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SHORT COMMUNICATION

NEW INDOLOPYRIDOQUINAZOLINE ALKALOIDS FROM *EUXYLOPHORA PARAËNSIS*

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Abstract—Two new indolopyridoquinazoline alkaloids euxylophoricine C (V) and euxylophorine B (VI), were isolated from the bark of *Euxylophora paraënsis* Hub. Their structures were elucidated on the basis of spectroscopic as well as chemical properties and confirmed by synthesis.

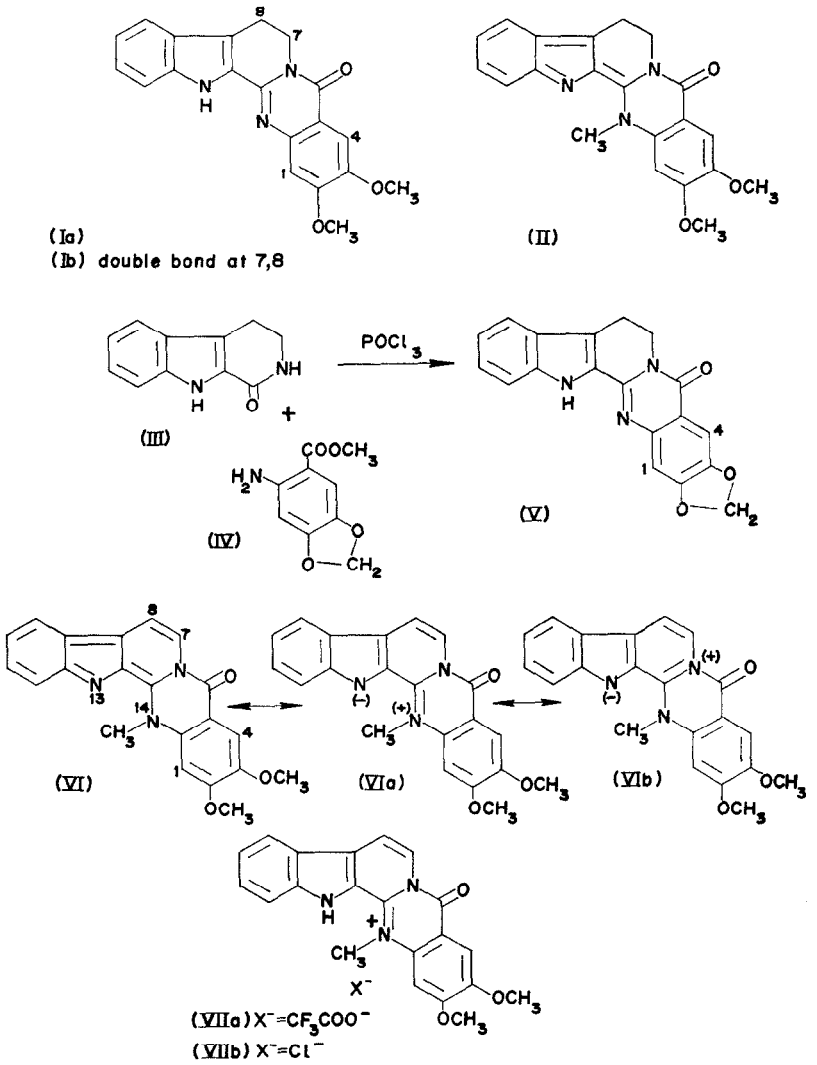
INTRODUCTION

FROM A methanolic extract of the thick, yellow bark of *Euxylophora paraënsis* Hub. (Rutaceae), a Brazilian forest tree, three alkaloids of the rare indolopyridoquinazoline group, i.e. euxylophoricine A (Ia), euxylophoricine B (Ib) and euxylophorine A (II), were isolated and identified.[1] Since very few alkaloids of this class are known,[2] it was of interest to investigate the other alkaloids of this plant. We now report the isolation, characterization and synthesis of two new indolopyridoquinazoline alkaloids, euxylophoricine C (V) and euxylophorine B (VI).

RESULTS AND DISCUSSION

The two alkaloids were isolated by alumina chromatography of the crude extract from the bark of *Euxylophora paraënsis* Hub. (see Experimental). Euxylophoricine C (V) was present in very small quantity; it was optically inactive, scarcely soluble in the common organic solvents and it crystallized from a large quantity of ethanol in yellowish crystals, m.p. 310–312°. From analytical and MS data, the molecular formula $C_{19}H_{13}N_3O_3$ was assigned to this compound. The peaks in the IR spectrum (Nujol) at 3350, 1655 and 940 cm^{-1} indicated the presence of a NH group, a tertiary amide function and a methylenedioxy group respectively. The UV maxima (CH_3CN) at 252, 337,350 and 368 nm (log ϵ 4·55, 4·50, 4·53 and 4·36) were in agreement with the presence of a strongly conjugated system. The NMR spectrum (CF_3COOH + 20% $CDCl_3$) showed two symmetrical triplets centered at δ3·58 and 4·32 corresponding to the $\equiv C—CH_2—CH_2—N=$ sequence; two singlets at

[1] L. CANONICA, B. DANIELI, P. MANITTO, G. RUSSO and G. FERRARI, *Tetrahedron Letters* 4865 (1968).
[2] M. HESSE, *Indolalkaloide in Tabellen*, p. 89, Springer-Verlag, Berlin (1964).



δ7·28 and 7·72 each one belonging to one aromatic proton; a complex signal of four aromatic protons between δ7·2 and 7·8; a singlet of two hydrogens at δ6·28 for a methylenedioxy group and a NH indolic group at δ10·60. The close similarity in spectroscopic properties with euxylophoricine A suggest that euxylophoricine C has structure (V), which was confirmed by synthesis.[3] Tetrahydronorharmanone-1 (III) was briefly refluxed in toluene with an excess of $POCl_3$. Addition of methyl 6-amino-3,4-methylenedioxybenzoate (IV) and heating at 110° for 3 hr, gave (V) identical in all respects to the natural product. Euxylophorine B (VI) crystallized from $CHCl_3$ in yellow orange needles, m.p. 268–271° dec., and it gave a strong yellow fluorescent spot on TLC in UV light. Analysis and MW were in agreement with the molecular formula $C_{21}H_{17}N_3O_3$. The alkaloid had no optical activity and showed UV maxima (CH_3CN) at 278 and 352 nm (log ϵ 4·47 and 4·70). The IR

[3] I. J. PACHTER, R. F. RAFFAUF, G. E. ULLYOT and O. RIBEIRO, *J. Am. Chem. Soc.* **82**, 5187 (1960).

spectrum (Nujol) exhibited no NH absorption, a carbonyl peak at 1690 and insaturation bands at 1618, 1605, 1555 and 1510 cm^{-1}. The NMR spectrum, carried out in CF_3COOH containing 20% of $CDCl_3$, corresponded to that of the trifluoroacetate of euxylophorine B (VIIa). It showed two singlets at δ4·30 and 4·22 for the two $—OCH_3$ groups; a slightly broad singlet at δ4·81 for the $—N—CH_3$ group; two singlets at δ8·05 and 7·37 for the two aromatic protons on the benzene nucleus bearing the two $—OCH_3$; a multiplet of four aromatic protons between δ7·4 and 8·3 and an AB system (J = 9 Hz) at δ9·34 and 8·32 attributed to the $\equiv C—CH=CH—N=$ sequence.[1]

Euxylophorine B formed a yellow hydrochloride (VIIb) from a methanolic solution containing HCl, m.p. 270–280° dec. Its IR spectrum (Nujol) showed peaks at 3320 (NH), 1710 (CO) and characteristic aromatic bands; the UV maxima (CH_3CN) were at 297, 335, 346 and 405 nm (log ε 4·28, 4·18, 4·53 and 3·85). Vacuum pyrolysis of the hydrochloride (VIIb) caused the elimination of methylchloride and allowed the isolation of euxylophoricine B (Ib) in good yield.

From all these data, structure (VI) was deduced for euxylophorine B and final proof was achieved by synthesis via dehydrogenation of euxylophorine A (II) with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in boiling benzene. Euxylophorine B is a further example of an anhydronium base and his structure can be adequately represented by resonance formulae such as (VI), (VIa) and (VIb).

EXPERIMENTAL

Capillary m.p. were uncorrected; NMR spectra were carried out at 60 Mc with TMS as internal standard; TLC were performed on silica gel; alumina Woelm was used for column chromatography.

Extraction and isolation. A 3·5-kg sample of dried ground bark of *Euxylophora paraënsis* Hub. was extracted at r.t. twice with 15 l. MeOH for 60 hr. The pooled methanolic solutions were concentrated to 1 l. and 100 ml were stirred with 150 ml of 5% aq. ammonia and extracted with two portions of 300 ml $CHCl_3$. The concentrated $CHCl_3$ solution was shaked twice with 200 ml of 5% HCl and the yellow solid of the mixed hydrochlorides removed by filtration. The crude hydrochloride (2·3 g) was stirred with 100 ml of 10% aq. NH_4OH and extracted with $CHCl_3$ (2 × 100 ml) to give 1·9 g of an orange red solid which after crystallization from $CHCl_3$ gave pure euxylophorine A.[1] The residue from the mother liquors of the above crystallization was chromatographed on 50 g of alumina II and eluted with benzene, benzene–acetone at increasing concentration of acetone up to 15% and then with benzene–acetone with 1% diethylamine. Fractions of 50 ml were collected and elution was followed by examining fractions by TLC.

Euxylophoricine C (V). The benzene eluates giving a single spot on TLC (eluent benzene–EtOAc, 17:3) were pooled and the solvent removed. The residue was crystallized from EtOH and gave 8 mg of pure (V) m.p. 310–312°. (Found: C, 68·91; H, 4·14; N, 11·93. $C_{19}H_{13}N_3O_3$ required: C, 68·88; H, 3·95; N, 12·68%.) M^+ 331; ν_{max} (Nujol) 3350, 1655, 1630, 1600, 1550 and 940 cm^{-1}; λ_{max} (CH_3CN) 252, 337, 350 and 368 nm (log ε 4·55, 4·50, 4·53 and 4·36); NMR (CF_3COOH + 20% $CDCl_3$): 3·58 δ (2H, t, J = 7 Hz, C-8$\underline{H}_2$), 4·82 (2H, t, J = 7 Hz, C-7$\underline{H}_2$), 6·28 (2H, s, $O—CH_2—O$), 7·28, s, C-1$\underline{H}$), 7·72 (1H, s, C-4$\underline{H}$), 7·2–7·8 (4H, m, aromatic protons), 10·60 (1H, broad s, N$\underline{H}$).

Synthesis of euxylophoricine C. To a solution of 230 mg of 1,2,3,4-tetrahydronorharmanone-1 in 70 ml of boiling toluene 0·14 ml of freshly distilled $POCl_3$ was added. The reaction mixture was stirred for 30 min and then 500 mg of methyl 6-amino-3,4-methylenedioxy benzoate was added. Heating was continued under reflux for 3 hr. The toluene layer was decanted and the residue treated with aqueous ammonia and $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, evaporated and the residue crystallized from EtOH to give 140 mg of synthetic euxylophoricine C, identical in all respects to the natural material.

Euxylophorine B (VI). The benzene–acetone–$NHEt_2$ (85:15:1) eluates gave a mixture of euxylophorine A and B. This mixture was rechromatographed on alumina and the fractions giving a single spot on TLC (EtOAc–$NHEt_2$, 19:1) with a strong yellow fluorescence at 350 nm, were mixed and solvent removed. The product (140 mg) crystallized from $CHCl_3$, m.p. 268–271° dec. (Found: C, 69·85; H, 4·65; N, 11·38. $C_{21}H_{17}N_3O_3$ required: C, 70·18; H, 4·77; N, 11·69%.) M^+ 359; ν_{max} (Nujol) 1690, 1618, 1605, 1555 and 1510 cm^{-1}; λ_{max} (CH_3CN) 278 and 352 nm (log ε 4·47 and 4·70); NMR (CF_3COOH + 20% $CDCl_3$): 4·22 δ (3H, s, $—OC\underline{H}_3$), 4·30 (3H, s, $—OC\underline{H}_3$), 4·81 (3H, broad s, $N_{14}—C\underline{H}_3$), 7·37 (1H, s, C—1$\underline{H}$), 8·05 (1H, s, C—4$\underline{H}$), 7·4–8·3 (4H, m, aromatic protons), 8·32 (1H, d, J = 9 Hz, C-8$\underline{H}$), 9·34 (1H, d, J = 9 Hz, C-7$\underline{H}$), 11·70 (1H, broad s, N_{13}-$\underline{H}$).

Euxylophorine B *hydrochloride* (VIIb). A solution of 100 mg of euxylophorine B in 100 ml MeOH was treated with a few drops of 5% HCl and left at r.t. for 1 day. The yellow precipitate was collected, crystallized from MeOH containing HCl, m.p. 270–280° dec. (Found: C, 62·87; H, 4·70; N, 10·26. $C_{21}H_{18}ClN_3O_3$ required: C, 63·80; H, 4·56; N, 10·62%.) ν_{max} (Nujol) 3320, 1710, 1615, 1580 cm^{-1}; λ_{max} (CH_3CN) 297, 335, 346 and 405 nm (log ϵ 4·28, 4·18, 5·43 and 3·85).

Conversion of euxylophorine B (VI) *into euxylophoricine B* (Ib). A sample of 20 mg of euxylophorine B HCl was sublimed at 260–270° at 0·01 mm until no more material was obtained. The sublimate (14 mg) was crystallized from $CHCl_3$-MeOH, m.p. 309–311°. There was no depression of the m.p. upon admixture with natural euxylophoricine B[1].

Synthesis of euxylophorine B. 150 mg of euxylophorine A, were dissolved in 250 ml C_6H_6 and treated with 160 mg of DDQ in 50 ml C_6H_6. The solution was boiled for 2 hr, then the solvent removed and the residue chromatographed on alumina. With C_6H_6–acetone–$NHEt_2$ (85:15:1) 35 mg of a product identical in all respect (TLC, m.m.p., UV) to natural euxylophorine B were eluted.

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Key Word Index—Euxylophora paraensis; Rutaceae; alkaloids; indolopyridoquinazolines; C and D, euxylophoricines.