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ALKALOIDS OF THREE *ASPIDOSPERMA* SPECIES

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Key Word Index—*Aspidosperma formosanum, A. campus-belus, A. desmanthum*; Apocynaceae; isolation; olivacine; uleine; 3-epiuleine; 1,13-dihydro-13-hydroxyuleine; aspidocarpine; lichexanthone; phthalimide; aspidoalbine.

Plants and sources. Aspidosperma formosanum A. P. Duarte (Formosa, Goiás, Brazil, 1965; APD herbarium register 9387); *A. campus-belus* A. P. Duarte (Campos Belos, Goiás, 1965, APD register 9481); *A. desmanthum* Benth. ex Müll.-Arg. (IPEAN, Belém, Pará, Brazil, 1965, APD register 9798). *Previous work*: None; *A. formosanum* is systematically close to *A. dasycarpon* [1] (Series Tomentosa); *A. campusnbelus* to *A. nigricans* [2] (Series Pyricolla); *A. desmanthum* to *A. exalatum* [3], *A. spruceanum* [2a], and *A. album* [4] (Series Nobile).

Bark. Hot continuous EtOH extraction followed by concn gave in each case about 10% syrupy extract. This was macerated with 2N HOAc, filtered, and divided into standard fractions [5] (letter code; method of obtention; percent of extract in the case of *A. formosanum, A. campus-belus*, and *A. desmanthum*, respectively); A, C_6H_6 extraction of the aq. HOAc solution, 0.87, 2.1, 1.47; B, $CHCl_3$ extraction of the same, 8.7, 1.4, 4.47; C, $CHCl_3$ extraction of the solution after neutralization with HCO^-_3, 2.53, 7.1, 2.2; D, $CHCl_3$ extraction after basification to pH 13 with NaOH, 1.75, 0.8, 0.83.

In the preliminary testing of the various extracts, olivacine (**1**) was noted as the principal base in fraction B of *A. campus-belus*, and a small quantity obtained by direct crystallization from MeOH was compared satisfactorily with material from *A. nigricans* [2].

In large-scale work, the following compounds were isolated (plant; fraction(s), isolation methods, compound name and structure number, yield based on dried bark, mp, other relevant data for characterization, confirmation of identity):

A. desmanthum. C, direct crystallization from MeOH, aspidoalbine (**2**), 0.05%, 174–175° (lit. 174–177° [4], 168° [2a]); MS showing possible impurity of the *N*-acetyl analogue (**3**) at *m/e* 414, but not evident in the NMR; comparison of spectral data [4].

A. formosanum. (1) A,B,C; direct crystallization from MeOH, or basic Al_2O_3 III eluting with hexane–C_6H_6 (1:1) to C_6H_6, or with toluene to toluene–EtOAc (1:1), or with hexane–CH_2Cl_2 (4:1) to CH_2Cl_2, or Si gel eluting with EtOAc–MeOH (9:1); uleine (**4**); 0.64%; 72–78°, but highly variable (known to be poorly crystalline and solvated and show wide melting ranges [2,6]); $[\alpha]_D^{27}$ +20° ($CHCl_3$; *c* 0.94), λ_{max}^{MeOH} nm 213, 307, 315 (log ε 4.38, 4.28, 4.24), $\nu_{max}^{CHCl_3}$ cm^{-1} 3534*m*, 2941*s*, 1767*w*, 1637*m*, 1621*m*, 1460*s*, 1445*s*, 1314*s*, 1148*m*, 1125*m*, 1098*m*, 1047*m*, 1007*m*, 977*w*, 935*w*, 911*w*, 873*s*, 839*m*, NMR (100 MHz, $CDCl_3$) δ 8.72 (1Hs, eliminated with D_2O; NH), 7.40–6.80 (4Hm; ArH), 5.18 and 4.84 (2 × 1Hs; $=CH_2$), 3.95 (1Hd, *J* 3 Hz; C-4), 2.16 (3Hs; N-Me), 1.04 (2Hq, *J* 6 Hz; C-14), and 0.76 (3Ht, *J* 6 Hz; C-15), MS M^+ 266 (100%) and fragmentation as published [7], comparison with an authentic sample (B. Gilbert). *Significance*: the large amount of this alkaloid present, its relatively facile isolation, and its unusual and suggestive 1-methylene-4-aminotetrahydrocarbazole structure, have led us to explore chemical transformations into analogues of antischistosomicidal drugs (preazaquinone methides), which will be reported upon in another Journal.

(2) A,B, after preliminary crystallization of uleine; neutral Al_2O_3 I eluting with hexane–C_6H_6 (4:1); 3-epiuleine (**5**); 0.013%; amorphous; UV identical to that of uleine, $\nu_{max}^{CHCl_3}$ cm^{-1} 3521*m*, 2941*s*, 1767*w*, 1637*m*, 1621*m*, 1460*s*, 1445*s*, 1314*s*, 1140*m*, 1125*m*, 1101*m*, 1043*m*, 1010*m*, 978*m*, 952*w*, 910*w*, 870*s*, 823*m*, NMR MHz, $CDCl_3$) δ 7.98

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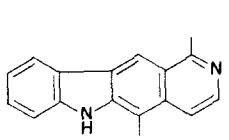
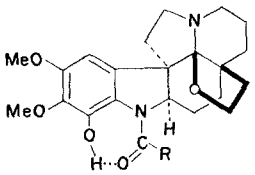
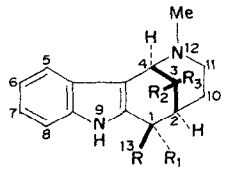


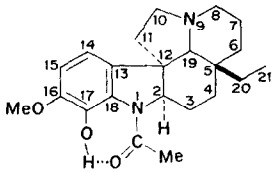
(1)



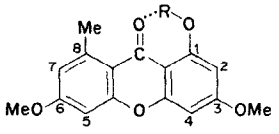
(2) R = Et
(3) R = Me



	R	R_1	R_2	R_3
(4)		$=CH_2$	Et	H
(5)		$=CH_2$	H	Et
(6)	CH_2OH	H	Et	H



(7)



(8) R = H
(9) R = Ac

(1Hs; NH), 7.40–6.80 (4Hm; ArH), 5.01 and 4.80 (2 × 1Hs; $=CH_2$), 3.86 (1Hd, *J* 2 Hz; C-4), 2.14 (3Hs; N-Me), and 0.96 (3Ht, *J* 6 Hz; C-15); comparison with literature data [8].

(3) C,D, after preliminary crystallization of uleine; EtOAc-soluble fraction over basic Al_2O_3 III eluting with EtOAc–MeOH (19:1), then purification over Florisil, same elution mixture; 1,13-dihydro-13-hydroxyuleine (**6**); 0.0070%; amorphous; $[\alpha]_D^{26}$ −66° (MeOH; *c* 0.25), λ_{max}^{MeOH} nm 219, 283, 290 (log ε 4.56, 3.90, 3.85), $\nu_{max}^{CHCl_3}$ cm^{-1} 3441*m*, 2920*s*, 1460*s*, 1449*sh*, 1380*m*, 1330*m*, 1210*s*, 1150*m*, 1100*m*, 1075*m*, 1040*s*, 1010*s*, 835*s*, NMR (100 MHz, $CDCl_3$) δ 9.18 (1Hs; NH), 7.50–7.06 (4Hm; ArH), 4.06 (2Hs, 1 eliminated with D_2O; C-4 + OH), 3.90 (2Hd, *J* 7 Hz; C-13), 3.10 (1Hm; C-1), 2.24 (3Hs; N-Me), 1.14 (2Hq, *J* 7 Hz; C-14), and 0.82 (3Ht, *J* 7 Hz; C-15), MS M^+ 284 (45%), *m/e* 266 (M^+-H_2O), then fragmentation as in uleine with base peak at *m/e* 168; comparison with an authentic sample (M. Ohashi) and with material prepared by hydroboration of uleine [1d].

(4) A,B, after preliminary crystallization of uleine; basic Al_2O_3 III eluting with toluene to toluene–EtOAc (9:1), then purification over Si gel eluting with EtOAc–MeOH (19:1); (+)-aspidocarpine (**7**); 0.013%, 169–170° (lit. [9] 168.5–169.5°); $[\alpha]_D^{25}$ +174° ($CHCl_3$; *c* 2.2), λ_{max}^{MeOH} nm 228.3, 262.5 (log ε 4.38, 3.72), ν_{max}^{KBr} cm^{-1} 2834*s*, 1629*s*, 1580*s*, 1439*s*, 1245*s*, 1080*s*, 801*s*, NMR (60 MHz, $CDCl_3$) δ 10.94 (1Hs, eliminated with D_2O; OH.....O=C), 6.63 (2 × 1Hd, nearly superimposed; ArH), 4.10 (1Hm; C-2), 3.86 (3Hs; OMe), 3.15 (2Hm; C-10?), 2.30 (3Hs; COMe), and 0.65 (3Ht, *J* 8 Hz; C-21). MS M^+ 370 (25%), base peak at *m/e* 124; comparison with an authentic sample (B. Gilbert) [2].

(5) A; direct crystallization (MeOH) or Florisil eluting with $CHCl_3$; lichexanthone (**8**); 0.0038%; 185–191° (lit. [10] 186–187°); λ_{max}^{MeOH} nm 242, 306 (log ε 4.37, 4.09), λ_{infl} 252, 269, 340 (log ε 4.18, 3.88, 3.63), $\lambda_{max}^{MeOH-NaOH}$ nm 239, 270, 308, 347, (log ε 4.54, 4.22, 4.12, 3.73), ν_{max}^{KBr} cm^{-1} 2941*w*, 1642*s*, 1613*s*, 1570*m*, 1307*m*, 1274*s*, 1205*s*, 1159*s*, 1028*m*, 840*s*, 820*s*, NMR (100 MHz, $CDCl_3$) δ 13.30 (1Hs, eliminated with D_2O; OH.....O=C), 6.64 (2Hs; C-5,7), 6.29 (2Hs; C-2,4), 3.85 (3Hs; OMe), 3.82 (3Hs; OMe), 2.85 (3Hs; ArMe), MS M^+ 286.074 (calcd for $C_{16}H_{14}O_5$, 286.084); O-acetate (**9**), not crystallized, ν_{max}^{KBr} cm^{-1} 2909*m*, 1754*m*, 1610*s*, 1570*m*, 1439*m*, 1262*m*, 1208*s*, 1159*m*, 1140*s*, 1063*m*, 898*m*, 830*m*, NMR (100 MHz; $CDCl_3$) δ 6.70 (1Hd, *J* 3 Hz; C-2), 6.61 (2Hs; C-5,7), 6.51 (1Hd, *J* 3 Hz; C-4), 3.89 (3Hs), 3.87 (3Hs), 2.53 (3Hs, ArMe), 2.40 (3Hs, ArOCOMe), MS M^+ 328, base peak at *m/e* 286; comparison of spectral data with those of a sample isolated from the lichen *Graphina confluens* Fée (D. O. Laux [11], O. R. Gottlieb). *Significance*: this compound probably came from a lichen present on the bark of *A. formosanum* and originally extracted along with it, though the quantity isolated is quite large, corresponding to at least 400 mg of lichen per kg of bark; this amount would have been noticed by the collector or in the laboratory, but no lichen was obviously present or reported. Perhaps some lichens can excrete metabolites into the bark itself.

(6) A; Florisil, eluting with $CHCl_3$–EtOAc (9:1); phthalimide; 0.0036%; 199–200° (MeOH); λ_{max}^{MeOH} nm 223.5, 292.5, NMR (60 MHz, acetone-d_6) δ 7.88 (4Hs; ArH), 2.87 (1Hs, eliminated with D_2O; CONHCO); comparison with a commercial sample. *Significance*: the source of this compound is problematical; chromatographic solvents were redistilled, and the large amount isolated (154 mg) makes it unlikely that it was due to contamination. While this cannot be rigorously eliminated, confirmation is desirable through recollection.

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A NEW INDOLOPYRIDOQUINAZOLINE IN THE BARK OF *EUXYLOPHORA PARAËNSIS*

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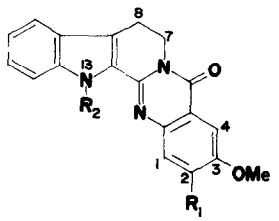
Key Word Index—*Euxylophora paraënsis*; Rutaceae; alkaloids; indolopyridoquinazolines; euxylophoricine F.

Several indolopyridoquinazoline alkaloids have been reported as constituents of the yellow bark of *Euxylophora paraënsis* Hub. (Rutaceae) [1–5]. Further investigation of the fraction containing 1-hydroxyrutaecarpine yielded a new related compound, euxylophoricine F, for which we now assign by spectroscopic methods structure (**1**), a conclusion confirmed by synthesis.



(**1**) R_1 = OH, R_2 = H
(**2**) R_1 = OMe, R_2 = Me
(**3**) R_1, R_2 = H
(**4**) R_1 = OCH_2Ph, R_2 = H

Euxylophoricine F, $C_{19}H_{15}O_3N_3$, $M^{+\cdot}$ at *m/e* 333, mp 226° (C_6H_6–petrol), exhibits the same UV spectrum as the other euxylophoricines and similar NMR spectrum (CF_3COOH + 20% $CDCl_3$) which comprises two deceptively simple triplets at δ 3.53 and 4.90 (*J* 7.0 Hz) for the ind $-CH_2-CH_2-N<$ system, a singlet at 4.20 for a methoxyl group, a singlet at 7.92 for an aromatic proton, deshielded by the neighbouring carbonyl group and a multiplet between 7.20 and 7.80 for 5 aromatic protons. The presence of a phenolic OH group was substantiated by IR absorption at 3300 cm^{-1} and by bathochromic shift to 304 nm in *N* aq. NaOH in UV spectrum. Methylation of (**1**) with MeI–K_2CO_3 in Me_2CO yielded N_{13}-methyleuxylophoricine A (**2**) indicating that euxylophoricine F was a 2,3-disubstituted rutaecarpine [6]. That the hydroxyl group was located at carbon 2 was clarified by a 20% NOE for the integrated area of C-4H at δ 7.90 on irradiating the methoxyl group at δ 4.20.

The relationship between (**1**) and the known indolopyridoquinazolines was confirmed by its conversion into 3-methoxyrutaecarpine (**3**) removing the OH group by hydrogenolysis of the respective urethane [7]. Finally, condensation of 4-benzyloxy-5-methoxyanthranilic acid methyl ester with 1,2,3,4-tetrahydronorharman-1-one in the presence of $POCl_3$ and subsequent hydrogenolysis gave (**1**) [8].

The occurrence of euxylophoricine F with euxylophoricines A and C and paraensine [2] suggests that (**1**) may be the biogenetic precursor of the other three alkaloids.

EXPERIMENTAL

Equipment and procedures were described in a preceding paper [5].

Isolation of euxylophoricine F. Si gel chromatography of the mother liquors of the crystallization of 1-hydroxyrutaecarpine afforded a single product (R_f 0.36; EtOAc–toluene–HCOOH, 4:5:1). Crystallization from C_6H_6–petrol gave pure euxylophoricine F mp 226°, as pale yellow needles. (Found: C, 68.34; H, 4.43; N, 12.72. $C_{19}H_{15}N_3O_3$ requires: C, 68.46; H, 4.54; N, 12.60%). MS (140°) *m/e* 333 ($M^{+\cdot}$, 100%), 332 (22%), 318 ($M^{+\cdot}$-Me, 15%), 166.5 (13%), metastable peaks at 303.6 (333 → 318) and 264.4 (318 → 290); ν_{max} 3300, 1650, 1630, 1580 and 1560 cm^{-1}; λ_{max} (MeOH) 247, 337, 347 and 364 nm (log ϵ 4.50, 4.48, 4.51 and 4.43); λ_{max} (MeOH + *N*NaOH) 304 nm; λ_{max} (MeOH + 6*N* HCl) 372 nm. Methylation (MeI–Me_2CO–K_2CO_3) gave material, identical in TLC, UV and MS with an authentic sample of N_{13}-methyleuxylophoricine A (**2**) [6].

Conversion of (**1**) *into 3-methoxyrutaecarpine* (**3**). 10 mg of euxylophoricine F was stirred at room temp. in 25 ml dry C_6H_6 with 5 mg of phenyl isocyanate in the presence of Et_3N until TLC showed disappearance of starting material. Removal of the solvent furnished a solid which was dissolved in 10 ml HOAc and hydrogenated in the presence of 10 mg of 10% Pd–C for 72 hr. Preparative TLC of the crude material