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TOTAL SYNTHESIS AND STRUCTURE REINVESTIGATION OF SO-CALLED ISOCHIMONANTHINE

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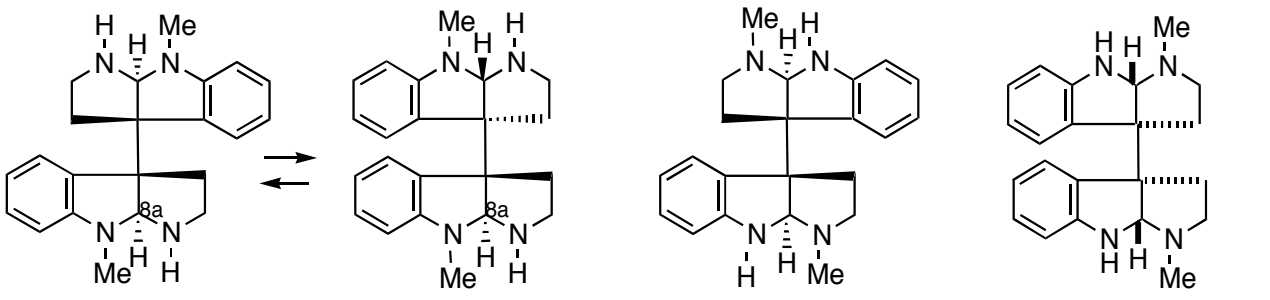
Abstract – The data for the proposed structure of isochimonanthine, a dimeric pyrrolidinoindoline alkaloid that was synthesized from tryptamine, were not identical with those of the natural product. Careful structure reinvestigation led to the conclusion that the so-called isochimonanthine was a *ca*. 1:1 mixture of (+)-chimonanthine and *meso*-chimonanthine.

Several dimeric pyrrolidinoindoline alkaloids,[1] such as chimonanthine and folicanthine, have been isolated from plants belonging to Calycanthaceae, Idiospermaceae, and Rubiaceae, as well as from dendrobatid frog. In our continuous chemical studies on the indole alkaloids of this type,[2-4] we have been interested in the structure of (+)-isochimonanthine (**1**), which was isolated from an Indonesian rubiaceous plant, *Argostemma yappii*.[5] The structure of (+)-isochimonanthine,[6] which was proposed based on spectroscopic data, was characterized by the unique behavior that it assumed two conformers in the ratio of 53:47 in solution at low temperature. To confirm the structure and to inspect this interesting phenomenon, we initially planned the total synthesis of a racemic compound.



1a **1b**

(+)-Isochimonanthine (**1**) (reported)

(+)-Chimonanthine (**2**)

meso-Chimonanthine (**3**)

Figure 1

For the synthesis of **1**, the dimerization of indole derivatives with hypervalent iodine (III) reagent, which was recently developed by us,[2] was applied. N_a-methyl-N_b-trimethylsilylethoxycarbonyl (Teoc) tryptamine (**5**), prepared from known compound (**4**),[7] was treated with 0.5 equiv. of iodobenzene bis(trifluoroacetate) (PIFA) and 0.5 equiv. of $NaHCO_3$ in CF_3CH_2OH at –40°C to give two separable dimerization products (**6**) and (**7**) in 36% and 17% yields, respectively. Their relative stereochemistry was elucidated by transformation into known compounds. Thus, on reduction with Red-Al in toluene, more polar product (**6**) gave *meso*-folicanthine (**8**), whereas less polar product (**7**) gave *rac*-folicanthine (**9**),[8] revealing the relative stereochemistry of the two dimerization products. For the completion of the total synthesis of **1**, racemate (**7**) was employed for further transformation. Removal of the two protective groups on nitrogen with tetrabutylammonium fluoride (TBAF) in THF gave target molecule (**1**) in the racemic form in 75% yield. However, the NMR spectral data of synthetic **1**[9] were different from those in the literature, in which a pair of signals of each proton and carbon (for example, 8a; δ_H 4.32 and 5.08, δ_C 83.07 and 82.29) in the molecule of **1** was reported. The authors claimed that this phenomenon was ascribed to the presence of two stable conformers (**1a**) and (**1b**) in solution, as shown in Figure 1. However, the chemical shifts of the *N*-Me groups (δ_H 2.32 and δ_H 2.46) in the literature, both of which were assigned to the methyl group on the nitrogen of aniline function, suggested that these groups existed on aliphatic nitrogen atoms, similar to chimonanthines (**2** and **3**). This led us to suppose that the isolated natural compound is a mixture of (+)-chimonanthine and *meso*-chimonanthine. To examine this possibility, we prepared a mixture of (–)-chimonanthine, which was isolated from *Chimonanthus praecox*,[3] and *meso*-chimonanthine[2] in the ratio of 1:1 and measured its ^{1}H- and ^{13}C-NMR spectra under the same conditions (in $CDCl_3$ at –25°C) as those in the literature, and obtained exactly the same NMR spectral data as those described in the report. As a result, we concluded that the isolated crystals named "isochiminanthine" were composed of (+)-chimonanthine and *meso*-chimonanthine in the ratio of *ca.* 1:1.

ACKNOWLEDGEMENTS

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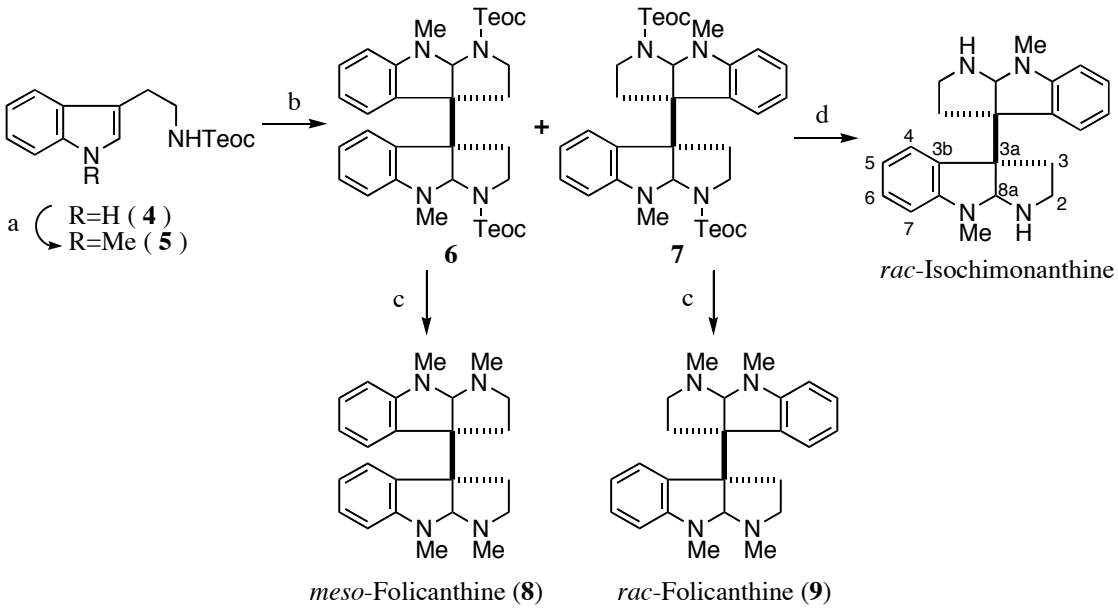

Scheme 1: *reagents and conditions* (a) MeI, NaH, DMF, -20ºC, 94%. (b) 0.5 equiv. PIFA, 0.5 equiv. $NaHCO_3$, CF_3CH_2OH, -40ºC; **6** : 36%, **7** : 17%. (c) Red-Al, Toluene, reflux; **8** : 96%, **9** : 95%. (d) TBAF, THF, rt, 75%

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9. Spectral data for synthetic **1** (amorphous powder): UV (MeOH) λ_{max}: 312, 254, and 209 nm. IR (neat) ν_{max}: 1602, 1496, and 735 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ [ppm]: 7.16 (2H, d, *J*=7.1, H-4 or H-7), 7.08 (2H, dd, *J*=7.5, 7.5, H-5 or H-6), 6.57 (2H, dd, *J*=7.4, 7.4, H-5 or H-6), 6.29 (2H, d, *J*=7.9, H-4 or H-7), 4.38 (2H, br-s, H-8a), 2.99 (2H, m), 2.80 (6H, s, N_1-C$\underline{H}_3$), 2.46 (4H, m), 2.14 (2H, m), 1.72 (2H, br-s, N_8-$\underline{H}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ [ppm]: 152.6, 131.4, 128.5, 124.2, 116.0, 104.8 (C-3b, C-4, C-5, C-6, C-7, C-7a), 87.5 (C-8a), 62.1 (C-3a), 45.8 (C-2), 38.7 (C-3), 31.1 (N_1-C$\underline{H}_3$). FAB-MS (NBA) *m/z*: 346 [M^+]. HR-FABMS (NBA/PEG): calcd for $C_{22}H_{26}N_4$ [M^+], found: 346.2130.