A Total Synthesis of ($\pm$)-Vincamine and ($\pm$)-Eburnamonine

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A synthesis of vincamine (**1**) and eburnamonine (**2**) is reported which involves a new route to the key intermediate (**8**).

Vincamine (**1**) and eburnamonine (**2**) are pentacyclic indole alkaloids isolated from *Vinca minor* [1–5] and *Hunteria eburnea* [6–8], respectively. Vincamine exhibits significant activity as an anti-hypertensive and sedative agent [9, 10] while eburnamonine is useful as a cerebrovascular agent [11, 12]. A clinical study conducted on geriatric patients showed that vincamine improves EEG pattern as well as associated neurological symptoms [13]. Several sterically non-selective [14–16] as well as stereocontrolled [17–19] syntheses of **1** and **2** have been developed.

In view of the reported pharmacological properties of vincamine and eburnamonine [20] we have developed a new route to these alkaloids involving a novel synthesis of the key intermediate (**8**) a com-

pound which contains four of the requisite five rings and two of the three chiral centers.

Butyraldehyde and morpholine were condensed by the method of Stork [21] to afford the morpholinoenamine (**3**). Alkylation of **3** with methyl acrylate gave the dialkylated product (**4**) which was hydrolysed with aq. acetic acid to give **5** in 45% yield, b.p. 80–84 °C, 6 mm; IR (CHCl₃): 1700 cm⁻¹ (–CHO), 1740 cm⁻¹ (–CO₂Me); NMR (CDCl₃): δ 0.90 (3H, t, CH₃), δ 3.61 (3H, s, CO₂Me), δ 4.35 (1H, m, CH), δ 9.59 (1H, s, CHO).

Condensation of **5** with tryptamine afforded a gum which on purification through a silica column gave a mixture of two diastereoisomeric compounds, which could readily be separated by preparative layer chromatography as **6** and **7**, each of which crystallized as white needles m.p. 185–186 °C and 230 °C respectively. The diastereoisomeric mixture of **6** and **7** when subjected to spectral studies showed, IR (KBr): 1620 cm⁻¹ (>N–C=O), 3300 cm⁻¹ (–NH); UV (EtOH): $\lambda_{\max}$ 225, $\lambda_{\min}$ 280 nm; NMR (CDCl₃): δ 0.8 (3H, t, CH₃), δ 1.20 (2H, m, CH₂), δ 2.5 (1H, m, CH), δ 3.65 (q, 2H, CH₂), δ 7.0–7.25 (4H, m, C₆H₅), δ 8.0 (1H, NH); MS: m/e 268 (M⁺), 239 (M⁺–Et), 170, 143; High resolution mass: 268.159, calculated for C₁₇H₂₀ON₂: 268.157.

Lithium aluminium hydride reduction of the diastereoisomeric mixture of **6** and **7** afforded the amine **8** in 20% over all yield; **8** is convertible to vincamine and eburnamonine by one of several routes [15, 22, 23]. This thus formally constitutes a total synthesis of these alkaloids.

Scheme 1

* Reprint requests to Prof. Atta-ur-Rahman.

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