A Total Synthesis of (±)-Vincamine and (±)-Eburnamonine

Atta-ur-Rahman* and Mumtaz Sultana

H. E. J. Research Institute of Chemistry,
University of Karachi, Karachi-32, Pakistan

Z. Naturforsch. **37b**, 793–794 (1982);
received December 8, 1981

Hunteria, Alkaloids, Vincamine, Eburnamonine

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

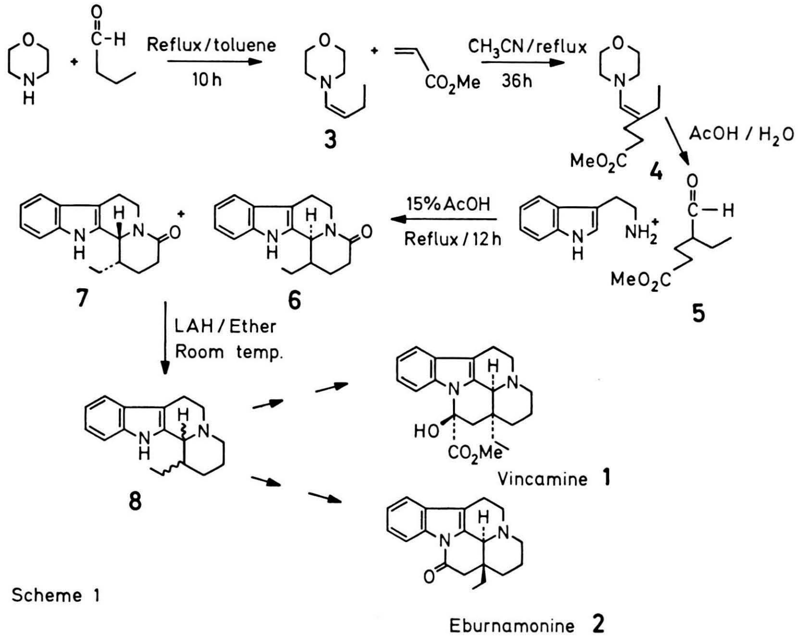
Vincamine (**1**) and eburnamonine (**2**) are pentacyclic indole alkaloids isolated from *Vinca minor* [1–5] and *Hunteria eburnea* [6–8], respectively. Vincamine exhibits significant activity as an antihypertensive and sedative agent [9, 10] while eburnamonine is useful as a cereberovascular agent [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 compound 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 (CHCl$_3$): 1700 cm^{-1} (–CHO), 1740 cm^{-1} (–CO$_2$Me); NMR (CDCl$_3$): δ 0.90 (3H, t, C$\underline{H}_3$), δ 3.61 (3H, s, CO$_2\underline{Me}$), δ 4.35 (1H, m, C$\underline{H}$), δ 9.59 (1H, s, C$\underline{H}$O).

Condensation of **5** with tryptamine afforded a gum which on purification through a silica column gave a mixture of two diasteroisomeric 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 (CDCl$_3$): δ 0.8 (3H, t, C$\underline{H}_3$), δ 1.20 (2H, m, C$\underline{H}_2$), δ 2.5 (1H, m, C$\underline{H}$), δ 3.65 (q, 2H, C$\underline{H}_2$), δ 7.0–7.25 (4H, m, C$_6$H$_5$), δ 8.0 (1H, NH); MS: *m/e* 268 (M$^+$), 239 (M$^+$–Et), 170, 143; High resolution mass: 268.159, calculated for C$_{17}$H$_{20}$ON$_2$: 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.

0340–5087/82/0600–0793/$ 01.00/0

[1] E. Schlittler and R. Furlenmeier, Helv. Chim. Acta **36,** 2017 (1953).
[2] J. Trojanek, O. Strouf, J. Holubek, and Z. Cekan, Tetrahedron Lett. **1961,** 702.
[3] J. Mokry, M. Shamma, and H. E. Sogster, Tetrahedron Lett. **1963,** 999.
[4] M. F. Bartlett, R. Sklav, A. F. Smith, and W. I. Taylor, J. Org. Chem. **28,** 2197 (1963).
[5] J. Trovjanek, Z. Koblicova, and K. Blaha, Chem. Ind. **1965,** 1261.
[6] M. F. Bartlett, W. I. Taylor, and Raymond-Hamet, C. R. Acad. Sci. Ser. C **249,** 1259 (1959).
[7] M. F. Bartlett and W. I. Taylor, J. Am. Chem. Soc. **82,** 5941 (1960).
[8] J. Mokry, I. Kompis, and P. Selcovic, Tetrahedron Lett. **1962,** 433.
[9] L. Szporny and K. Szasz, Ar. Exp. Pathol. Pharmakol. **236,** 296 (1959).
[10] Z. Szabo and Z. Nagy, Arzneim-Forsch. **10,** 811 (1960).
[11] M. F. Bartlett, W. I. Taylor, and Raymond-Hamet, C. R. Acad. Sci. Ser. C **240,** 1470 (1955).
[12] E. A. Trutneva and V. V. Berezhinskaya, Farmakol. Toksikol. **29,** 171 (1966).
[13] P. Mikus, O. Polak, and P. Ochsenreiter, Pharmakopsychiatr. **6,** 39 (1973).
[14] M. E. Kuehne, J. Am. Chem. Soc. **86,** 2946 (1964).
[15] M. E. Kuehne, Lloydia **27,** 435 (1964).
[16] K. H. Gibson and J. E. Saxton, Chem. Commun. **1969,** 1940.
[17] Cs. Szantay, L. Szabo, and G. Kalaus, Tetrahedron Lett. **3,** 191 (1973).
[18] S. Takano, S. Hatakeyama, and K. Ogasawara, J. Chem. Soc. Perkin Trans. I, **1980,** 457.
[19] K. H. Gibson and J. E. Saxton, Tetrahedron **33,** 833 (1977).
[20] "The Vinca Alkaloids", (edited by W. I. Taylor and N. R. Franswortli), Chap. 6, Dekker, New York 1973.
[21] G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovics, and R. Terrel, J. Am. Chem. Soc. **85,** 206 (1963).
[22] E. Wenkert and B. Wickberg, J. Am. Chem. Soc. **87,** 1580 (1965).
[23] J. L. Hermann, R. J. Cregge, J. E. Richman, G. R. Kieczykrwski, S. N. Normandin, M. L. Quesada, C. L. Semmelhack, A. J. Poss, and R. H. Schlessinger, J. Am. Chem. Soc. **101,** 1540 (1979).