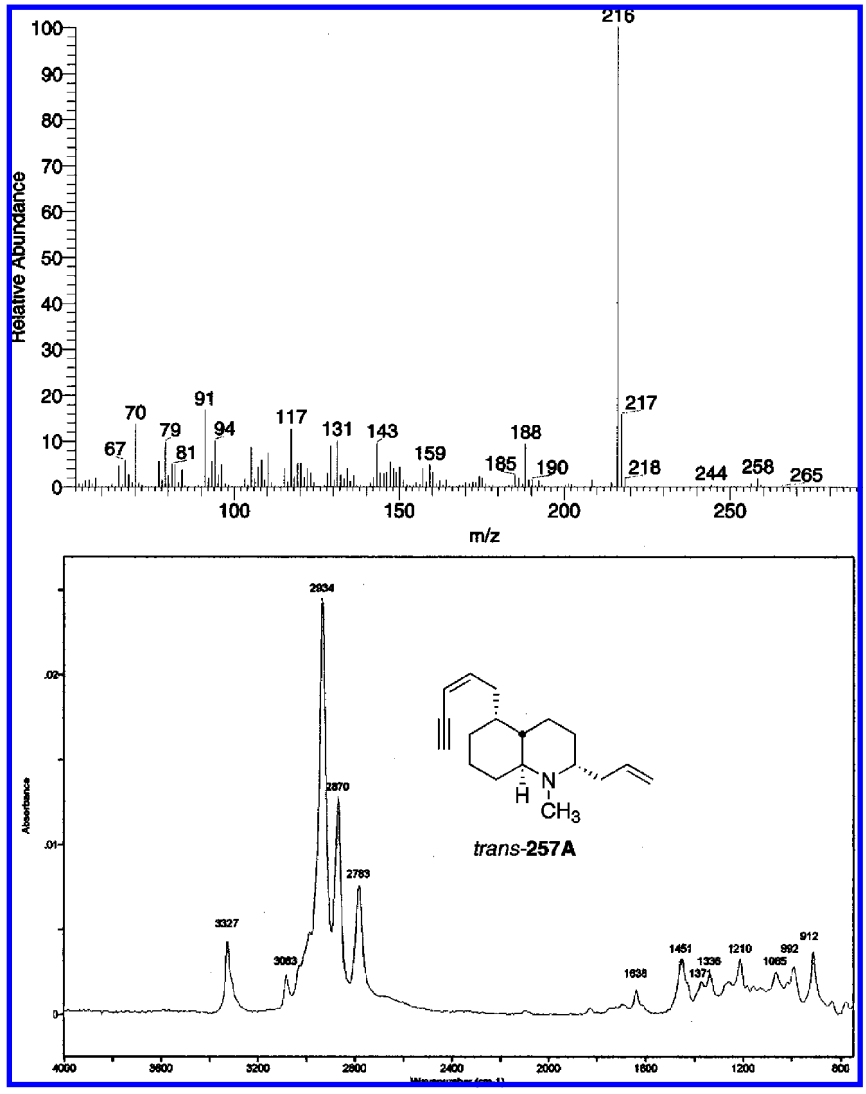

Figure 2. Mass spectrum and GC-FTIR spectrum of *N*-methyldecahydroquinoline *trans*-**257A**.

of *trans*-**257A** are shown in Figure 2. The strong, sharp Bohlmann band at 2783 cm^{-1} is expected of an *N*-methyldecahydroquinoline and is in marked contrast to the weak Bohlmann bands of decahydroquinolines, such as *cis*- and *trans*-**243A**.[9−11]

Profiles of major, minor, and trace alkaloids in other species/populations of poison frogs of the genus *Ameerega* are provided in the Supporting Information (Table S1). *N*-Methyldecahydroquinoline *trans*-**257A** was found in several species. In two populations of *Ameerega trivittata, cis*-**257A** also was detected and identified by comparison to the *N*-methyl derivative of decahydroquinoline *cis*-**243A**. Three other alkaloids, namely, **233C**, **237U**, and **263R**, previously reported as decahydroquino-

lines,[1] proved to be *N*-methyldecahydroquinolines. All were found in *Ameerega* species/populations (see Table S1, Supporting Information). One of the *N*-methyldecahydroquinolines proved to be *trans*-**233C**, shown to be identical to the *N*-methyl derivative of *trans*-**219A**, and another is *N*-methyldecahydroquinoline **237U**, established as being identical to an *N*-methyl derivative of decahydroquinoline **223F**. *N*-Methyldecahydroquinoline **263R** was present as a trace alkaloid in an undescribed *Ameerega* species (number 19 of Table S1, Supporting Information), while the corresponding decahydroquinoline **249D** occurred as a trace alkaloid in this species and as a minor alkaloid in one population of *A. trivittata.* A previously unreported alkaloid, now coded as **283F**, was detected in *Ameerega cainarachi* (see Table S1, Supporting Information) and is an *N*-methyldecahydroquinoline, identical to an *N*-methyl derivative of decahydroquinoline, *trans*-**269AB**. In addition, a previously undescribed decahydroquinoline, now coded as **245Q**, was detected as a trace alkaloid in a population of *A. trivittata* from Suriname (see Table S1, Supporting Information). Structures, some of which are tentative with respect to relative configurations, of the aforementioned decahydroquinolines are shown in Figure 1.

The possibility was considered that *N*-methyldecahydroquinolines detected in this study were artifacts arising from adventitious formaldehyde present in methanol used to prepare extracts or for injection into the GC-MS. We have observed incidentally such a reaction with pyrrolidines and methanol evident during the GC injection, but in the work reported here we are confident that the methylated decahydroquinolines are present naturally and did not arise either on standing in methanol or during the GC injection because of the following findings. We find in the 24 *Ameerega* extracts (Tables 1 and S1, Supporting Information) many cases in which (1) one, several, or many *cis* and *trans* decahydroquinolines are present and none are methylated (e.g., extracts 2, 3, 4, 5, 10, 15, and 16); (2) one, several, or many *cis* and *trans* decahydroquinolines are present and only one is methylated (e.g., extracts 1, 6, 7, 11, 12, 14, 20, 21, 22, and 24); and (3) more than one *N*-methyldecahydroquinoline is present but many other decahydroquinolines are not methylated (e.g., extracts 13, 19, and 23). The three *Adelphobates* extracts (Table S2, Supporting Information) have one or two decahydroquinolines, but no *N*-methyldecahydroquinolines. These observations constitute strong presumptive evidence that the *N*-methyldecahydroquinoline class described in this study is not an artifact.

Other alkaloids also found in these extracts are reported here for the first time. A previously undescribed 5,6,8-trisubstituted indolizidine, now coded as **245P**, was detected as a trace alkaloid in the Bolivian frog *A. picta* (Table 1). Its structure is shown in Figure 1. Four other previously unreported alkaloids were detected as trace alkaloids in frogs of the genus *Ameerega*, and the code designations and spectroscopic properties are reported in the Experimental Section. One of these, coded as **239AA**, is proposed to be an *N*-methyl-2-butyl-5-heptylpyrrolidine. Because this alkaloid is postulated as an *N*-methylpyrrolidine, artifactual methylation of a putative 2-butyl-5-heptylpyrrolidine of molecular weight 225 could result in **239AA**, as mentioned in the paragraph above. A structure for the second of those previously unreported alkaloids, an izidine, **239CC**, is unknown. The third of these alkaloids, unclassified **235CC**, appears to be an aromatic amide and may be an impurity. Alkaloid **235CC** occurred in the same extract (*Ameerega* sp., number 19 of Table S1, Supporting Information) as Unclass **191C**, which has proved to be an *N*,*N*-diethyltoluamide (a commercial mosquito repellent, likely introduced as a contaminant by a collector). A structure is not proposed also for the fourth previously unreported alkaloid, unclassified **225N**, detected as a trace alkaloid in the 1993 collection of *A. cainarachi* (Table S1, Supporting Information).

At present, it would appear that the *N*-methyldecahydroquinolines occur only in Amazonian species of the genus *Ameerega*, although we remain open to the possibility of their occurrence in other dendrobatid genera. Nearly all alkaloids in skins of dendrobatid frogs are thought to be sequestered from dietary sources.[1] Certain decahydroquinolines have been found in myrmicine ants,[12−15] and these ants are proposed to be the putative source of decahydroquinolines and of "izidines" with a carbon skeleton consisting of a linear carbon chain.[13] In addition, histrionicotoxins are thought to originate from myrmicine ants,[1] but as yet have not been detected in ant extracts. Histrionicotoxins were present in dendrobatid frogs (*Dendrobates auratus*) raised in terraria in Panama on a diet of leaf-litter arthropods,[16] suggesting the presence of histrionicotoxins in locally available arthropods.

Histrionicotoxins and decahydroquinolines are the predominant alkaloids present in all of the Amazonian *Ameerega* species examined thus far, with one exception (*Ameerega silverstonei*; see below). The presence of major, minor, and trace alkaloids in extracts of the *Ameerega* species is summarized in Table S3 of the Supporting Information. However, alkaloids that occurred only in trace amounts in the *Ameerega* species are not included in the summary of Table S3, Supporting Information. It is evident that most of the major and minor alkaloids are histrionicotoxins and decahydroquinolines, suggesting an availability of arthropod prey items containing such alkaloids (presumably myrmicine ants) in the Amazon basin and that such arthropods are perhaps targeted by the frogs. The one exception among the Amazonian *Ameerega* species was *A. silverstonei* of Peru, in which no histrionicotoxins nor decahydroquinolines were detected (see Table S1, Supporting Information). *A. silverstonei* occurs at higher elevations (>1000 m) of the Amazonian drainage than do the other *Ameerega* species,[17] suggesting a difference in arthropod availability with elevation. A similar situation occurs in the dendrobatid genus *Oophaga*, from Central America, and the Chocó region of western Colombia and Ecuador. The lowland species *Oophaga histrionica* and *Oophaga sylvatica* both contained histrionicotoxins in their skin, whereas their close relative, *Oophaga lehmanni*, from higher elevations in the Andes, did not.[4,18] Subsequent feeding experiments demonstrated that *O. lehmanni* readily accumulates histrionicotoxin when provided in the diet, indicating that the absence of histrionicotoxins in wild-caught specimens is the result of the absence of a dietary source and not the inability to sequester this class of alkaloids.[19]

There is only one *Ameerega* species examined in this study that does not occur in the Amazon drainage. That species is *Ameerega erythromos*, which occurs in the Pacific lowlands of Ecuador. *A. erythromos* had relatively low levels of alkaloids, and no histrionicotoxins or decahydroquinolines were detected (see Table S1, Supporting Information, and summary in Table S3, Supporting Information). However, a sympatric dendrobatid frog, *O. sylvatica* (formerly *Dendrobates histrionicus*[3]), did contain several histrionicotoxins,[4] suggesting that the absence of these alkaloids in *A. erythromos* is not based on differences in arthropod availability. *A. erythromos* and its sister species *Ameerega andina* are the only two South American members of the genus *Ameerega* that occur west of the Andes.[3] Given the large geographic difference in location between these two species and all other members of the genus *Ameerega*, it is interesting to note that *A. erythromos* lacks the histrionicotoxins and decahydroquinolines that are characteristic of all other members of the genus *Ameerega* east of the Andes (the only other exception being *A. silverstonei*, see above) and further suggests that the evolutionary relationships of these species require further analysis. *A. andina* has not yet been analyzed for alkaloids.

From the three Amazonian species of the genus *Adelphobates* in this study, *A. castaneoticus, A. galactonotus,* and *A. quinquevittatus,* the latter two had a more diverse array of skin alkaloids (see Table S2, Supporting Information) than did the Amazonian *Ameerega* species. The straight-chain-derived histrionicotoxins and decahydroquinolines were present as major or minor alkaloids, but these species also contained branched-chain-derived pumiliotoxins, allopumiliotoxins, and 5,8-disubstituted and 5,6,8-trisubstituted indolizidines. The dietary source of branched carbon-chain alkaloids appears to be mites, not ants.[20−23] However, pumiliotoxins also have been reported in extracts of formicine ants.[24] The alkaloid profile of the third species, *Adelphobates castaneoticus*, was, like the Amazonian *Ameerega* species, dominated by putative ant alkaloids, in this case by six histrionicotoxins. However, *N*-methyldecahydroquinolines were not detected, even in trace amounts, in any of the *Adelphobates* species.

The predominance of putative ant alkaloids, such as the histrionicotoxins and decahydroquinolines, in all *Ameerega* species except *A. silverstonei* and *A. erythromos* may reflect a difference in prey utilization; perhaps most *Ameerega* species consume mainly ants, while *A. silverstonei* and *A. erythromos* consume mainly mites. However, in *A. silverstonei*, this could also reflect differences in the relative availability of certain alkaloid-containing arthropods in lower as compared to higher elevations of the Amazon drainage. The Amazonian *Adelphobates* species, which currently has a more diverse array of skin alkaloids than the *Ameerega* species, may consume ants and mites. Another possibility for these observed differences in alkaloid profiles is that the uptake-sequestering systems differ in selectivity among different lineages of frogs. A study of five species of dendrobatid frogs from four genera, namely, *Dendrobates auratus*, *Epipedobates anthonyi* (formerly *Epipedobates tricolor*), *Phyllobates bicolor*, *Adelphobates castaneoticus*, and *Adelphobates galactonotus*, suggested differences in the relative sequestration of a decahydroquinoline compared to sequestration of a pumiliotoxin.[2] In addition, *D. auratus* and both *Adelphobates* species converted the ingested pumiliotoxin **251D** to the more toxic allopumiliotoxin **267A** by a stereospecific hydroxylation, while frogs in the genera *Epipedobates* and *Phyllobates* species did not.[2] Finally, it is not known whether *Ameerega* species obtain *N*-methyldecahydroquinolines from a dietary arthropod source, perhaps found only in the Amazon, or are able to metabolize decahydroquinolines by *N*-methylation, or perhaps lack a demethylation process that could be common in other dendrobatids. Additional research is warranted on the origin, structures, and bioactivity of the extensive array of alkaloids found sequestered in the skin of dendrobatid frogs.

Experimental Section

General Experimental Procedures. Mass spectrometry data were obtained with a Thermo Electron-Fisher Corporation Polaris Q instrument using a Focus gas chromatograph with a Restek RTX-5MS capillary column (30 m, 0.25 mm i.d.), programmed from 100 to 280 °C at 10 deg/min. The GC-EIMS and GC-FTIR spectra were obtained with a Hewlett-Packard model 5890 gas chromatograph with an HP-5 capillary column (30 m, 0.32 mm i.d.), programmed as above, and interfaced with a Hewlett-Packard model 5971 mass selective detector and a model 5965B infrared detector (narrow band 4000−750 cm^{-1}). A Hewlett-Packard ChemStation was used to generate EIMS and FTIR spectra.

The *N*-methylation of decahydroquinolines was performed "on-line" on the Polaris GC-MS instrument or on the Hewlett-Packard GC-MS-FTIR instrument by injecting 1 μL of a methanolic alkaloid extract or a methanol solution of a known decahydroquinoline together with 0.5 μL of aqueous formaldehyde and 0.5 μL of formic acid. The methylation reaction occurs in the injector with the products being observed after GC chromatography at the MS detector or the FTIR detector.

Properties of Previously Unreported Alkaloids. (The tabulation of alkaloids and format of properties follow that of the Appendix in the Supporting Information of ref 1.).

225N. Unclass. '$C_{14}H_{27}NO$'. t_R 9.61. MS: *m*/*z* 275 (<1), 154 ($C_9H_{16}NO$, 100), 112 ('$C_6H_{16}NO$', 18). FTIR ν_{max} moderate, broad Bohlmann bands 2806, 2706 cm^{-1}; OH 3660 cm^{-1}; enamine or imine 1637 cm^{-1}; strong band 1093 cm^{-1}. 1D.

235CC. Unclass. '$C_{14}H_{21}NO_2$'. t_R 12.62. MS: *m*/*z* 235 (8), 86 (100), 58 (12). FTIR ν_{max} amide 1719 cm^{-1}; aromatic 1481 cm^{-1}.

239AA. *N*-Me-Pyrrolidine. '$C_{16}H_{33}N$'. t_R 10.09. MS: *m*/*z* 239 (<1), 238 (2), 182 (85), 180 (21), 140 (100), 84 (26). 0D.

239CC. Izidine. '$C_{15}H_{29}NO$'. t_R 12.55. MS: *m*/*z* 239 (<1), 238 (2), 224 (1), 210 (2), 140 (100). 1D.

245P. 5,6,8-I. $C_{17}H_{27}N$. t_R 11.05. MS: *m*/*z* 245 (10), 152 (100), 110 (7), 70 (4). 0D. Tentative structure in Figure 1.

245Q. DHQ. '$C_{17}H_{27}N$'. t_R 10.11. MS: *m*/*z* 245 (<1), 244 (1), 204 (100). 1D. Tentative structure in Figure 1.

283F. *N*-Methyl-DHQ. '$C_{20}H_{29}N$'. t_R 15.48. MS: *m*/*z* 283 (3), 282 (7), 268 (9), 218 (36), 216 (100). 0D. Tentative structure in Figure 1.

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Supporting Information Available: Alkaloid profiles for the additional 12 *Ameerega* species and the three *Adelphobates* species of dendrobatid frogs are available in Tables S1 and S2, respectively. A summary of the presence of major, minor, and some of the trace alkaloids for all *Ameerega* species is available in Table S3. This information is available free of charge via the Internet at http://pubs.acs.org.

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