A new tryptophan derived alkaloid from *Evodia rutaecarpa* (Juss.) Benth. et Hook

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Summary. The first tryptophan-derived indolopyridoquinazoline alkaloid has been isolated from the fruits of *Evodia rutaecarpa* (Jussieu) Bentham et Hook. Its structure is deduced on the basis of spectral data and enantioselective synthesis. The compound has been assigned the absolute configuration (7*S*,13b*S*)-7-carboxy-8,13,13b,14-tetrahydro-14-methylindolo[2′,3′:3,4]pyrido[2,1-b]quinazolin-5(7*H*)-one.

Although most indole alkaloids are formally derived from tryptamine, there have recently been discovered a rapidly expanding class of non-isoprenoid and monoterpenoid alkaloids, which retain the carboxylic group of their tryptophan precursor[1].

In continuation of our earlier studies[2] on the quinazoline alkaloids, we report on the isolation and structure determination of the first indolopyridoquinazoline alkaloid ascribable to this class of tryptophan-derived compounds. After isolating rutaecarpine and evodiamine by neutral alumina chromatography of the methanolic extract of the fruits of *E. rutaecarpa* (Juss.) Benth. et Hook, methylation (CH_2N_2, MeOH–$CHCl_3$, r.t., 24 h) of the acidic chromatographic residue and purification by repeated preparative TLC on silica gel (benzene:diethyl ether, 1:1, R_f 0.44) gave a small amount (8 mg from 3.5 kg of dried fruits) of an amorphous colourless compound $C_{21}H_{19}N_3O_3$ [by HRMS, M^+ m/e 361.1417 (M^+ calcd, m/e 361.1421)], $[\alpha]_D^{20°}+441°$ ($CHCl_3$, c 1), CD (MeOH) λ_{max} 227 ($\Delta\varepsilon+5.58$), 257 (+11.89), 284 (+2.05), 292 (+3.10), 315 (+3.20), to which the structure **Ib** was proposed on the basis of the following data.

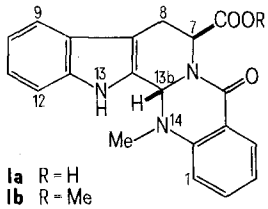
The UV-spectrum (MeCN) (λ_{max} 268, 281, 289 and 330 nm) was identical to that of evodiamine[3], pointing out the presence of an indolic chromophore and of an anthranilic one, both confirmed by ^{1}H-NMR signals (100 MHz, $CDCl_3$), 7 aromatic protons between δ 7.10–7.70, 1 aromatic proton as dd (J_1 8.0 Hz, J_2 1.5 Hz) at δ 8.16 and N*H* at δ 8.41. Besides a tertiary amide band at 1665 cm^{-1} and a NH-band at 3475 cm^{-1}, the IR-spectrum ($CHCl_3$) showed a carbomethoxy group (1745 cm^{-1}), also confirmed by a signlet at δ 3.59 in the NMR-spectrum. The mass spectrum (EI, 70 eV, 100°) of **Ib** supported strongly an evodiamine-type structure, showing peaks at m/e 134 (a) arising from N-methylanthranilic moiety, while fragments at m/e 302 (M^+-CO_2Me), 300 (M^+-CO_2Me-2H), 229 (b), 201 (c) were reminiscent of a tetrahydro-β-carboline substituted at α-position to N_b by a carbomethoxy group[4]. Furthermore, the NMR-spectrum showed a singlet for a N–C*H*$_3$ group at δ 2.46, a broad singlet ($W_{1/2}$, 3 Hz) at δ 6.22 for C-13b*H* and a typical ABX pattern at δ 3.22 (J_{AB} 16.0 Hz, J_{AX} 6.0 Hz), 3.55 (J_{AB} 16.0 Hz, J_{BX} 1.5 Hz), 5.76 (J_{AX} 6.0 Hz, J_{BX} 1.5 Hz) for C-8*Hα*, C-8*Hβ* and C-7*H*. Both C-8*Hα* and C-8*Hβ* signals exhibited a similar additional homobenzylic coupling ($^5J \sim 1.5$ Hz) with C-13b*H*, as confirmed by double resonance experiments.

The shielding and coupling constant values for the ABX system signals were accounted for only by assuming an axially oriented CO_2Me group and an equatorially oriented C-7*H* deshielded by the coplanar amidic carbonyl neighbouring group.

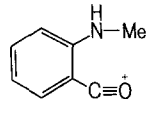
The carbomethoxy group localization at the C-7 and the absolute configuration of this centre were provided by synthesizing **Ib** from (3*S*)-3-carbomethoxy-4,9-dihydro-3*H*-pyrido[3,4-b]indole hydrochloride and N-methylanthranilic acid in THF containing 1 equiv. of pyridine in the presence of PPh_3-CBr_4[5]. A priori, one might have expected 2 C-13b epimeric compounds to obtain but, interestingly enough, only the 'natural' stereoisomer was formed (25% yield) under these mild conditions.

The observed stereospecificity could be explained on the basis of the steric and stereoelectronic requirements of the transition state(s). The carbomethoxy group of the tetrahydro-β-carboline from the β-equatorial to the β-axial orientation by the severe nonbonded interactions with the amide carbonyl group and, by analogy to the addition stereochemistry to olefinic type double bond, the $NHCH_3$ attack took place on the face opposite to the closer carbomethoxy group. **Ib** was recovered unchanged after basic- (MeONa, MeOH, r.t., 5 h) and acid-catalyzed (AcOH, reflux, 6 h) equilibrations suggesting that all the steric dipolar interactions and orbital overlap requirements were favorable only in the C-13b-βH epimer. Hence the structure **Ib** of (7*S*, 13b*S*)-7-carbomethoxy-8,13,13b,14-tetrahydro-14-methylindolo[2′,3′:3,4]pyrido[2,1-b]quinazolin-5(7*H*)-one is suggested for the isolated methyl ester, the naturally occurring carboxy alkaloid being **Ia**.

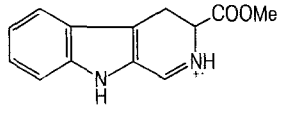
Work is continuing to confirm the proposed absolute configuration at C-13b[7] and to search for a more efficient synthetic way to **Ib**.



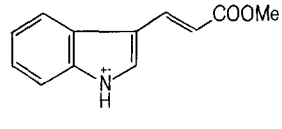
Ia R = H
Ib R = Me



a



b



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7 In this case it was not possible to establish the absolute configuration at C-13b by utilization of CD data (as for the yohimbine and heteroyohimbine alkaloids[6]) because the dipolar coupling between the electronic transitions of the indolic and anthranilic chromophores perturbed the Cotton effect sign in an unpredictable way.