

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

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Summary: A synthesis of vincamine (8) and eburnamonine (9) is reported which involves a new route to the key intermediate (7)

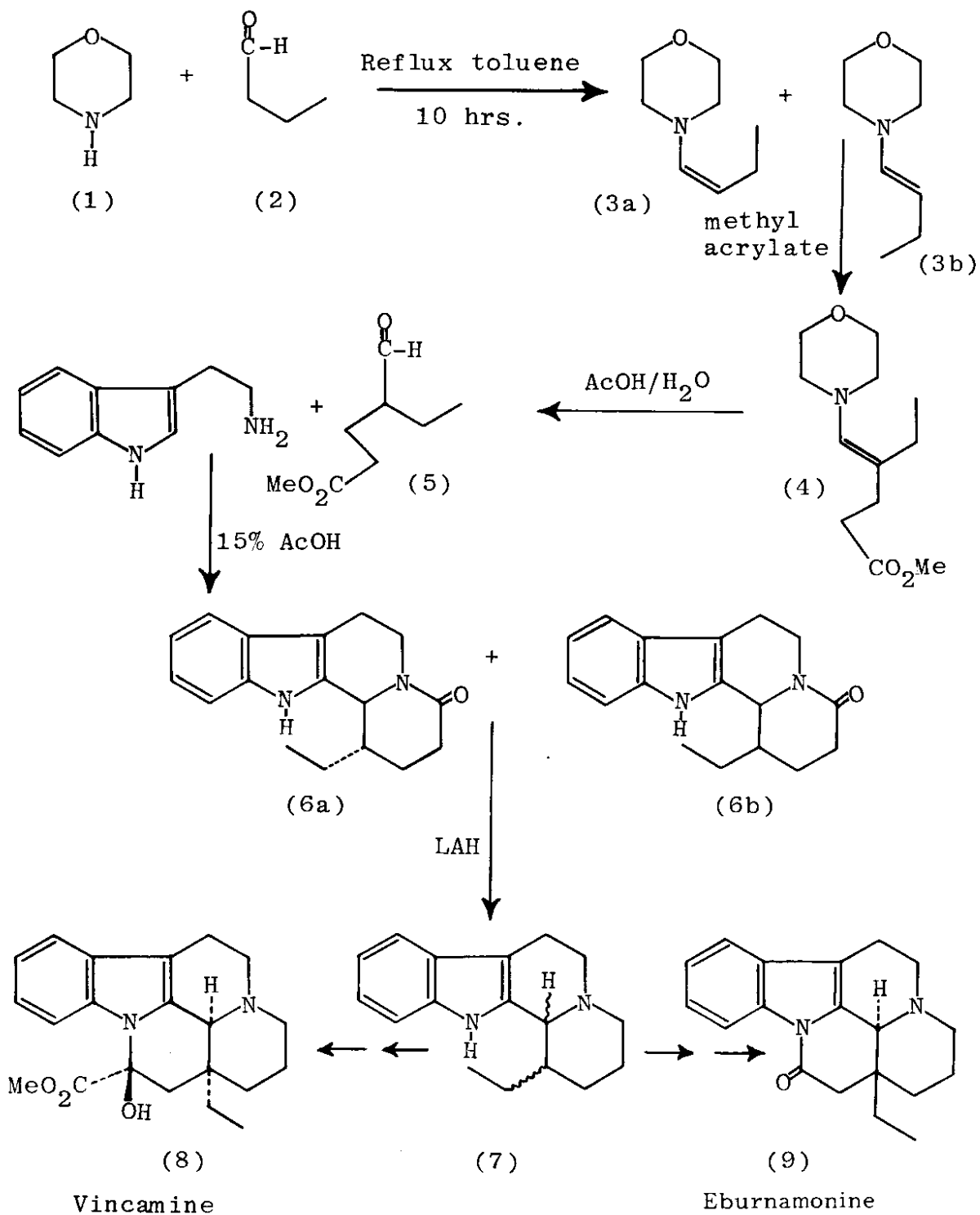
The pharmacological activity [1] of vincamine (8) and eburnamonine (9) has attracted organic chemists to develop new synthetic approaches to them, particularly during recent years. The first synthesis of eburnamonine was reported [2] in 1960 whereas the first synthesis of vincamine was published by Kuehne [3] in 1964, and since then a number of syntheses using some newly development methodology have been accomplished [4-10].

Our continuing interest in the synthesis of indole alkaloids [11-15] has prompted us to develop a simple synthesis of (+)-vincamine (8). (Scheme 1) This involves a new route to the key intermediate (7), the unsaturated form of which has been prepared previously by Wenkert [6] and later by Szantay [7] by different routes and which has been transformed to vincamine (8) and eburnamonine (9) in good yields. Our approach to this intermediate is based on the alkylation of butyraldehyde (2) via its morpholino-enamine (3).

Butyraldehyde (2) was refluxed with morpholine in toluene using Dean and Stark's apparatus until no further separation of water was seen. The reaction mixture was then distilled first at atmospheric pressure to remove the low-boiling fractions and later at reduced pressure (35 mm, 110°C) to obtain the pure enamine (3) (50% yield). The purity of the product was confirmed by gas-liquid chromatography. The

substance showed a strong band in the I.R. spectrum at 1660 cm^{-1} characteristic of the N-C=C group. The mass spectrum afforded the parent peak at m/z 141, with other prominent fragmentation peaks appearing at 140 (M^+-1), 126 (M^+-15), 96 and 56. High resolution mass spectral determination on the molecular ion afforded the exact mass to be 141.1149 which was in agreement with its molecular formula $C_8H_{15}NO$ (calculated for $C_8H_{15}NO$: 141.1153). The n.m.r. spectrum of the product was consistent with that expected for structure (3).

The enamine (3) when refluxed with methyl acrylate in acetonitrile for 36 hrs. afforded the crude alkylated product (4) which was purified by fractional distillation under vacuum and was stored at low temperatures. The I.R. spectrum of the product showed the presence of an ester carbonyl absorption at 1730 cm^{-1} . The mass spectrum afforded the molecular ion at m/z 227. A significant peak occurred at m/z 212 due to the loss of the methyl group, while other prominent peaks were present m/z 154, 141, 126, 112 and 100. An accurate mass measurement gave the exact mass of the parent ion to be 227.1501 (calculated for $C_{12}H_{21}NO_3$: 227.1523). The n.m.r. spectrum of the product showed a singlet at δ 4.64 integrating for three protons for the methoxy group. A triplet at δ 3.64 which overlapped with the singlet of the methoxy group was



Scheme 1

meters. Ultra violet spectra were recorded on a Unicam SP-800 A spectrophotometer or a Shimadzu U.V. 240 instrument. Nuclear magnetic resonance spectra were recorded on Jeol JNM-PMX 60 and Bruker - FT - WP 100-SY instrument using tetramethylsilane as an internal standard.

Preparation of Morpholine Enamine (3)

Butyraldehyde (1.0 mole, 88.5 ml) and morpholine (2.0 moles, 172 gms) were refluxed in dry toluene (300 ml) for 6 hours in a Dean and Stark's apparatus. After the elimination of water (18.0 ml, 1.0 mole) was complete the heating was stopped and the reaction flask was allowed to cool.

The reaction mixture was distilled first at atmospheric pressure to remove the unreacted butyraldehyde and morpholine and later under vacuum to give the morpholine enamine (3) as a colourless viscous liquid (b.p. 110°C, 32 mm), (14 gm, 70%), U.V. spectrum λ_{\max} (MeOH) 210, 270, λ_{\min} 225 nm; I.R. spectrum ν_{\max} 1660 cm^{-1} (C=C); mass spectrum: m/z 141.1153 (M^+ , calcd. for $C_8H_{15}NO$: 141.1149), 139, 126, 125, 124, 123; N.M.R. spectrum ($CDCl_3$): 0.90 (t, 3H, CH_3-CH_2 , $J = 7.7\text{Hz}$), 2.07 (q, 2H, CH_3-CH_2 , $J = 7.6\text{Hz}$), 3.63 (t, 4H, CH_2-O-CH_2), ($J = 6.4\text{Hz}$), 5.49 (d, 1H, $N-CH=CH$, $J = 9.5\text{Hz}$), 4.46 (m, 1H, $HC=CH-CH_2$).

Preparation of 3-Morpholine-2-Ene-Hexanoate (4)

The morpholinoenamine (3) (14 gms, 0.09 mole) was dissolved in acetonitrile (75.0 ml) and the solution was cooled to 0°C. Methyl acrylate (9.2 gms, 10.0 ml) in acetonitrile (20.0 ml) was added dropwise to the enamine. After the addition was complete the reaction

mixture was stirred at ambient temperature for 5 hours and then refluxed for 36 hours. It was distilled at atmospheric pressure to remove acetonitrile and then under vacuum. The fraction boiling at 130-135°C (10 mm) was collected as the alkylated product (4) (8 gms, 60%); U.V. spectrum: λ_{\max} (MeOH) 210, 275 λ_{\min} 250 nm; I.R. spectrum ν_{\max} 1730 cm^{-1} (C=O ester); mass spectrum: m/z 227.1501 (M^+ , calcd. for $C_{21}H_{21}NO_3$: 227.1523), 212, 196, 195, 194, 180, 173, 172, 171; N.M.R. spectrum ($CDCl_3$): 4.28 (s, 1H, $CH=CH$), 0.96 (t, 3H, CH_3-CH_2 , $J = 5.9\text{Hz}$).

Preparation of Methyl 4-Formyl Hexanoate (5)

The alkylated product (4) (4.0 gms, 17 m. moles) was refluxed in aqueous acetic acid (50%, 30 ml) for 24 hours. The reaction mixture was cooled and extracted with ether (3 x 50 ml); the ether extracts were dried (sodium sulfate) and evaporated to give a brown gum (5) (1.0 gm, 45% yield); U.V. spectrum: λ_{\max} (MeOH) 210, 270, λ_{\min} 220 nm; I.R. spectrum: ν_{\max} 1700 cm^{-1} (C=O, aldehyde), 1740 cm^{-1} (C=O, ester); mass spectrum m/z 158.0941 (M^+ , calcd. for $C_8H_{14}O_3$: 141.0942), 172, 173, 147, 146, 145; N.M.R. spectrum: δ 1.00 (t, 3H, $J=8\text{Hz}$, CH_3-CH_2), δ 3.42 (t, 2H, $J=8\text{Hz}$, CH_2-CH_2), δ 9.36 (s, 1H, CHO).

Preparation of Ethyl-4-oxo-1,2,3,4,6,7,12-Octahydro-Indolo (2,3-a) Quinolizine (6)

The aldehyde (5) (4.0 gms, 0.02 mole) was dissolved in aqueous acetic acid (30 ml, 15%), and the solution was stirred under nitrogen. Tryptamine

(3.92 gms, 0.02 mole) dissolved in aq. acetic acid (20 ml, 15%) was added dropwise to the stirred solution of the aldehyde, the entire addition being completed in about half an hour. The assigned to the methylene protons adjacent to oxygen. A triplet centered at δ 2.62 was assigned to the methylene protons adjacent to the nitrogen. A downfield singlet resonating at δ 4.28 was attributed to the olefinic proton. A high field triplet at δ 0.96 was assigned to the terminal methyl group.

The product (4) was hydrolysed on treatment with acid. Aqueous work up of the reaction mixture afforded a crude oily product which was distilled to afford the pure hydrolysed product. The I.R. spectrum of the substance showed absorptions at 1740 cm^{-1} and 1700 cm^{-1} which were assigned to the carbonyl groups of the ester and aldehyde functionalities respectively. The mass spectrum showed the expected fragmentation pattern, the molecular ion appearing at m/z 158. Accurate mass measurement of M^+ ion showed its exact mass to be 158.0941 (calculated for $C_8H_{14}O_3 = 158.0942$). The n.m.r. spectrum of the compound showed a downfield singlet at δ 9.36 integrating for one proton which was attributed to the aldehyde functionality. Other signals included a triplet centered at δ 3.42 ($J = 8\text{ Hz}$) assigned to the methylene protons, and a high field triplet at δ 1.00 ($J = 8\text{ Hz}$) assigned to the methyl group.

Condensation of the aldehyde (5) with tryptamine was achieved by refluxing it with tryptamine in aqueous acetic acid (15%) for a prolonged period. The reaction mixture after appropriate work-up afforded a gum, t.l.c. of which showed two major spots moving very close to each other along with some minor products. The two major products were separable by

column chromatography followed by preparative layer chromatography. The two isomers (6a) and (6b) crystallised out after chromatographic separation as white needles m.p. $185-86^\circ\text{C}$ and 230°C respectively. The diastereoisomeric mixture on spectroscopic analysis showed a band at 1620 cm^{-1} in the I.R. spectrum characteristic of the amide carbonyl absorption, whereas the U.V. spectrum was typically indolic. The mass spectrum afforded the M^+ ion at m/z 268 while other significant peaks were present at 239, 211, 170, 143, 111, 97 and 85. An exact mass measurement by peak matching showed the molecular weight to be 268.1592 (calculated for $C_{17}H_{20}ON_2 = 268.1511$). The n.m.r. spectrum of the mixture showed a high field triplet at δ 0.8 ($J = 6.5\text{ Hz}$) which was assigned to the methyl groups at C-14 and a multiplet at δ 1.20 was assigned to the methylene proton of the angular ethyl group. The C-16 methine proton resonated as a multiplet at δ 2.53 and a quartet centered at δ 3.65 integrating for two protons was assigned to the methylene protons at C-17. The aromatic protons were recorded as complex multiplets in the region δ 7.14 to δ 7.28.

Lithium aluminium hydride reduction of (6) gave the amine (7). The IR spectrum showed the absence of the amide function and the U.V. was characteristic of the indole nucleus. The mass spectrum recorded the M^+ peak at m/e 254; other prominent peaks were present at 253, 239, 225, 197 and 149.

The tetracyclic amine (7) a compound which contains four of the requisite five rings and two of the three chiral centres is convertible to vincamine and eburnamonine via the Wenkert's intermediate by one of several routes [6,7]. This therefore constitutes a formal total synthesis of these alkaloids.

Experimental

Mass spectra were recorded on a Varian MAT 112-S mass spectrometer coupled to the Spectrosystem 188 computer. High resolution mass spectra were recorded on Varian MAT 312 mass spectrometer. Infra-red spectra were recorded on a Pye-Unicam SP-200G or a Jasco-IRA-I infra-red spectrophotometer. Reaction mixture was refluxed for 12 hours and was worked up by shaking first with chloroform (2 x 10 ml) to remove the acidic substances, the aqueous (acidic) layer was basified with sodium carbonate and extracted with chloroform (3 x 50 ml). The combined chloroform extracts were dried over anhydrous sodium sulphate and concentrated to give a brown gum. The purification of the gum was affected by passing through a silica column. Elution with 80% pet. ether 20% chloroform gave the required diastereoisomeric mixture. The mixture was separated by preparative layer chromatography to give two isomers as white needles, m.p. 185-186°C and 230°C respectively. The separation of the isomer was not found necessary at this stage as the subsequent step causes loss of asymmetry. Therefore the spectroscopic data of the stereoisomers mixture was recorded; U.V. spectrum λ_{\max} (MeOH) 225, 280, λ_{\min} 250 nm; I.R. spectrum: ν_{\max}^{-1} 1620 cm^{-1} (C=O, amide) 3300 cm^{-1} (N-H); mass spectrum: m/z 268.1591 (M^+ , calcd. for $C_{17}H_{20}N_2O$: 268.1572); N.M.R. spectrum: δ 0.8 (3H, t, CH_3), δ 1.20 (2H, m, CH_2), δ 2.5 (1H, m, CH), δ 3.65 (q, 2H CH_2), δ 7.0-7.25 (4H, m, C_6H_5), δ 8.0 (1H, s, NH).

Preparation of 1-Ethyl-1,2,3,4,6,7,12-Octahydro-Indolo-(2,3-a)-Quinolizine (7)

The amide (6), (15 mg, 0.05 m.mole) was dissolved in anhydrous ether (20 ml). Fresh lithium aluminium hydride (50 mg) was carefully added to the magnetically stirred solution. The solution was stirred for 30 minutes and excess of lithium aluminium hydride was carefully destroyed with drops of water. The aqueous solution was extracted with ether (2 x 20 moles); the ether extracts were dried over anhydrous sodium sulphate and evaporated to give the amine (6), (3 mg, 20% yield); U.V. spectrum: λ_{\max} (MeOH) 225, 280, nm λ_{\min} 250 nm; I.R. spectrum: ν_{\max}^{-1} 3300 cm^{-1} (N-H); mass spectrum: m/z 254.1780 (M^+ , calcd. for $C_{17}H_{22}N_2$: 254.1782), 253, 239, 225, 205, 197, 184, 183.

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