THE ALKALOIDS OF *TELITOXICUM PERUVIANUM*

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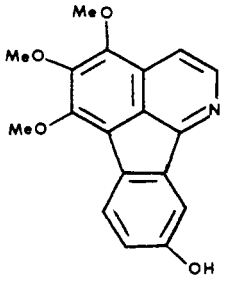
ABSTRACT.—The alkaloid fraction of the Amazonian species *Telitoxicum peruvianum* (Menispermaceae) was found to contain the known alkaloids norrufescine (**1**), lysicamine (**6**), and subsesseline (**2**) as well as the new alkaloids telitoxine (**3**), peruvianine (**4**), and telazoline (**7**). Structures are proposed for the new alkaloids on the basis of spectroscopic data.

As part of a continuing study of the alkaloids of the family Menispermaceae, we have investigated a number of plants of the South American genus *Abuta* (1–3). We now wish to report the isolation of some of the alkaloid constituents of *Telitoxicum peruvianum*, a species of the related and hitherto unexamined Amazonian genus *Telitoxicum* (4, 5).

The total tertiary alkaloids were partitioned into phenolic and nonphenolic bases by extraction with 5% sodium hydroxide. The phenolic alkaloid fraction afforded, after separation by column chromatography on silica gel, the two known alkaloids, norrufescine (**1**) (1) and subsesseline (**2**) (6), and the two new alkaloids telitoxine (**3**) and peruvianine (**4**).



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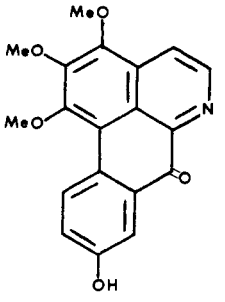

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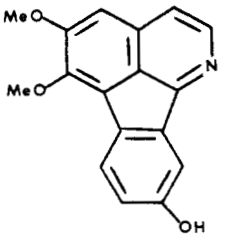
Telitoxine (**3**) was obtained as yellow flakes, mp 273–275°. Its high resolution mass spectrum indicated the molecular composition $C_{17}H_{13}NO_3$. The ultraviolet spectrum of telitoxine was similar to that of the azafluoranthene alkaloid, norrufescine. Its nmr spectrum revealed a substitution pattern slightly different from that of norrufescine. The singlet at δ 7.18 was assigned to the C–3 proton; the remainder of the spectrum consisted of two methoxyls (δ 4.06 and 4.07), a pair of doublets (2 H, 6 Hz) at δ 8.50 and at δ 7.53, doublets at δ 7.82 (1 H, $J=9$ Hz) and at δ 7.57 (1 H, $J=2$ Hz), and a quartet at δ 6.92 (1 H, $J=9$ Hz and 2 Hz). The small ortho coupling constant of 6 Hz is consistent with the assignment of the δ 8.50 and δ 7.53 signals to pyridine ring protons at C–2 and C–3, respectively. Based on spectral evidence, structure (**3**) was assigned to telitoxine, making it a hydroxy derivative of triclisine (**5**) isolated from *Triclisia gilletti* (Dewild) Staner (7).

Peruvianine (**4**) crystallized from methanol as red orange prisms, mp 252–255°



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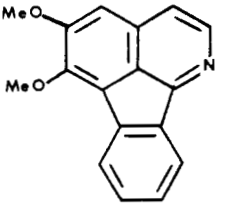

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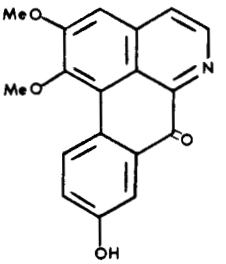
(dec.). Its high resolution mass spectrum indicated the molecular composition $C_{18}H_{13}NO_4$. Its ultraviolet spectrum showed maxima at 238, 271, 369 and 432 nm; an alkaline bathochromic shift of the maximum to 510 nm indicated the presence of a phenolic function. Its nmr spectrum revealed the presence of two methoxyls (δ 4.05 and 4.15) and six aromatic protons. Of these, the pair of doublets at δ 8.04 and 8.83 were assigned to the B ring protons of an oxoaporphine; the remainder of the spectrum consisted of doublets at δ 7.91 (1 H, $J=2$ Hz) and at δ 9.18 (1 H, $J=10$ Hz), a singlet at δ 7.58 (1 H), and a quartet at δ 7.34 (1 H, $J=10$ Hz and 2 Hz). From the splitting pattern, it can be concluded that the 9-position of the oxoaporphine is substituted by a hydroxyl group. Structure **4** may, therefore, be assigned to peruvianine.



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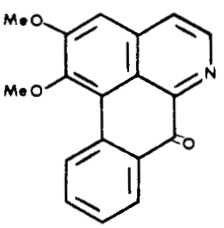
Countercurrent separation of the non-phenolic base afforded the known alkaloid lysicamine (**6**) (8) and the new alkaloid telazoline (**7**).

Telazoline (**7**) was obtained as reddish brown prisms, mp 240–243°. Its high resolution mass spectrum indicated the molecular formula $C_{17}H_{12}N_2O_2$. The ultraviolet spectrum of telazoline exhibited maxima at 251, 283, and 470 mm. Its nmr spectrum showed the presence of a methoxyl at δ 4.09; the rest of the spectrum consisted of seven aromatic proton signals as a singlet at δ 7.00 (1 H), a pair of doublets at δ 7.66 and δ 8.75 (1 H each, $J=5$ Hz), a pair of multiplets



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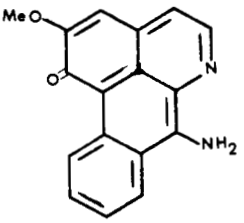

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at δ 7.44 and 7.69 (1 H each), and a pair of doublets at δ 8.51 and δ 8.57 (1 H each, $J=8$ Hz). These signals correspond to an isolated proton, a pair of ortho protons, and the ring proton of the D ring of an aporphine alkaloid. The tentative structure **7** is suggested for telazoline. An X-ray crystallographic analysis will be necessary to confirm this structural assignment, in view of the small amount of material available.

EXPERIMENTAL[1]

PLANT MATERIAL.—The plant material was collected in Peru (San Martin) during March 1971. A voucher specimen identified by Dr. B. A. Krukoff (Honorary Curator, New York Botanical Garden and Consulting Botanist of Merck, Sharp and Dohme Research Laboratories) was placed in the herbarium of the New York Botanical Garden. The woody stems were air dried and milled to a coarse powder.

EXTRACTION AND FRACTIONATION.—The ground plant material (5.91 kg.) was moistened with 1:1 ammonium hydroxide and extracted exhaustively with ethyl acetate-ethanol (9:1). The extract was concentrated and then partitioned between methylene chloride and 2% sulfuric acid to obtain the methylene chloride soluble neutral fraction (89 g). The aqueous layer was basified with ammonium hydroxide (1:1) and extracted with methylene chloride to give the total bases (7.65 g). The total base fraction was partitioned between methylene chloride and 5% sodium hydroxide to obtain the phenolic base faction I (2.25 g) and the non-phenolic bases (5.40 g). The non-phenolic bases were partitioned again with 5% sodium hydroxide to give the phenolic base fraction II (0.60 g) and the non-phenolic base fraction (4.98 g).

CONSTITUENTS OF PHENOLIC BASE FRACTION I.—The phenolic base fraction I (2.25 g) was dissolved in methanol and let stand overnight. The resulting reddish orange crystals (0.15 g), when recrystallized from hot methanol, yielded pure subsesseline (**2**), mp 247–249° (lit. (6) mp 223–226°). The residue from the mother liquor (1.12 g) was chromatographed on silica by gradient elution with hexane-ethyl acetate, ethyl acetate, ethyl acetate containing methanol, and finally methanol. Effluent fractions of 500 ml were evaporated to dryness, and the residues were weighed and analyzed by tlc. The two fractions collected with hexane-ethyl acetate (3:1) (fractions 2–3), on evaporation followed by crystallization from methanol-chloroform, gave yellow-orange crystals of norrufescine (**1**) (1.5 mg), mp 232–234° (lit. (1) mp 235–238°). The infrared spectrum of this sample was identical with that of an authentic sample of norrufescine.

Fractions 4–5 eluted from the column with ethyl acetate gave, after crystallization from methanol-methylene chloride-chloroform, yellow crystals of telitoxine (**3**) (3.6 mg); mp 273–275°; uv λ max (EtOH) 233 (log ϵ 4.29), 243 (4.30), 277 (4.14), 288 (4.14), 298 (4.10), 307 sh (3.70), 322 (3.55), 350 (3.41) and 367 nm (3.55); after addition of NaOH λ max 233 (4.26), 245 (4.20), 255 (4.21), 279 sh (3.89), 288 sh (3.94), 307 sh (4.17), 314 (4.20), 345 sh (3.20), 355 (3.20), 373 (3.20) and 448 (3.00); nmr (360 MHz, acetone-d_6) δ 4.06 and 4.07 (3 H each, s), 6.92 (1 H, dd, $J=9$ and 2 Hz), 7.18 (1 H, s), 7.57 (1 H, d, $J=2$ Hz), 7.82 (1 H, d, $J=9$ Hz), 7.53 and 8.50 (1 H each, d, $J=6$ Hz); high resolution mass spectrum: calcd. for $C_{17}H_{13}NO_5$: 279.0891, found: 279.0890.

Subsesseline (**2**) (identified by its mp 247–249° and mixed mp, and ir as compared with an authentic sample) was obtained from the fractions 7–10. The residue from fraction 11, eluted with 8% methanol in ethyl acetate, on crystallization from methanol gave red orange crystals of peruvianine (**4**) (3 mg), mp 252–255°; uv λ max (EtOH) 238 (log ϵ 4.42), 271 (4.43), 289 sh (4.04), 328 sh (3.63), 369 (3.57) and 432 nm (3.57); after addition of NaOH λ max 243 (4.40), 285 (4.44), 319 sh (4.20), 370 sh (3.69) and 510 nm (3.59); nmr (250 MHz, acetone-d_6) δ 4.05 and 4.15 (3 H each, s), 7.34 (1 H, dd, $J=10$ and 2 Hz), 7.58 (1 H, s), 7.91 (1 H, d, $J=2$ Hz), 8.04 (1 H, d, $J=5$ Hz), 8.83 (1 H, d, $J=5$ Hz) and 9.18 (1 H, d, $J=10$ Hz); high resolution mass spectrum: calcd. for $C_{18}H_{13}NO_4$: 307.0840, found: 307.0854.

CONSTITUENTS OF PHENOLIC BASE FRACTION II.—This fraction (0.34 g) was subjected to flash chromatography over silica gel 60. No homogeneous characterizable compounds could be isolated from the fractions.

CONSTITUENTS OF NON-PHENOLIC BASE FRACTION.—This material was subjected to gradient pH-countercurrent distribution (26 transfers) between chloroform and citrate-phosphate buffer, starting with pH 6.6 and ending with pH 3.0. The acidic aqueous layers from the tubes, upon basification and reextraction with chloroform, failed to give appreciable quantities of any alkaloids.

The residual chloroform solutions left in the countercurrent machine were separated into three fractions after monitoring by tlc. The residues from the chloroform solutions in the

[1]Melting points are uncorrected. Nmr spectra (tetramethylsilane as internal standard), uv spectra, and mass spectra were determined on Bruker 360 and 250, Perkin Elmer 202 and 270 spectrometers, respectively. High resolution mass spectra were determined on a Hitachi-Perkin-Elmer RMH-2 instrument.

first six tubes were combined to give 0.111 g of material, which was chromatographed on silica gel 60 (2 g) with chloroform as eluent; 20 ml fractions were collected. The residue from fractions 5–7 (16 mg) was crystallized from methanol-methylene chloride. Further recrystallization from methanol-chloroform gave golden yellow flakes of lysicamine (**6**) (4.5 mg), mp 200–201.5° (lit. (8) mp 210–211°).

Chloroform solutions from tubes 7–15, after evaporation, gave a residue (0.21 g) which was subjected to column chromatography over silica gel 60, by gradient elution with hexane-ethyl acetate, ethyl acetate, ethyl acetate containing methanol and methanol; 15 ml fractions were collected. The residue from fractions 23–40 (0.03 g), eluted with 10% methanol in ethyl acetate, was crystallized from methanol-methylene chloride to give reddish brown prisms of telazoline (**7**) (9 mg), mp 240–243°; uv λ max (EtOH) 242 sh (log ε 4.52), 251 (4.53), 283 (4.47), 317 sh (3.93) and 470 nm (4.08); after addition of NaOH λ max 241 sh (4.54), 250 (4.55), 273 (4.47), 324 sh (3.85), 370 (3.33), 471 nm (4.62); nmr (360 MHz, $CDCl_3$), δ 4.09 (3 H, s), 7.00 (1 H, s), 7.44 (1 H, m), 7.66 (1 H, d, J=5 Hz), 7.69 (1 H, m), 8.51 (1 H, d, J=8 Hz), 8.57 (1 H, d, J=8 Hz) and 8.75 (1 H, d, J=5 Hz); high resolution mass spectrum: calcd. for $C_{17}H_{12}N_2O_2$: 276.0894, found: 276.0909.

ACKNOWLEDGMENT

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