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DIETARY SOURCE FOR SKIN ALKALOIDS OF POISON FROGS (DENDROBATIDAE)?

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Abstract—A wide range of alkaloids, many of which are unknown elsewhere in nature, occur in skin of frogs. Major classes of such alkaloids in dendrobatid frogs are the batrachotoxins, pumiliotoxins, histrionicotoxins, gephyrotoxins, and decahydroquinolines. Such alkaloids are absent in skin of frogs (*Dendrobates auratus*) raised in Panama on wingless fruit flies in indoor terraria. Raised on leaf-litter arthropods that were collected in a mainland site, such terraria-raised frogs contain tricyclic alkaloids including the beetle alkaloid precoccinelline, 1,4-disubstituted quinolizidines, pyrrolizidine oximes, the millipede alkaloid nitropolyzonamine, a decahydroquinoline, a gephyrotoxin, and histrionicotoxins. The profiles of these alkaloids in the captive-raised frogs are closer to the mainland population of *Dendrobates auratus* at the leaf-litter site than to the parent population of *Dendrobates auratus* from a nearby island site. Extracts of a seven-month sampling of leaf-litter insects contained precoccinelline, pyrrolizidine oxime **236** (major), and nitropolyzonamine (**238**). The results indicate a dietary origin for at least some "dendrobatid alkaloids," in particular the pyrrolizidine oximes, the tricyclic coccinellines, and perhaps the histrionicotoxins and gephyrotoxins.

Key Words—Alkaloids, indolizidines, pyrrolizidines, histrionicotoxins, coccinellines, dendrobatid frogs, insects, millipedes.

INTRODUCTION

A diverse range of alkaloids occur in the skin of poison frogs of the neotropical family Dendrobatidae, where they presumably serve in chemical defense against

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predators (Daly and Myers, 1967; Daly et al., 1987). Although presumed to be elaborated by poison frogs for storage in so-called granular skin glands (Neuwirth et al., 1979), the absence of such skin alkaloids in captive-raised frogs (Daly et al., 1980, 1992) suggests a possible dietary origin. 3,5-Disubstituted pyrrolizidines, 3,5-disubstituted indolizidines, 2,5-disubstituted pyrrolidines, and 2,6-disubstituted piperidines occur in ants (Jones and Blum, 1983), and tricyclic coccinellines occur in beetles (Ayer et al., 1976). Although the pyrrolizidine oximes have been found only in frog skin (Tokuyama et al., 1992), a related alkaloid, nitropolyzonamine, occurs in a millipede (Meinwald et al., 1975). However, many of the so-called "dendrobatid alkaloids" have never been detected in insects or other leaf-litter prey: These include the batrachotoxins, histrionicotoxins, gephyrotoxins, 5,8-disubstituted indolizidines, 2,5-disubstituted decahydroquinolines, 1,4-disubstituted quinolizidines, epibatidine, pyrrolizidine oximes, and the pumiliotoxin–allopumiliotoxin–homopumiliotoxin class. Thus, it is possible that dietary precursors rather than the alkaloids themselves might be supplied from leaf-litter prey.

Dendrobatid frogs (*Dendrobates auratus*) raised in Hawaii in outdoor terraria on a diet consisting mainly of termites and wild fruit flies had nearly the same profile of alkaloids as wild-caught Hawaiian frogs (Daly et al., 1992). However, levels were much lower, and an indolizidine **195B** that was absent in wild-caught frogs was present in the captive-raised frogs and the beetle alkaloid precoccinelline that was present in wild-caught frogs was absent in the captive-raised frogs. Recently, an uptake system, whereby dietary alkaloids are accumulated into skin of dendrobatid poison frogs of the genera *Dendrobates*, *Phyllobates*, and *Epipedobates* has been discovered (Daly et al., 1994). The system is absent in frogs of the non-alkaloid-containing dendrobatid genus *Colostethus*. The uptake system accumulated batrachotoxins, histrionicotoxins, pyrrolizidines, indolizidines, quinolizidines, decahydroquinolines, and pumiliotoxins. Pyrrolidines and piperidines did not appear to be accumulated. The presence of such a system strongly suggests that dietary alkaloids from insects or other small prey would accumulate in skin and could account for some or even all of alkaloids detected in skin of poison frogs. In order to explore this possibility, dendrobatid frogs (*Dendrobates auratus*) were raised in Panama in inside terraria either on wingless fruit flies or on leaf-litter arthropods collected from a site where a population of this dendrobatid frog occurs.

METHODS AND MATERIALS

Tadpoles of the poison frog *Dendrobates auratus* were collected on Isla Taboga in June 1992. Ten juvenile frogs were obtained. Eight were raised for seven months on leaf-litter arthropods in inside terraria and two were raised as controls on wingless fruit flies.

Frogs were housed in small glass terraria. Each of the terraria had a large aluminum Berless funnel mounted above it. Once or twice a week, about 18 liters of fresh moist leaf litter was placed in each of the funnels. As the 75-W light bulbs suspended above the funnels warmed and dried the leaf litter, the invertebrate inhabitants retreated down toward the cooler and moister litter near the bottom of the funnel, finally falling into the terrarium below. A total of about 29 leaf-litter collections were provided to each frog. During this period a total of 21 leaf-litter collections of arthropods were placed in alcohol for later analysis. The leaf litter was collected on the northern slope of Ancon Hill in Panama at a forest site in which a population of *Dendrobates auratus* occurred. Although collections of leaf-litter arthropods served as the primary food for the set of eight frogs, the diet was occasionally augmented with termites, ants, or fruit flies. Even with this supplemental nutrition, only three of the eight frogs fed on leaf-litter arthropods survived for the seven-month period. The set of two frogs served as controls and were fed only a strain of wingless fruit flies. The frogs had not attained full adult size in seven months. The snout–vent (s-v) lengths of the leaf-litter insect-fed frogs were 15 mm, 16 mm, and 19 mm, while the s-v lengths of the control frogs were 17 and 19 mm.

Two adult frogs from the leaf-litter site on Ancon Hill were collected for analysis of skin alkaloids. Their s-v lengths were 30 mm and 32 mm. Three adult frogs of the parent stock from Isla Taboga were collected for analysis of skin alkaloids. Their s-v lengths were 31 mm, 31 mm, and 27 mm.

Skins were extracted and alkaloid fractions were prepared as described (Daly et al., 1992). Analysis was by gas chromatography in conjunction with mass spectrometry and infrared spectroscopy, in order to identify the alkaloids present (see Daly et al., 1992, 1993, 1994). The gas chromatograms depicted in the figures were obtained with a 6-ft (2 mm ID) 1.5% OV-1-packed column with a flame ionization detector. A sample of 2 μl of a methanolic alkaloid fraction equivalent to 2 mg wet weight skin was injected at a column temperature of 150°C. After the solvent maximum had passed (0.3 min), the column was programmed to 280°C at 10°C/min.

RESULTS AND DISCUSSION

A number of alkaloids were found to be present in skin extracts from frogs raised on leaf-litter arthropods. Structures of these alkaloids or of representatives of a class of alkaloids are shown in Figure 1.

The two control frogs raised on wingless fruit flies exhibited virtually no alkaloids in skin extracts (Figure 2A). There was, however, a trace amount of the pyrrolizidine oxime **236**. Frogs of this species raised at the National Aquarium in Baltimore and in Minnesota under similar conditions had no skin alkaloids (Daly et al., 1992, 1994).

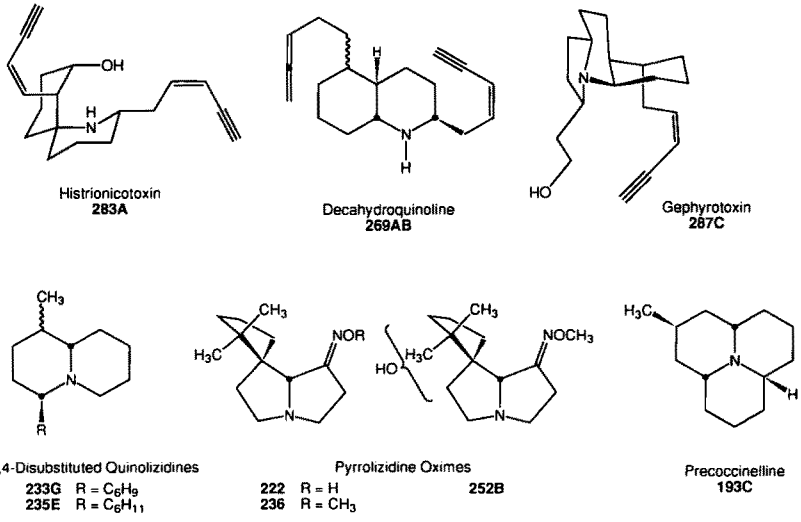

FIG. 1. Structure of alkaloids present in skin of frogs (*Dendrobates auratus*) raised on a diet of leaf-litter arthropods. Structures of decahydroquinoline **269AB**, pyrrolizidine oxime **252B**, and **233G** and **235E** have not yet been rigorously established by isolation and nuclear magnetic resonance spectral analysis. Structures of other apparent tricyclic alkaloids (**205D**, **219H**, **219I**, and **231H**) present in these frogs are unknown.

The three frogs raised on leaf-litter arthropods, by contrast, had substantial amounts of several alkaloids. The gas chromatographic profile for one of these is shown in Figure 2B. The two other frogs exhibited almost identical profiles. The major alkaloid for each frog was the pyrrolizidine oxime **236**. Minor alkaloids were the tricyclic precoccinelline (**193C**), a decahydroquinoline (**269AB**), and several histrionicotoxins (**283A**, **285A**, **285C**, **287A**). The amounts of the decahydroquinoline and histrionicotoxins were less in the other two frogs (data not shown). Other alkaloids consisted of additional tricyclic alkaloids of unknown structure (**205D**, **219H**, **219I**, **231H**), 1,4-disubstituted quinolizidines (**233G**, **235E**), a gephyrotoxin (**287C**), and pyrrolizidine oximes **222** and **252B**. A trace amount of the known millipede alkaloid nitropolyzonamine (**238**) was detected. The level of the major alkaloid (pyrrolizidine oxime **236**) in the captive-raised frogs was actually much greater than the levels in one of the wild-caught frogs from the leaf-litter site on Ancon Hill (Figure 3A and B) and in all three of the wild-caught frogs from the site of the parental stock on Isla Taboga (Figure 3C–E). Eighteen of the 21 alkaloids (86%) in the captive-raised frogs were shared with one or both of the wild-caught frogs of the leaf-litter site. Only ten alkaloids (48%) were shared with any of the three wild-caught frogs of the parental stock. The three pyrrolizidine oximes (**222**, **236**, **252B**) are shared in

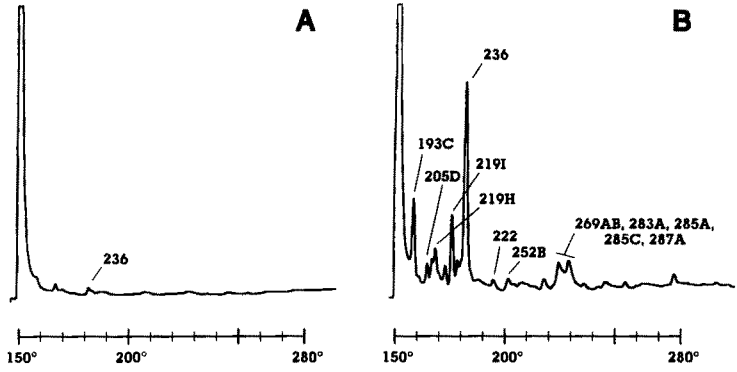

FIG. 2. Gas chromatographic profiles for alkaloids accumulated into skins of captive-raised poison frogs (*Dendrobates auratus*). (A) Alkaloid fraction from two *Dendrobates auratus* raised in terraria on wingless fruit flies. Snout-vent (s-v) length: 17 and 19 mm. (B) Alkaloid fraction from a *Dendobrates auratus* raised in a terrarium on leaf-litter arthropods, s-v: 19 mm. Similar profiles, but with smaller amounts of histrionicotoxins were obtained from two other frogs raised on leaf-litter arthropods. Gas chromatograms were obtained as described in Methods and Materials. The column is programmed from 150 to 280°C at 10°C/min. Emergent temperatures can differ somewhat with different columns and variations in flow rates. Code numbers for alkaloids are based on nominal molecular weight of each alkaloid and, if necessary, an identifying letter. For further details on gas chromatographic mass and infrared spectral identification of alkaloids, see Daly et al. (1987, 1992, 1993).

nearly all cases, as is the beetle alkaloid precoccinelline (**193C**). A comparison of alkaloids in all extracts is presented in Table 1 along with the results of previous analyses of skins obtained from frogs of the Isla Taboga site from 1968 to 1975 (see Daly et al., 1987). The variability seen in the two individual wild-caught frogs from Ancon Hill and the three individual wild-caught frogs from Isla Taboga is interesting. Earlier studies on individual variation in *Dendrobates auratus* from Isla Taboga and of *Dendrobates pumilio* from Isla Bastimentos, Bocas, Panama suggested that such individual variation was minimal. The present comparisons suggest that although the spectrum of alkaloids is similar for individuals from each population, the relative amounts (and hence the gas chromatographic profile) can vary considerably. Each population has a relatively distinctive spectrum of alkaloids, as has been the case for many prior studies on dendrobatid frogs (see Daly et al., 1987). If the two frogs from Ancon Hill are compared, only 23 of 47 alkaloids (49%) are shared, but if the trace alkaloids are excluded then 14 of 16 alkaloids (88%) are shared. Similarly, if the three frogs from Isla Taboga are compared, only 28 of 53 alkaloids (52%) are shared by all three frogs, but if the trace alkaloids are excluded then 13 of 15 alkaloids

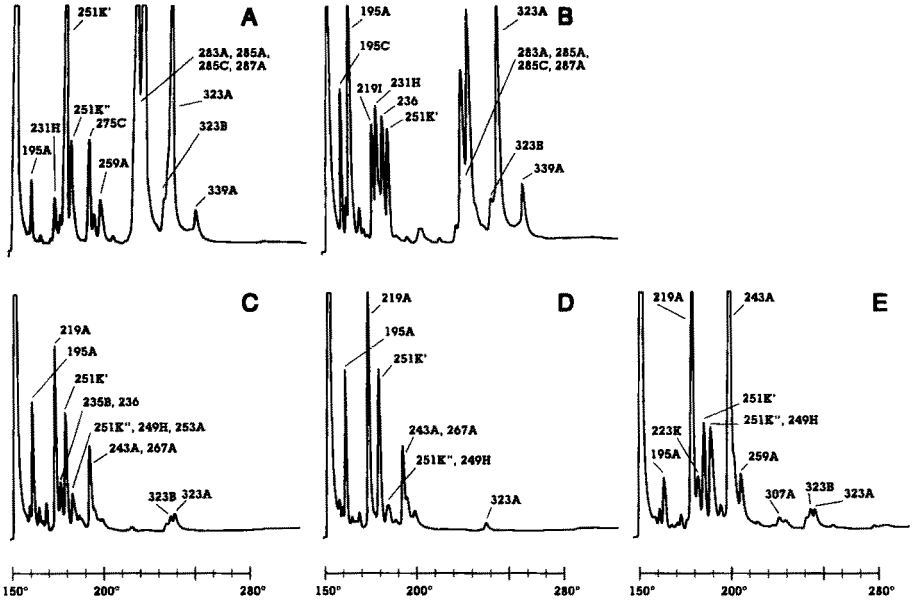

FIG. 3. Gas chromatographic profiles for alkaloids in skins of wild-caught poison frogs (*Dendrobates auratus*). (A) Alkaloid fraction from wild-caught *Dendrobates auratus*, Ancon Hill, Panama, s-v: 32 mm. (B) Alkaloid fraction from wild-caught *Dendrobates auratus*, Ancon Hill, Panama, s-v: 30 mm. (C) Alkaloid fraction from wild-caught *Dendrobates auratus*, Isla Taboga, Panama, s-v: 31 mm. (D) Alkaloid fraction from wild-caught *Dendrobates auratus*, Isla Taboga, Panama, s-v: 27 mm. (E) Alkaloid fraction from wild-caught *Dendrobates auratus*, Isla Taboga, Panama, s-v: 31 mm. Gas chromatographic parameters as in legend to Figure 1.

(87%) are shared. When the mainland (Ancon Hill) and the island frogs are compared, 33 of 66 alkaloids (50%) are found in both sets, but often not in all frogs of each set. When trace alkaloids are excluded, 17 of 23 alkaloids (74%) are found in both sets.

The present results strongly suggest a contribution from alkaloids of leaf-litter prey to the profile of alkaloids in dendrobatid frogs. It should be noted that all of the decahydroquinolines, with one exception, and all of the pumiliotoxins and allopumiliotoxins that were present in wild-caught frogs from both the mainland leaf-litter site and the parental island site were completely absent in the captive-raised frogs. Isomers of the pyrrolizidine **251K**, one isomer of which occurs in certain ants (Jones et al., 1991), were present as major or minor alkaloids in all of the wild-caught frogs, but were absent in the captive-raised frogs. The absence of certain alkaloids suggests either that such alkaloids do

TABLE 1. ALKALOIDS IN SKIN EXTRACTS OF *Dendrobates auratus*

Alkaloids[a]	Captive-raised on leaf-litter insects	Wild-caught					Isla Taboga pooled skins
		Ancon Hill		Isla Taboga			
	1B	2A	2B	2C	2D	2E	1968–1975
Histrionicotoxins							
235A		+		+	+	+	++
259A		++		+	+	++	++
261A		+				+	
283A	++	++	++			+	
285A	++	+++	++	+	+	+	
285C	+++	+++	+++			+	
287A	++	+++	+++			+	
287B	+		+			+	
Pumiliotoxins							
237A				+			
251D				+	+	+	++
277B		+	+	+		+	
297B							+
307A		+	++	+	+	++	++
307B		+	+	+	+	+	++
323A		+++	+++	++	++	++	+++
Allopumiliotoxins							
253A				++	+		+
267A			+	++	++	+	+++
305A					+		
323B		++	++	++	+	++	+
325A		+		+		+	
339A		++	++	+	+		+
339B							+
341A							+
357							+

TABLE 1. CONTINUED

Alkaloids[a]	Captive-raised on leaf-litter insects	Wild-caught					
		Ancon Hill		Isla Taboga			Isla Taboga pooled skins
	1B	2A	2B	2C	2D	2E	1968–1975
Decahydroquinolines							
195A		++	++	+++	++	++	+++
211A			+	+			
219A				+++, +	+++, +	+++, +	+++
243A				++, +	++, +	+++, +	+++
269AB	++		+				
3,5-Pyrrolizidines							
223B							+
223H			+				
249I*			+	+			
251K(K′, K″)[b]		+++, ++	++, +	+++, ++	++, ++	++, ++	
3,5-Indolizidines							
195B			+				
223AB		+					
275C		++					
277C*			+		+		
5,8-Indolizidines							
167A							+
181B							+
203A				+	+	+	+
223A[c]				+, +	+, +	+, +	+
223D						+	
235B			+	++	+	+	
1,4-Quinolizidines							
181A							+
195G*				+	+	+	
223C							+
233G*	+	+	+				

235E	+, +		+, +	+			
249H*			+	++	++	++	
275A							+
Gephyrotoxins							
287C	+	+	+				
Pyrrolizidine oximes							
222	+	+	+	+	+	+	
236	+++	+	++	++	+	+	
252B	+		+	+	+	+	
Nitropyrrolizidines							
238[d]	+						
252C*	+						
254*	+						
Tricyclics[e]							
193C[f]	++	+	++	+	+	+	
205B				+			
205D*	++		+				
207F			+	+	+		
207J*			+	+	+		
207L*			+				
219H*	++		+				
219I*	++	+	+				
231H*	+	++	++				
263E*						+	
Piperidines							
223K*						++	
239L*						+	
Unknowns							
185							+
217C*				+	+		
243E*				+	+	+	
263D*		+	+	+	+	+	
265I*		+	+			+	

TABLE 1. CONTINUED

Alkaloids[a]	Captive-raised on leaf-litter insects	Wild-caught					Isla Taboga pooled skins
		Ancon Hill		Isla Taboga			
	1B	2A	2B	2C	2D	2E	1968–1975
Unknowns							
265J*			+	+	+		
267B							+
271C*		+	+				
295A							+
309B							+

[a] For structures see Daly et al. (1993), for distribution in dendrobatid frogs see Daly et al. (1987). The amounts (+++ = major, ++ = minor, + = trace) follow the notation used in prior publications. Where two or more entries are given separated by commas, this indicates two or more isomers in their order of elution from the gas chromatograph. Additional trace alkaloids were detected, but adequate data for characterization were not obtained. Previously unreported alkaloids are designated by asterisks and will be reported in detail elsewhere.

[b] Two isomers occur: the first to elute (K′) is the *exo,exo* (5*Z*,8*E*) isomer identical with an ant pyrrolizidine (Jones et al., 1991); the second is either the *exo,endo* or *endo,exo* isomer.

[c] The alkaloid(s) that have been designated **223A** may represent more than one structural class. Initially, **223A** was postulated to be a quinolizidine (Daly et al., 1992), but further analyses indicate that **223A** in many extracts is an 8-ethyl-5-propylindolizidine with in addition a 6-ethyl substituent (unpublished results). Alkaloid **223A** is now listed as 5,8-indolizidine in Table 1. Two isomers occur in these extracts.

[d] Alkaloid **238** is identical to nitropolyzonamine, an alkaloid known from a millipede (Meinwald et al., 1975).

[e] "Tricyclics" refer to compounds whose mass spectra appear related to those of the coccinellines, which occur in beetles (Ayer et al., 1976). Some of these alkaloids may prove to have uniquely different structures from the coccinellines.

[f] Alkaloid **193C** is identical to precoccinelline, an alkaloid known from beetles (Ayer et al., 1976).

not have a dietary origin in dendrobatid frogs or that they are present in insects or other prey that were not collected by the present technique using Berless funnels.

A combined extract from 21 collections of leaf-litter arthropods made over the seven-month period afforded one major alkaloid and two minor alkaloids (Figure 4). The major alkaloid was pyrrolizidine oxime **236**, while the minor alkaloids were the beetle alkaloid precoccinelline (**193C**) and the millipede alkaloid nitropolyzonamine (**238**). Because of the identity of the carbon skeleton to that of nitropolyzonamine, it seems likely that the pyrrolizidine oxime **236** and other such oximes (**222**, **252B**) are also of millipede origin. The demonstration in the present experiments that such pyrrolizidine oximes are nearly certainly of dietary origin, presumably from small neotropical millipedes, explains previously puzzling observations on the occurrence of such oximes in one population of *Dendrobates pumilio* from Isla Bastimentos, Bocas, Panama. Such oximes

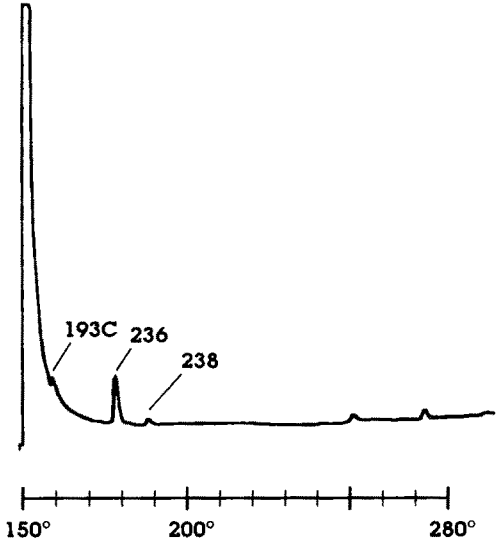

FIG. 4. Gas chromatographic profiles for alkaloids from combined extracts of leaf-litter arthropods. Combined extracts from 21 collections of leaf-litter arthropods made with Berless funnels over the seven-month period were extracted with ethanol and the pooled ethanol extract evaporated to a volume of 100 ml in vacuo at 30°C using a rotary evaporator. Alkaloids were separated by solvent partitioning as described (see Daly et al., 1987). The alkaloids were then dissolved in 0.5 ml methanol and analyzed (see Methods and Materials). The gas chromatogram was obtained with an injection of 0.2 μl. The code numbers for precoccinelline and nitropolyzonamine are **193C** and **238**, respectively.

were undetectable in skin extracts obtained in 1971 and 1972 (see Tokuyama et al., 1992), but three pyrrolizidine oximes (**222**, **236**, and **252A**) were significant, albeit minor, alkaloids in extracts obtained in 1981 and later years. The most likely explanation is that subtle changes in habitat have favored an increase in the abundance of millipedes that contain such pyrrolizidine oxime alkaloids.

The present preliminary study poses many questions, particularly with regard to the origin or source of several major classes of "dendrobatid alkaloids." Of the present alkaloids apparently accumulated from the diet in captive-raised frogs, precoccinelline most certainly originates from small beetles and the pyrrolizidine oximes, most likely from small millipedes. The histrionicotoxins, the pumiliotoxins, the gephyrotoxins, the decahydroquinolines, and 1,4-disubstituted quinolizidines are not known in nature except from frog skin. Although present in significant amounts in skin extracts of captive-raised frogs, neither the histrionicotoxins nor the quinolizidines were detected in extracts of the leaf-litter arthropods. Furthermore, levels of histrionicotoxins in the wild-caught frogs from the leaf-litter site were orders of magnitude higher than in frogs raised on leaf-litter arthropods. Thus, if histrionicotoxins do come from dietary sources, the present method for collection of arthropod prey is woefully inadequate. Clearly, an extensive study on the complete set of arthropods, including flying insects and other small creatures that could serve as food for dendrobatid frogs, and on the alkaloids present in such food sources needs to be conducted.

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