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Structure revision of mitragynaline, an indole alkaloid in *Mitragyna speciosa*

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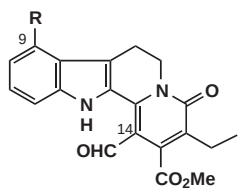
Abstract—The structure of mitragynaline, an indole alkaloid isolated from Malaysian *Mitragyna speciosa*, was revised as formula **3** by analysis of the NMR spectra measured at low temperature and by chemical transformation with DDQ oxidation from the known alkaloid mitragynine (**5**).

An indole alkaloid, mitragynaline, was first isolated from the young leaves of Malaysian *Mitragyna speciosa* Korth. (Rubiaceae),[1] which is a plant used in traditional medicine in the Malay Peninsula, is used as a stimulant like coca or as a substitute for opium.[2] The chemical structure of mitragynaline (**1**), proposed in 1991, has an unusual skeleton featuring the presence of a carbon function at the C-14 position, among the hitherto known indole alkaloids found in higher plants (Fig. 1). During the chemical[3] and pharmacological[4] studies on the *Mitragyna* alkaloids, we have had a keen interest in this structurally unique alkaloid from both synthetic and biological viewpoints. Along this line, we commenced a chemical study on the structure of nauclefidine,[5] whose UV spectrum had been used for the structure elucidation of mitragynaline. As a result, we have revised the structure of nauclefidine[6] and, therefore, structure re-elucidation of mitragynaline became an urgent objective. In this communication, we propose a new structure of mitragynaline, revised by exhaustive NMR analysis and by partial synthesis from mitragynine (**5**)[3a,b,7] via an abnormal oxidative reaction.

Mitragynaline ($C_{22}H_{24}N_2O_4$, $[\alpha]_D^{24}$ –4.3 (*c* 0.34, $CHCl_3$)),[8] which was obtained by reinvestigation of the young leaves of *M. speciosa* native to Malaysia, showed weak signals in the ^1H and ^{13}C NMR spectra when measured at ambient temperature in $CDCl_3$. As shown in Fig. 2, some widely swollen signals in the downfield area were observed in the ^1H NMR spectrum. In the ^{13}C NMR spectrum, only 16 signals, including some tiny peaks, were observed although the presence of 22 carbons in the molecule was demonstrated by the high-resolution MS spectrum. When the solvent was changed to DMSO-d_6, two clear signals (δ 11.7 and 9.8) appeared in the downfield region in the ^1H NMR spectrum. Further, the ^{13}C signals also sharpened generally, but only 7 and 13 signals were observed in the sp^3 and sp^2 areas, respectively.

Consequently, the NMR spectra of mitragynaline was measured at low temperature (–50°C) in $CDCl_3$, resulting in the appearance of all the proton and carbon signals corresponding to the molecular formula. The presence of a 9-methoxyindole nucleus, an ethane bridge at C-5–C-6, an ethyl group at C-20, an sp^3



R=OMe : mitragynaline (**1**)
R=H : corynantheidaline (**2**) (Published Structures)

Figure 1.

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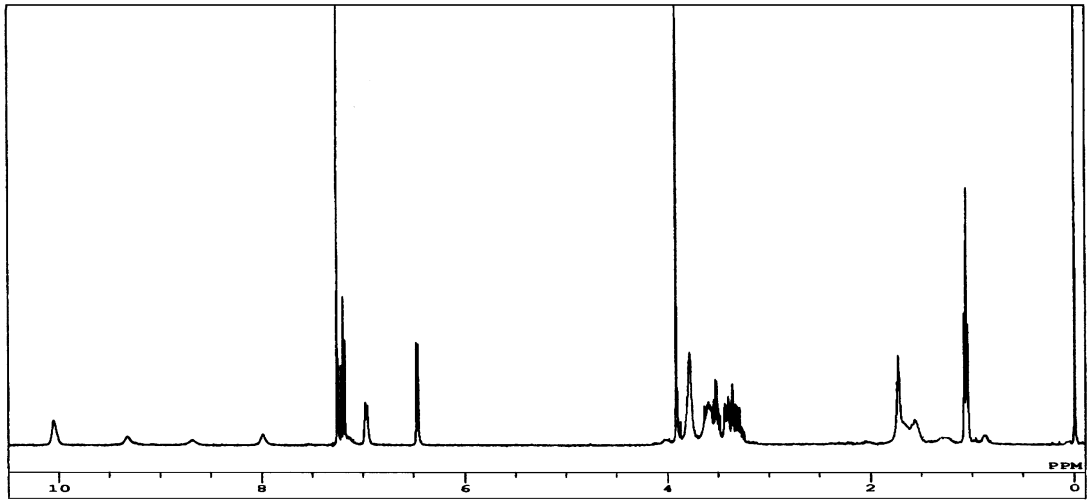

Figure 2.

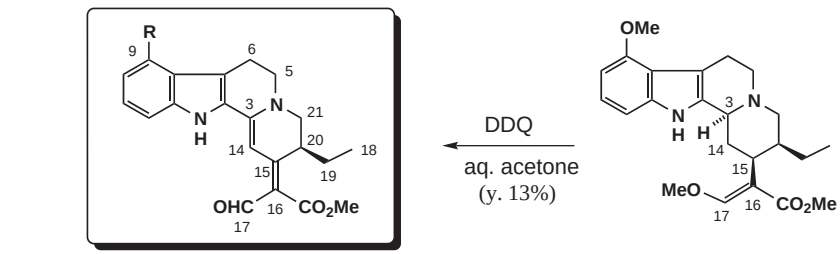

Figure 3.

carbon at C-21, and a methoxycarbonyl group, all of which are the fundamental structural units in the common Corynanthe-type monoterpenoid indole alkaloids, has been clarified. The ^{13}C NMR and HMBC spectra at low temperature disclosed the presence of six conjugated sp^2 carbons including ester and aldehyde carbonyls, besides the aromatic carbons due to the indole nucleus. The UV spectrum, exhibiting an absorption at 486 nm, also indicated a high degree of unsaturation in the molecule. The quite characteristic proton signal observed at δ 8.28 (1H, singlet), which was finally recognized at low temperature, was unambiguously assigned to be the proton at C-14 by the HMQC spectrum, since this signal has HMBC connectivities with the C-2, C-3, C-15, C-16 and C-20 carbons. The HMBC correlation between the aldehyde proton at δ 10.0 and the carbons at C-15 and C-16 indicated the location of the aldehyde residue at C-17. All the above findings, as well as biogenetic considerations, enabled us to compose the molecular structure of the mitragynaline to be that of **3**. The geometry at C-16 was elucidated by NOE observation between H-14 and the aldehyde proton.

Recently, we have demonstrated the potent opioid agonistic properties of mitragynine (**5**), a major indole alkaloid of this plant, and of mitragynine pseudoindoxyl, an oxidative derivative of mitragynine, whose analgesic activity is more potent than that of morphine.[9] Based on these results, we studied the preparation of various kinds of oxidative derivatives of mitragynine for the development of new and potent analgesic agents. When mitragynine (**5**) was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), we obtained unexpectedly mitragynaline in 13% yield as one of the oxidation products (Fig. 3). The semi-synthetic compound (mp 220–221°C) was identified with the natural product by comparison of their chromatographic behaviors, UV, ^1H and ^{13}C NMR, and mass spectra. The optical rotation of the semi-synthetic compound was levorotatory ($[\alpha]_D^{24}$ −2.4 (*c* 0.45, $CHCl_3$)), establishing the absolute stereochemistry at the C-20 position. Although the DDQ oxidation of indole derivatives is generally known to produce 3-acylindole derivatives,[10] the mechanism of this abnormal reaction, including the oxidative double bond formation at the C-3–C-14 position, demethylation of the vinyl ether moiety in **5**, and additional oxidation at the C-15–C-16 position, remains obscure.

Corynantheidaline (**2**) has been simultaneously isolated from *M. speciosa* together with mitragynaline and the structure was proposed as a H-9 analogue of **1**. Based on the spectroscopic comparison of these two compounds, here we propose the new structure **4** as corynantheidaline.

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8. Mitragynaline (**3**): $[\alpha]_D^{24}$ −4.3 (*c* 0.34, $CHCl_3$); UV (MeOH) λ_{max} (log ε): 486 (4.83), 456 (sh 4.62), 348 (3.97), 264 (4.30), 224 (sh 4.39) nm; EIMS *m*/*z* (%): 380 (M^+, 100), 351 (33), 323 (35), 291 (31). HR-FABMS (NBA): calcd for $C_{22}H_{25}N_2O_4$ (MH^+) 381.1790, found: 381.1814; ^1H NMR (600 MHz, $CDCl_3$, −50°C) δ: 12.44 (1H, s, *N*a-H), 10.03 (1H, s, H-17), 8.28 (1H, s, H-14), 7.21 (1H, dd, J=8.0, 8.0, H-11), 7.02 (1H, d, J=8.0, H-12), 6.45 (1H, d, J=8.0, H-10), 3.93 (3H, s, 9-OCH_3), 3.71 (3H, s, CO_2CH_3), 3.82 and 3.68 (each 1H, m, H_2-21), 3.59 and 3.52 (each 1H, m, H_2-5), 3.54 (1H, m, H-20), 3.43 and 3.35 (each 1H, m, H_2-6), 1.75 and 1.59 (each 1H, m, H_2-19), 1.10 (3H, t, J=6.9, H_3-18); ^{13}C NMR (150 MHz, $CDCl_3$, −50°C) δ: 189.96 (C-17), 168.98 ($\underline{C}O_2Me$), 164.75 (C-15), 154.86 (C-9), 152.79 (C-3), 140.68 (C-13), 126.52 (C-11), 125.86 (C-2), 117.45 (C-7), 115.81 (C-8), 105.75 (C-12), 105.02 (C-16), 98.79 (C-10), 98.34 (C-14), 55.12 (9-OCH_3), 51.16 (C-5), 50.98 ($CO_2\underline{C}H_3$), 50.40 (C-21), 36.57 (C-20), 23.63 (C-19), 21.73 (C-6), 12.20 (C-18).
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