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A NEW INDOLOPYRIDOQUINAZOLINE IN THE BARK OF *EUXYLOPHORA PARAËNSIS*

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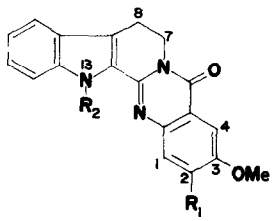
Several indolopyridoquinazoline alkaloids have been reported as constituents of the yellow bark of *Euxylophora paraënsis* Hub. (Rutaceae) [1–5]. Further investigation of the fraction containing 1-hydroxyrutaecarpine yielded a new related compound, euxylophoricine F, for which we now assign by spectroscopic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

gave 4 mg 3-methoxyrutaecarpine as confirmed by TLC and spectral data with an authentic sample [5].

Synthesis of 4-benzyloxy-5-methoxyanthranilic acid methyl ester. 4-benzyloxy-5-methoxy-2-nitrobenzaldehyde (prepared according to Julia *et al.* [9]) was oxidized in dioxane (20 ml) with a slight excess of Ag_2O (from 4.5 g $AgNO_3$ and 80 ml *N* NaOH) at 65°. After 30 min the mixture was filtered, the filtrate acidified and exhaustively extracted with $CHCl_3$. Evaporation of the solvent gave the crude nitro acid which was dissolved in dry MeOH, saturated with dry HCl. By refluxing for 2 hr, removal of the solvent and crystallization from petrol gave pure 4-benzyloxy-5-methoxy-2-nitro benzoic acid methyl ester, mp 135° as pale yellow needles. (Found: C, 60.22; H, 4.69; N, 4.41. $C_{16}H_{15}NO_6$ requires: C, 60.56; H, 4.77; N, 4.41%). ν_{max} (Nujol) 1745 and 1584 cm^{-1}; NMR ($CDCl_3$) δ 3.90 (3 H, *s*, OMe), 3.97 (3 H, *s*, COOMe), 5.22 (2 H, *s*, CH_2–Ph), 7.11 (1 H, *s*, C-6 H), 7.42 (*m*, 5 H; aromatic protons), 7.56 (1 H, *s*, C-3H). To 5 g of the aforementioned compound in 45 ml 10% HOAc was added 6 g reduced Fe powder portionwise over 1.5 hr. The mixture was heated at 80° and after 2 hr was poured into ice. Extraction with Et_2O and crystallization from *iso*-Pr_2O afforded 4-benzyloxy-5-methoxyanthranilic acid methyl ester (86%) as colourless needles, mp 138°. (Found: C, 66.67; H, 6.00; N, 4.72. $C_{16}H_{17}NO_4$ requires: C, 66.88; H, 5.96; N, 4.88%). ν_{max} (Nujol) 3485, 3370, 1682 and 1625 cm^{-1}; NMR ($CDCl_3$) δ 3.88 (3 H, *s*, COOMe), 5.18 (2 H, *s*, CH_2–Ph), 5.60 (2 H, *br s*, NH_2, exchanged with D_2O), 6.22 (1 H, *s*, C-3 H), 7.39 (1 H, *s*, C-6 H), 7.42 (5 H, *m*, aromatic protons).

Synthesis of 2-benzyloxy-3-methoxyrutaecarpine (**4**) 250 mg of 4-benzyloxy-5-methoxyanthranilic acid methyl ester and 120 mg of 1, 2, 3, 4-tetrahydronorharman-1-one in 100 ml of toluene were condensed in the presence of 120 mg of $POCl_3$[8]. 2-benzyloxy-3-methoxyrutaecarpine (**4**) was obtained in 43% yield as long needles, mp 250° (CH_2Cl_2). (Found C, 74.01; H, 5.09; N, 9.87. $C_{26}H_{21}N_3O_3$ requires: C, 73.74; H, 5.00; N, 9.92%). λ_{max} (MeOH) 254, 336, 351 and 369 nm (log ϵ 4.48, 4.48, 4.50 and 4.41); ν_{max} (Nujol) 3340, 3030, 1660, 1650 and 1460 cm^{-1}; NMR (C_5D_5N) δ 3.18 (2 H, *t*, *J* 7.0 Hz, C-8 H_2) 3.86 (3 H, *s*, OMe), 4.45 (2 H, *t*, *J* 7.0 Hz, C-7 H_2), *ca* 5.10 (obscured by H_2O, CH_2-Ph), 8.00 (1 H, *s*, C-4 H); NMR (CF_3COOH + 20% $CDCl_3$) 3.50 (2 H, *t*, *J* 7.0 Hz, C-8 H_2), 4.18 (3 H, *s*, OMe), 4.87 (2 H, *t*, *J* 7.0 Hz, C-7 H_2), 5.43 (2 H, *br s*, CH_2-Ph), 7.88 (1 H, *s*, C-4 H); MS (130°) at *m/e* 423 (M^+, 63%), 332 (M^+-CH_2Ph, 25%), 304 (26%), 91 (100%).

Hydrogenolysis of (**4**) *to euxylophoricine F.* A soln of 50 mg of (**4**) in 150 ml of EtOAc was stirred with 10 mg of 10% Pd–C in an atmosphere of H_2 at room temp. for 1 hr. The catalyst was filtered off and the solvent removed. Crystallization from C_6H_6–light petrol afforded 28 mg of pure euxylophoricine F (**1**), identical in TLC, mp, UV, IR spectra with the natural product.

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