# The Configuration of (+)-Evodiamine: a Long-standing Problem in the Chemistry of Indole Alkaloids

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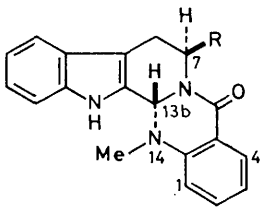
The absolute configuration (*S*) of the long-known indole alkaloid (+)-evodiamine (**1**) has been established by correlation with (*S*)-tryptophan *via* (7*S*,13b*S*)-carboxyevodiamine (**2**).

(+)-Evodiamine (**1**) was isolated more than sixty years ago[1] from the unripe fruits of *Evodia rutaecarpa* (Juss.) Benth. et Hook (Rutaceae), one of 365 ancient drugs described in 'Sheng Nung Pênts'ao Ching,' the prototype Chinese herbal.[2] The quinazolinocarboline (**1**) is one of the few optically active indole alkaloids possessing only one stereocentre and, despite extensive studies, the absolute configuration is as yet undetermined. The lability of (**1**) towards acids and oxidising agents[3] thwarted a delineation of the stereochemistry at C-13b by degradative experiments. Furthermore, no stereochemical information can be deduced with confidence from the c.d. spectra (250—300 nm) owing to the unpredictable dipolar coupling between the indole and anthranilic electronic transitions ($^1L_b$ and $^1L_a$). Herein we report the determination of chirality for (**1**) by correlation with the natural product carboxyevodiamine (**2**),[4] which is assigned the (7*S*,13b*S*)-configuration.

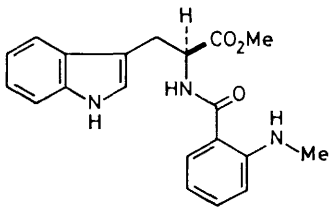
The amide (**3**) [m.p. 130 °C; $^1$H n.m.r. δ ($CDCl_3$) 2.79 (d, *J* 5 Hz, NMe), 3.68 ($CO_2Me$), and 5.04 (dt, *J* 7 and 5 Hz, H-7)], available by diphenylphosphoryl azide-promoted coupling[5] of (*S*)-tryptophan methyl ester hydrochloride and *N*-methylanthranilic acid [dimethylformamide (DMF), *N*-methylmorpholine, room temp., 20 h], was subjected to amidomethylenation *via* the agency of *N*,*N*-dimethylmethyleneammonium chloride[6] [tetrahydrofuran (THF), 40 °C, 15 min] to give the dihydroquinazolinone (**4**) [$^1$H n.m.r. δ ($CDCl_3$) 2.53 (NMe), 3.65 ($CO_2Me$), and 4.32 and 4.45 (AB system, *J* 17 Hz, $NCH_2$-N)]. Compound (**4**) underwent dehydrogenation and concurrent cyclisation on treatment with $Hg(OAc)_2$–$Na_2$(edta) (edta = ethylenediaminetetra-acetate) in AcOH–$H_2O$ (9:1) (90 °C, 2 h) to give the product (**5**)† together with its 13b-epimer (**6**)‡ with 10:1 selectivity in 82% overall yield. The transformation of (**3**) into a 6:4 diastereomeric mixture of (**5**) and (**6**) was performed in a single step (62%) using neat trimethyl orthoformate in the presence of $NH_4Cl$ as catalyst (50 °C, 1 h). The $^1$H n.m.r. values for H-7 in (**5**) and (**6**) are those expected for pseudo-equatorial *vs.* pseudo-axial protons in half-chair systems, respectively, and the 1,3-*cis*-arrangement of H-7 and H-13b in (**6**) was verified by a maximum enhancement of 6% in an H-7 {H-13b} nuclear Overhauser experiment. The relief of the unfavourable dipolar and steric interactions ($A^{1,2}$-strain) between coplanar $CO_2Me$ and amide carbonyl causes a rapid equilibration of (**6**) in AcOH (100 °C) to give the thermodynamic product (**5**). Thus, (7*S*,13b*S*)- and (7*S*,13b*R*)-stereochemistries are assigned to (**5**) and (**6**), respectively. Compound (**5**), on mild hydrolysis ($BBr_3$, $CH_2Cl_2$, −20 °C,

† Compound (**5**): $^1$H n.m.r. δ (200 MHz, $CDCl_3$) 3.22 (H-8α), 3.56 (H-8β), 5.88 (H-7), and 6.23 (H-13b) (ABXY system: $J_{AB}$ −16.2, $J_{AX}$ 6.6, $J_{AY} = J_{BX}$ 2.0, $J_{BY}$ 1.5, and $J_{XY}$ 0 Hz, calculated by iterative analysis using the program PANIC); $^{13}$C n.m.r. δ ($CDCl_3$) 23.0 (C-8), 36.7 (NMe), 52.1 (C-7), and 67.9 p.p.m. (C-13b).

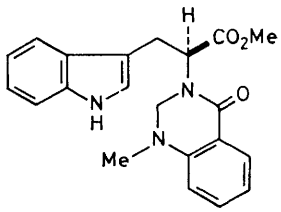
‡ Compound (**6**): m.p. 265 °C ($CHCl_3$–$Pr^i_2O$); c.d., nm (Δε), 226 (−10.8), 250 (−2.2), 254 (−2.8), 272 (+1.6), 284 (+0.4), 289 (+1.0), 292 (0), and 300 (+1.2); $^1$H n.m.r. δ ($CDCl_3$) 2.90 (NMe), 3.18 (H-8α), 3.64 (H-8β), 5.23 (H-7), and 5.69 (H-13b) (ABXY system: $J_{AB}$ −16.5, $J_{AX}$ 6.8, $J_{AY}$ 1.5, $J_{BX}$ 4.8, $J_{BY}$ 1.0, and $J_{XY}$ 0 Hz), 3.68 ($CO_2Me$), 8.08 (dd, *J* 8 and 3 Hz, H-4), and 8.40 (NH); $^{13}$C n.m.r. δ ($CDCl_3$) 22.3 (C-8), 37.4 (NMe), 53.6 (C-7), and 69.6 p.p.m. (C-13b).



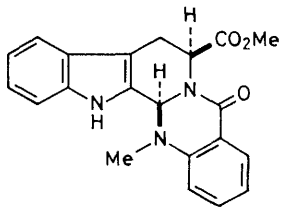
(1) R=H
(2) R=$CO_2H$
(5) R=$CO_2Me$
(7) R=CN



(3)



(4)



(6)

1 h), gave the product (**2**) [$^1$H n.m.r. δ ($CDCl_3$) 2.44 (NMe), 5.76 (dd, *J* 6 and 2 Hz, H-7), and 6.18 (s, H-13b); c.d., nm (Δε), 257 (+11.6), 282 (+1.8), 285 (+2.1), 288 (+1.7), and 293 (+3.0)] which was converted with chlorosulphonyl isocyanate[7] ($CH_2Cl_2$, DMF, 0 °C, 2 h) into the corresponding nitrile (**7**) which on reductive decyanation[8] ($NaBH_4$, diglyme, 60 °C, 20 h) gave (+)-evodiamine (**1**)§ [c.d., nm (Δε), 257 (+6.25 *vs.* +7.81 in natural evodiamine), 280 (+1.17, +1.50), 284 (+1.60, +1.90), 287 (+1.20, +1.50), and 292 (+1.95, +2.60)] in 28% overall yield.

The occurrence of (+)-(**2**) and (+)-evodiamine (**1**) together in *Evodia rutaecarpa* (with the same 13b*S* configuration) suggests that (*S*)-tryptophan is a reasonable precursor of (**1**) and that the decarboxylation occurs in a later step.[9]

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§ The synthetic material had $R_F$, $^1$H n.m.r., and mass spectroscopic data identical to those of the natural product. In independent experiments it was established that C-13b in (**1**) had not suffered epimerization during the three-step sequence.