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ALKALOIDS OF SOME SOUTH AMERICAN *ERYTHROXYLUM* SPECIES*

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Key Word Index—*Erythroxylum*; Erythroxylaceae; chemotaxonomy; tropane alkaloids; cuscohygrine; nortropacocaine.

Abstract—Fourteen South American species of *Erythroxylum* representing four sections of the genus were examined for tropane and related alkaloids. The alkaloid content of the dried material ranged from 0.002 to 0.20%. Commonly, the alkaloids involved were esters of various tropanols with benzoic and phenylacetic acids. A new alkaloid, nortropacocaine, was isolated from *E. mamacoca*. Mass spectrometry indicated the existence of other new bases, cuscohygrine and, in some species dihydrocuscohygrine. Chemotaxonomic implications are discussed.

INTRODUCTION

In recent years, considerable attention has focused on the examination of tropical American *Erythroxylum* species for the possible presence of cocaine and cinnamoylcocaine [1–3]. Generally, in wild species the amount of these alkaloids found, if any at all, is extremely low and does not compare in quantity with the commercial varieties of coca derived from the species *E. coca* Lam. and *E. novogranatense* (Morris) Hieron [3]. The Old World species produce a considerable range of other tropane alkaloids [4–6] but, with the exception of *E. vacciniifolium* Mart. [7], no investigation for the occurrence of these alkaloids in the neotropical species appears to have been undertaken. In this report we record our findings on the examination of 13 such species, six of them referable to section *Archerythroxylum* (Table 1). Most of the plant material examined was obtained by one of us (T.P.) during fieldwork associated with the current taxonomic revision of the neotropical species.

RESULTS AND DISCUSSION

Alkaloids were extracted in ether from the alkalinized plant material and fractionated by prep. TLC. After elution, the separated zones of alkaloids were examined, where possible, by the preparation of picrate derivatives and by spectroscopy. In some instances where the small quantity of product or the presence of mixtures prevented the complete characterization of the bases, mass spectroscopy gave evidence of the component moieties of the alkaloids. The results are shown in Table 2.

Section *Archerythroxylum* comprises over 60 species and the six examined contained alkaloids in the range 0.06–0.20% compared with all but one of the species examined from sections *Macrocalyx*, *Rhabdophyllum* and *Leptogramme* which were much lower in alkaloid content (0.002–0.04%). In the six species, benzoic acid and, to a lesser extent, phenylacetic acid were the predominant esterifying acids and the alkamine moieties of the alkaloids were principally tropan-3-ols, tropan-3,6-diols and their derivatives. 3β-Benzoyloxytropane is of common occurrence and this very limited 3β-series of alkaloids has been extended by the characterization of the new alkaloid 3β-benzoyloxynortropane (nortropacocaine) from *E. mamacoca* Mart. Dihydrocuscohygrine (first reported in *E. coca* [8]) and cuscohygrine are present in some species. The occurrence of cuscohygrine as the major alkaloid of *E. cataractarum* Spruce ex. Peyr. is the first instance of such in the genus. Bases of the above types are also found in the cocaine-producing *E. coca* and *E. novogranatense*; no cocaine or cinnamoylcocaine was detected in any of the species listed in Table 1. However, using sensitive, specific assays for cocaine, Holmstedt *et al.* [2] and Plowman and Rivier [3] reported the following percentage concentrations for some of the same samples (voucher numbers in parentheses): *E. cataractarum* 0.00 (4265); *E. cumanense* H.B.K. 0.0000 (7673); *E. glaucum* O. E. Schulz 0.0003 (5453); *E. mamacocca* 0.0000 (5959); *E. shatona* Macbride 0.0004, 0.0005 (6046); *E. ulei* O. E. Schulz 0.00; *E. amazonicium* 0.0000 (7676).

The new alkaloid, nortropacocaine, was characterized by spectroscopic analysis and by partial synthesis. In addition to the alkaloids isolated above, mass spectroscopy has indicated the presence of other new bases but insufficient plant material was available for their further study.

Before any overall chemotaxonomic conclusions can be drawn regarding the occurrence of tropane alkaloids throughout the genus, further detailed phytochemical studies on more species are required. In this study, tropacocaine was found in *E. ulei* of section *Leptogramme* and in two species (*E. mamacoca* and *E. argentinum*) of section *Archerythroxylum*, but not in species of sections *Macrocalyx* and *Rhabdophyllum*. *Erythroxylum ulei* is more closely related to species of section *Archerythroxylum* and should be excluded from *Leptogramme* which is, in fact, a heterogeneous and

*Part 4 in the series "Alkaloids of the Genus *Erythroxylum*". For part 3 see ref. [6].

Table 1. Plant materials

Species	Plant habit and locality	Date collected	Collector, number and location of voucher specimen*
Section *Archerythroxylum* O. E. Schulz			
E. argentinum O. E. Schulz	Regenerating growth from mature tree 5 m high. Cultivated. Royal Botanic Gardens, Sydney, Australia	1980	Haegi 2008 (NSW)
E. cataractarum Spruce ex. Peyr.	Shrub 0.5–3.0 m tall. El Tablazo. Alt. 2200 ft. NE. end of Sierra de la Macarena, Dept Meta Colombia	September 1974	Plowman *et al.* 4265 (COL, ECON, F, INPA, K, NY)
E. cumanense H.B.K.	Tree. Reforested hills. Jardín Botánico, Caracas, Venezuela	June 1972	Montes s.n. (NOT)
	Tree 10 m tall in seasonally dry forest. Reforested hills. Jardín Botánico, Caracas, Venezuela	February 1979	Plowman 7673 (F, GB, RB, US, VEN)
E. glaucum O. E. Schulz	Tree 8 m tall. Between Casitas and El Huásimo. Alt. 480 m. Dept Tumbes, Peru	February 1976	Plowman 5435 (COL, F, GH, K, MO, NY, S, USM)
E. mamacoca Mart.	Shrub on steep, rocky, moist forested slopes. Road from Las Palmas to Chinchao, Huachipa, above Río Chinchavito. Alt. 900–100 m. Prov. Leoncio Prado, Dept Huánuco, Peru.	April 1976	Plowman 5959 (ECON, F, K, INPA, MO, NY, USM)
E. shatona Macbride	Tree 7 m tall. Flat secondary forest. 24 km from Tarapoto on road to Juanjui. Alt. 300 m. Prov. San Martín, Dept San Martín, Peru	May 1976	Plowman 6046 (ECON, F, K, NY, US, USM)
Section *Leptogramme* O. E. Schulz			
E. ulei O. E. Schulz	Diffusely branched small tree. 3.5 m tall. Left bank of Río Huallaga, Miramar, 1–2 km down river from Tocache Nuevo. Alt. 500 m. Prov. Mariscal Cáceres, Dept San Martín, Peru	December 1981	Plowman *et al.* 11419 (ECON, F, U, USM)
	Small understory tree 3–4 m tall growing on steep slope immediately below large limestone boulders. Limestone hills opposite airport. Tingo María, Prov. Leoncio Prado, Dept Huánuco, Peru	December 1981	Plowman *et al.* 11277 (F, U, USM)
	Small understory treelet 2.5 m tall. Growing on steep slope immediately below limestone boulders. Limestone hills opposite airport. Tingo María, Prov. Leoncio Prado, Dept Huánuco, Peru	December 1981	Plowman *et al.* 11278 (ECON, F, U)
Section *Macrocalyx* O. E. Schulz			
E. macrocnemium Mart.	Unbranched treelet 4 m tall in forest understory. Puente Palo Blanco (Río Tocache). 10 km W. of Tocache Nuevo on road to Puerto Pizana. Alt. 550–650 m. Prov. Mariscal Cáceres, Dept San Martín, Peru	December 1981	Plowman *et al.* 11315 (F, GH, K, U, USM)
E. macrophyllum Cav.	Treelet 2.5 m tall in forest in open, somewhat disturbed area. Puente Palo Blanco (Río Tocache). 10 km W. of Tocache Nuevo on road to Puerto Pizana. Alt. 550–560 m. Prov. Mariscal Cáceres, Dept San Martin, Peru	December 1981	Plowman *et al.* 11360 (ECON, F, NY, U, USM)
	Tree 20 m tall in cut-over primary forest. Trail to Shunté, *ca* 10 km W. of Tocache Nuevo, E. of Río Tocache. Alt. 550 m. Prov. Mariscal Cáceres, Dept San Martín, Peru	December 1981	Plowman *et al.* 11377 (ECON, F, MO, NY, U, USM)

Section *Rhabdophyllum*			
O. E. Schulz			
E. amazonicum Peyr.	Tree 8 m tall. Hills above campus of Universidad Simón Bolívar. Baruta, Estado Miranda, Venezuela	February 1979	Plowman 7676 (F, GH, K, MO, NY, U, USM)
E. citrifolium St. Hil.	Guyana	June 1972	Rayman s.n. (NOT)
E. fimbriatum Peyr.	Treelet 3 m tall on steep slope in forest understory. Limestone hills opposite airport. Alt. 720 m. Prov. Leoncio Prado, Dept Huánuco, Peru	December 1981	Plowman *et al.* 11250 (ECON, F, USM)
	Tree 6 m tall in forest. Quebrada de Huaquisha, right bank of Río Huallaga, opposite Tocache Nuevo. Alt. 500–600 m. Prov. Mariscal Cáceres, Dept San Martín, Peru	December 1981	Plowman *et al.* 11400 (F, USM)
E. mucronatum Benth.	Tree 5–6 m growing on steep, rocky outcrop above Rio Tulumayo between Quimirí and La Merced. Alt. 700 m. Prov. Tarma, Dept Junín, Peru	March 1976	Plowman and Kennedy 5683 (F, GH, K, NY, US, USM)
	Small tree 5 m tall. Trail to Shunté, *ca* 10 km W. of Tocache Nuevo, E. of Río Tocache. Alt. 550 m. Prov. Mariscal Cáceres, Dept San Martín, Peru	December 1981	Plowman *et al.* 11375. (ECON, F, MO, NY, U, USM)

*Abbreviations of herbaria taken from ref. [14].

Table 2. Alkaloids of South American *Erythroxylum* species*

	Weight sample (g)	Total alkaloid (% dry wt calculated as tropacocaine)	Alkaloid constituents
Section *Macrocalyx*			
E. macrocnemium	47	0.002	Three bases (TLC)
E. macrophyllum P 11360	18	0.002	Six bases (TLC)
P 11370	47	0.002	Six bases (TLC)
Section *Rhabdophyllum*			
E. amazonicum	28	0.09	3α-Benzoyloxytropan-6β-ol [9]; three uncharacterized bases
E. citrifolium	25	0.03	Three bases (TLC)
roots	450	0.01	Four bases (TLC)
E. fimbriatum P 11400	44	0.04	Tropine; two uncharacterized ester alkaloids; one other alkaloid
P 11250	15	0.03	Three bases (TLC)
E. mucronatum P 5683	13	0.02	Two ester alkaloids
P 11375	210	0.01	Three uncharacterized bases
Section *Leptogramme*			
E. ulei P 11419	78	0.01	Tropacocaine; two uncharacterized bases
P 11277	26	0.01	Four bases (TLC)
Section *Archerythroxylum*			
E. argentinum leaves	180	0.20	Tropacocaine (principal alkaloid); hygrine; cuscohygrine; an ester alkaloid involving benzoic acid; an unresolved mixture having tropine, dihydroxynortropane and benzoic acid moieties
twigs	225	0.03	Acetates and benzoates of nortropanols; ? 3-acetoxynortropan-6-ol
E. cataractarum	26	0.20	Cuscohygrine (principal alkaloid); ? dihydrocuscohygrine in admixture with a tropanol ester; an uncharacterized base—? a propanoyl ester of nordihydroxytropandiol
E. cumanense P 7673	23	0.06	Two uncharacterized ester alkaloids with respective M_rs of 287 and 423 (acetate of 'roots' below)
E. cumanense roots Montes S. M.	210	0.11	6β-Benzoyloxytropan-3α-ol [10, 11]; 3-phenylacetoxynortropan-6-ol [9]; new base with mass spectral fragmentation consistent with 3-acetoxy-6,7-dibenzoyloxytropane; esters involving trimethoxybenzoic acid
E. glaucum	20	0.10	6β-Benzoyloxytropan-3α-ol [10, 11] (principal alkaloid); dihydrocuscohygrine; two uncharacterized ester alkaloids
E. mamacoca	18	0.11	3β-Benzoyloxynortropane (nortropacocaine)—a new alkaloid; tropacocaine; esters with benzoyl and phenylacetoxy moieties
E. shatona	55	0.10	Four uncharacterized ester alkaloids with probable phenylacetoxy and benzoyl moieties

*Aerial parts unless otherwise stated.

artificial assemblage. The occurrence of tropacocaine would seem to support placing *E. ulei* in *Archerythroxylum*. However, this alkaloid has also been reported in some African species [6, 9].

The base 6β-benzoyloxytropan-3α-ol was identified from both *E. cumanense* H.B.K. and *E. glaucum* O. E. Schulz and has not been found in other South American species; it has been recorded in the African species *E. zambesiacum* [10] and in the genus *Knightia* (Proteaceae) [11]. *Erythroxylum cumanense*, from the Caribbean coast of South America, is closely related to *E. glaucum* which occurs only along the Pacific coast of southern Ecuador. Both species occur in seasonally dry habitats along sea coasts and both are small trees with stiff, horizontal branches. Although the two species are specifically distinct, it is of interest that they share an apparently rare compound. Esters involving trimethoxybenzoic acid are found in some Old World species [6], but that they are not exclusive to them is indicated by the present report for *E. cumanense* roots and previously for *E. vacciniifolium* [7].

EXPERIMENTAL

Plant material. Collection details for the species examined are given in Table 1.

Extraction and fractionation of alkaloids. The alkaloids were extracted from the moistened and basified [$Ca(OH)_2$] powdered material in Et_2O and purified by the Stas-Otto procedure as previously described for tropane alkaloids [12]. Total bases were determined by titration and the alkaloid mixture fractionated initially by TLC and prep. TLC using silica gel and Me_2CO–H_2O–NH_4OH (specific gravity 0.88) (80:15:2).

Characterization of alkaloids. Bases were eluted from chromatograms with Me_2CO and characterized by comparison with authentic samples using standard methods of analysis. New alkaloids and mixtures of alkaloids were examined by IR and mass spectrometry, and by chemical means according to the amount of sample available. Details for particular species are given below. Except where indicated otherwise, R_f values refer to the above system.

Erythroxylum amazonicum (*voucher Plowman* 7676). Leaves

28 g. Three bases: (a) R_f 0.28; IR ν_{max} cm^{-1}: 1720, 3450 (ester CO and OH); (b) R_f 0.79, IR ν_{max} cm^{-1}: 1715, 3420 (ester CO and OH); (c) R_f 0.85, IR and low resolution MS in accord with authentic 3α-benzoyloxytropan-6β-ol.

E. fimbriatum (*voucher: Plowman* et al. 11400). Aerial parts 15 g. Four bases: (a) R_f (three systems) and colour reactions of tropine; (b) R_f 0.73, IR ν_{max} cm^{-1}: 1715 (ester CO); (c) R_f 0.85, IR ν_{max} cm^{-1}: 1740, 3420 (ester CO and OH); (d) R_f 0.94.

E. mucronatum (*voucher: Plowman* et al. 11375). Aerial parts 210 g. Three bases: (a) R_f 0.29, IR ν_{max} cm^{-1}: 1720 (ester CO); (b) R_f 0.79, IR ν_{max} cm^{-1}: 1720 (ester CO); (c) R_f 0.94, IR ν_{max} cm^{-1}: 1740, 3400 (ester CO, OH).

E. ulei (*voucher: Plowman* et al. 11419). Leaves 78 g. Three bases: (a) R_f 0.32. IR ν_{max} cm^{-1}: 1710 (ester CO); (b) tropacocaine [R_f, IR and MS of picrate compared with authentic material. (Found: $[M]^+$, 245.1400. Calc. for $C_{15}H_{19}NO_2$: 245.1376.)]; (c) R_f 0.76.

E. argentinum (*voucher: Haegi* 2008). Leaves 180 g. Five bases: (a) hygrine [R_f, mp and mmp of picrate, IR and MS compared with authentic material. (Found: $[M]^+$, 141.1143. Calc. for $C_8H_{15}NO$: 141.1130.)]; cuscohygrine [R_f, mp, IR and MS of dipicrate as authentic material. (Found: $[M]^+$ 224.1874. Calc. for $C_{13}H_{24}N_2O$: 224.1840.)]; (c) tropacocaine (R_f, mp and mmp, IR, MS of picrate as authentic material); (d) R_f 0.77, IR ν_{max} cm^{-1}: 1690–1730, 3440 (broad CO absorption, OH); MS *m/z* 122.0358 (calc. for $PhCO_2H$ 122.0368), 105.0300 (calc. for PhCO: 105.0340); (e) R_f 0.90, IR ν_{max} cm^{-1}: 1725, 3460 (ester CO and OH), MS ions characteristic of a substituted nortropandiol were *m/z* 142, 125 and 108.0792 (calc. for $C_7H_{10}N$: 108.0770, see also ref. [13]). Twigs 225 g. Two fractions: (a) R_f 0.87, IR ν_{max} cm^{-1}: 1690–1720, 3480 (mixed carbonyls and OH), MS *m/z* 105.0306 (PhCO); (b) picrate poorly crystalline, mp 159°, IR ν_{max} cm^{-1}: 1720, 3490 (ester CO, OH), MS *m/z* (rel. int.): included 185 $[M]^+$, 142 $[M-MeCO]^+$ (187), 126 $[M-MeCOO]^+$ and/or a tropandiol moiety), 125, tropandiol residue (25), 124, presence of tropanol ester, 108, 83 (100).

E. cataractarum (*voucher: Plowman* et al. 4265). Leaves 26 g. Two fractions by prep. TLC (silica gel, $CHCl_3$–Et_2NH, 9:1): (a) cuscohygrine [R_f, mp and mmp of dipicrate as authentic material. (Found: $[M]^+$, 224.1876. Calc. for $C_{13}H_{24}N_2O$: 224.1840.)]; (b) on further resolution by the standard TLC system three bases were indicated. The slowest running base had R_f 0.27, IR ν_{max} cm^{-1}: 1735, 3440 (ester CO, OH), MS *m/z* included $[M]^+$ 199 (? $C_{10}H_{17}NO_3$), 142 [? $M-C_3H_5O]^+$ and tropandiol signals. The faster running zone probably contained dihydrocuscohyrine (R_f 0.52, $[M]^+$, 226) and an unidentified tropanol (MS *m/z* (rel. int.): 124 (19).

E. glaucum (*voucher: Plowman* 5435). Leaves 20 g. Three chromatographic bands: (a) a mixture of possibly dihydrocuscohygrine ($[M]^+$, 266) and a tropanol ester [IR ν_{max} cm^{-1}: 1720; MS *m/z* (rel. int.): 124 (12)]; (b) 6β-benzoyloxytropan-3α-ol [R_f values in three systems, IR and MS as authentic alkaloids. (Found: $[M]^+$, 261.1366. Calc. for $C_{15}H_{19}NO_3$: 261.1366.)]; (c) R_f 0.91, a mixture of two ester bases.

E. cumanense. Roots 210 g. Four chromatographic bands: (a) this was resolved into two components, the first was uncharacterized, IR ν_{max} cm^{-1}: 1720 (ester CO) affording evidence of a trimethoxybenzoic acid moiety [MS *m/z* 195.0658. (Calc. for $C_{10}H_{11}O_4$: 195.0657.)] associated with a nortropan-3,6-diol [MS *m/z* 108.0806. (Calc. for $C_7H_{10}N$: 108.0770.)]; the second component was 6β-benzoyloxytropan-3α-ol [R_f value, mp, mmp, IR, MS of picrate as authentic compound. (Found: $[M]^+$, 261.1384.)]; (b) a mixture of tropandiol esters involving trimethoxybenzoic acid (MS *m/z* 195.0646); (c) 3-phenylacetoxynortropan-6-ol. [IR, MS as authentic compound. (Found: $[M]^+$, 261.1399. Calc. for $C_{15}H_{19}NO_3$: 261.1366.)] Hydrolysis gave phenylacetic acid (TLC, MS); (d) a mixture of bases, MS included *m/z* 423.1678 $[M]^+$ (Calc. for $C_{24}H_{25}NO_6$: 423.1760), 155.0922 [? acetoxypyridinium. (Calc. for $C_8H_{13}NO_2$ 155.0968.)], 105.0326 (100%) (PhCO).

E. mamacoca (*voucher: Plowman* 6046). Leaves 18 g. Three bases: (a) 3β-benzoyloxynortropane, R_f 0.44, IR ν_{max} cm^{-1}: 1720 (ester CO), MS *m/z* (rel. int.): included 231 $[M]^+$, 121, 110 (100), 105 (45), 81, 80, 77 (42), 69, 68. The base had the same properties (R_fs in three systems, IR, MS) as the synthesized compound (see below); (b) tropacocaine (R_f, IR, MS as authentic compound); (c) an uncharacterized mixture containing esters of tropanols (MS *m/z* 124, 110) and benzoic (MS *m/z* 122, 105) and phenylacetic (MS *m/z* 135, 119, 91) acids.

E. shatona (*voucher: Plowman* 6046). Leaves 55 g. Four alkaloids showing ester carbonyl absorptions; phenylacetic and benzoic acids indicated by MS.

Synthesis of 3β-*benzoyloxynortropane.* To a stirred soln of tropacocaine hydrobromide (0.12 g) in H_2O (1.0 ml), adjusted to pH 7.0 with $NaHCO_3$, was added $KMnO_4$ (0.15 g). The pH was kept constant by the addition of H_2SO_4 (0.5 m) over 1 hr at 30°. Ppted MnO_2 was removed and 3β-benzoyloxynortropane recovered in CH_2Cl_2 from the alkalinized (Na_2CO_3) soln. The base afforded a picrate, feathery crystals from aq. ethanol, mp 234°. (Found: C, 52.07; H, 4.35; N, 11.5. $C_{14}H_{17}NO_2 \cdot C_6H_3N_3O_7$ requires: C, 52.2; H, 4.35; N, 12.2%.)

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