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On the Indole Alkaloid, Nauclefidine; Structure Revision, Synthesis, and a Biomimetic Transformation from the Vincoside Lactam.

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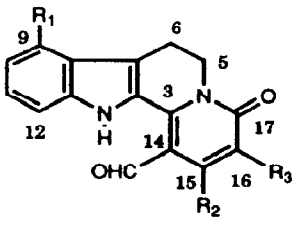
Abstract: The structure of a *Nauclea* indole alkaloid, nauclefidine, was revised as formula **12** based on synthetic studies and the biomimetic transformation of the vincoside lactam (**14**) based on the suggested biogenetic route.

In the course of our study on *Mitragyna speciosa* (Rubiaceae),[1] the leaves of which have been known for their narcotic-like properties in traditional use in Thailand, we have become interested in the chemical structures as well as the pharmacological properties of the novel indole alkaloids, corynantheidaline (**1**) and mitragynaline (**2**), isolated from the leaves of Malaysian *Mitragyna speciosa*.[2] To establish the efficient and general synthetic route of the basic skeleton of these alkaloids, we have initiated the synthesis of a simple alkaloid, nauclefidine (**3**).[3] This has been isolated from *Nauclea officinals*, which has been used as an anti-inflammatory and antibacterial agent in folk medicine in China, and the structure was elucidated by spectroscopic analysis. In this paper, we describe the synthetic study as well as the biogenetic consideration of nauclefidine, which led us to revise the structure of nauclefidine as formula **12**.



1: R_1=H, R_2=CO_2Me, R_3=Et
2: R_1=OMe, R_2=CO_2Me, R_3=Et
3: R_1=R_2=R_3=H

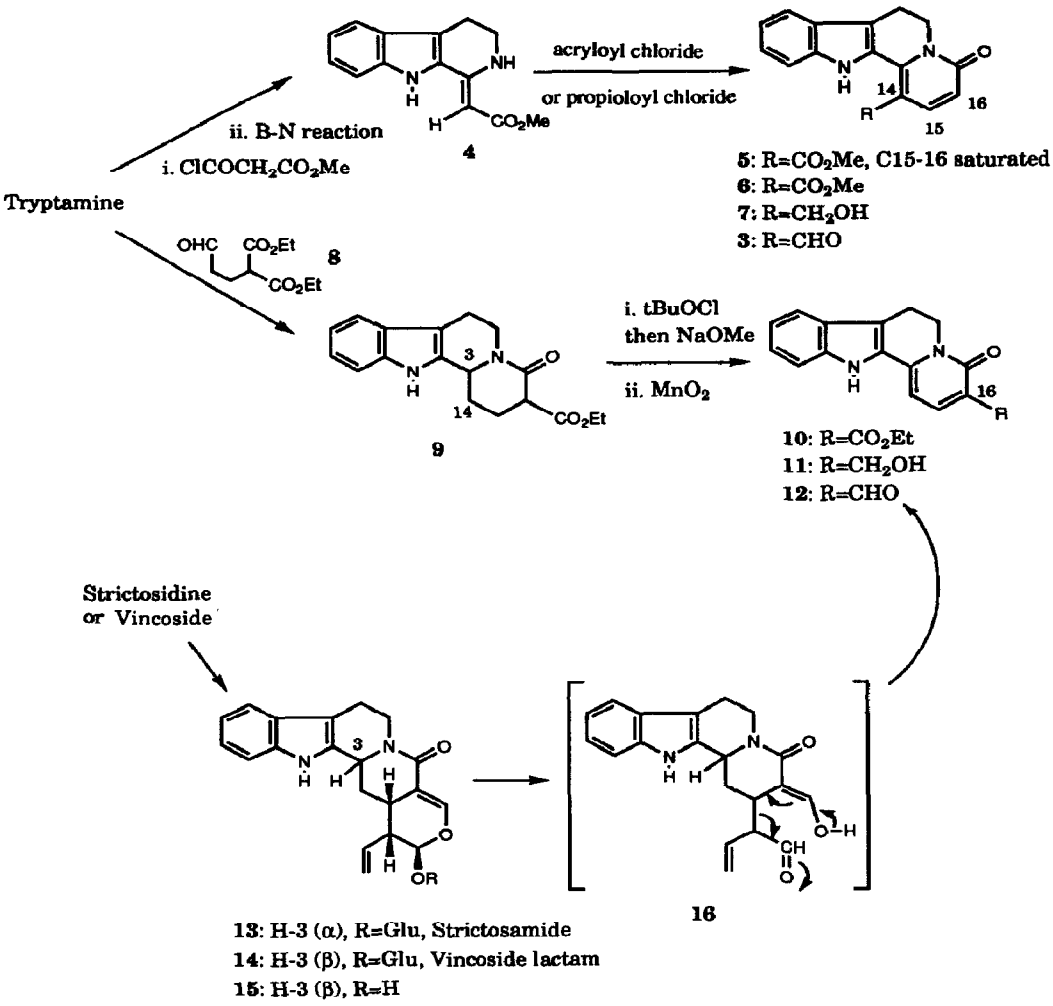
The pyridone ring skeleton possessing a C1 unit (formyl group) at the C-14 position in formula **3** was prepared as follows. Reaction of tryptamine with $ClCOCH_2CO_2Me$ gave the amide,[4] which led to the enamine (**4**) (mp. 148-152°C) by the Bischler-Napieralski reaction. The enamine (**4**) was condensed with acryloyl chloride under the two phase conditions (1N NaOH aq, benzene, cat. n-Bu_4NHSO_4, rt) to afford the dihydropyridone[5] derivative (**5**) (mp. 149-152°C) in 73% yield. The use of propioloyl chloride[6] instead of acryloyl chloride under the same conditions gave the desired pyridone compound (**6**) (mp. 146-151°C) in 52% yield. The ester group at C-14 was converted to the aldehyde through DIBALH reduction (y. 80%) and then oxidation of the resultant primary alcohol (**7**) with activated MnO_2 (y. 88%). However, the synthetic compound (**3**)[7] was not identical with the natural nauclefidine in terms of mp, behavior on TLC, UV, IR, and NMR spectra.

Another structure (**12**) for nauclefidine, which would satisfy the spectroscopic data of the natural product, was suggested as a possible alternative. Especially, the unusual absorption maximum in the long wave region (439 nm, log ε: 4.44) in the UV spectrum of natural nauclefidine could be interpreted by structure (**12**) rather than **3**. Furthermore, from a biogenetic point of view, structure **12** seemed to be quite reasonable. Thus, this simple indole alkaloid could also be derived from strictosidine or related compounds, like the common monoterpenoid indole alkaloids.[8] From the fragmentation in the aglycone of strictosamide (**13**) or the vincoside lactam (**14**), the C4 unit was eliminated and subsequent oxidation (aromatization) of the D-ring would produce nauclefidine (**12**).

To prove this structure, the total synthesis of **12** was initially carried out. The lactam-ester (**9**) was prepared by Pictet-Spengler cyclization of tryptamine and the aldehyde (**8**).[9] The double bond was introduced to the C3-C14 position in **9** by oxidation with *t*-BuOCl followed by treatment with NaOMe in MeOH[10] to yield the dihydropyridone derivative (mp. 221.5-224°C) in 74% yield. The D-ring was further oxidized with activated MnO_2 to afford the pyridone derivative (**10**) (mp. 277-281°C) in 81% yield. Finally, the ester group at the C-16 position was transformed to the aldehyde *via* the reduction (DIBALH, y. 71%)-oxidation (MnO_2, y. 89%) sequence. The direct comparison (mp., TLC, UV, MS, ^{1}H-NMR) of the synthetic **12**[11] and natural product fully confirmed its identity. The structure of nauclefidine has now been determined as 4,6,7,12-tetrahydro-4-oxo-indolo[2,3-*a*]quinolizine-3-carboxaldehyde.

In keeping with the above biogenetic speculation, vincoside lactam aglycone (**15**),[12] corresponding to a plausible biogenetic precursor of (**12**), was heated with 10% aqueous sulfuric acid in dioxane for 5.5 h. Through the elimination of the crotonaldehyde unit and subsequent auto-oxidation of the D-ring, nauclefidine (**12**) was produced in 15% yield, which was identical with the natural product in all respects (mp, TLC, UV, MS, and ^{1}H-NMR spectra). This result chemically supports our biogenetic hypothesis of nauclefidine.

Based on this knowledge, further synthetic studies of *Mitragyna* alkaloids are currently under way in this laboratory.



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7) Selected data for compound **3**: mp. 184.5-186°C (from EtOAc); IR ν_{max} (KBr) 3200, 1640 cm^{-1}; UV λ_{max} (EtOH) 212 (4.37), 228 (4.37), 300 (4.09), 389 (4.30) nm; MS m/z (%), 264 (M+, 100), 249 (56), 235 (38), 206 (23), 178 (12); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 12.66 (1H, s, NH), 9.59 (1H, s, CHO), 7.70 (1H, d, *J* 9.4 Hz, H-15), 7.63 (1H, dd, *J* 8.0, 1.0 Hz, H-9), 7.52 (1H, dd, *J* 7.7, 1.0 Hz, H-12), 7.37 (1H, ddd, *J* 8.0, 7.7, 1.0 Hz, H-11), 7.18 (1H, ddd, *J* 8.0, 7.7, 1.0 Hz, H-10), 6.56 (1H, d, *J* 9.4 Hz, H-16), 4.58 (2H, t, *J* 7.2 Hz, H_2-5), 3.14 (2H, t, *J* 7.2 Hz, H_2-6); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 190.1 (CHO), 161.8 (C-17), 144.8 (C-3), 144.3 (C-15), 137.7 (C-13), 126.7 (C-11), 126.6 (C-2), 124.4 (C-8), 120.9 (C-10), 119.97 (C-7), 119.96 (C-9), 116.2 (C-16), 113.0 (C-12), 111.2 (C-14), 42.2 (C-5), 19.3 (C-6).

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11) ^{13}C-NMR data of **12**: (125 MHz, DMSO-d_6) δ; 188.6 (CHO), 161.7 (C-17), 144.5 (C-3), 140.3 (C-15), 139.2 (C-13), 126.9 (C-2), 125.4 (C-11), 124.9 (C-8), 120.7 (C-16), 120.17 (C-9 or C-10), 120.16 (C-10 or C-9), 117.4 (C-7), 112.2 (C-12), 100.1 (C-14), 18.8 (C-6), (The signal at C5 is concealed by the solvent peak.).

12) The aglycone (**15**) was obtained by enzymatic hydrolysis of the vincoside lactam (**14**). Aimi, N.; Shito, T.; Fukushima, K.; Itai, Y.; Aoyama, C.; Kunisawa, K.; Sakai, S.; Haginiwa, J.; Yamasaki, K. *Chem. Pharm. Bull.* **1982**, *30*, 4046.

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