STUDIES ON THE SYNTHESES OF HETEROCYCLIC AND NATURAL COMPOUNDS. PART 949[1]. A TOTAL SYNTHESIS OF (±)-CORYNANTHEIDOL

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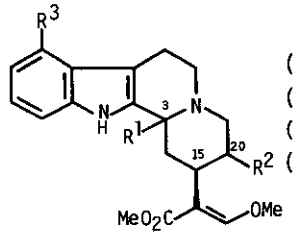
Abstract —— A facile synthesis of (±)-corynantheidol (17) has been achieved by the application of enamine annelation using 3,4-dihydro-1-methyl-β-carboline (5) and dimethyl 3-methoxyallylidenemalonate (6). Stereochemical assignment for catalytic hydrogenation products of the corresponding enamides has also been investigated.

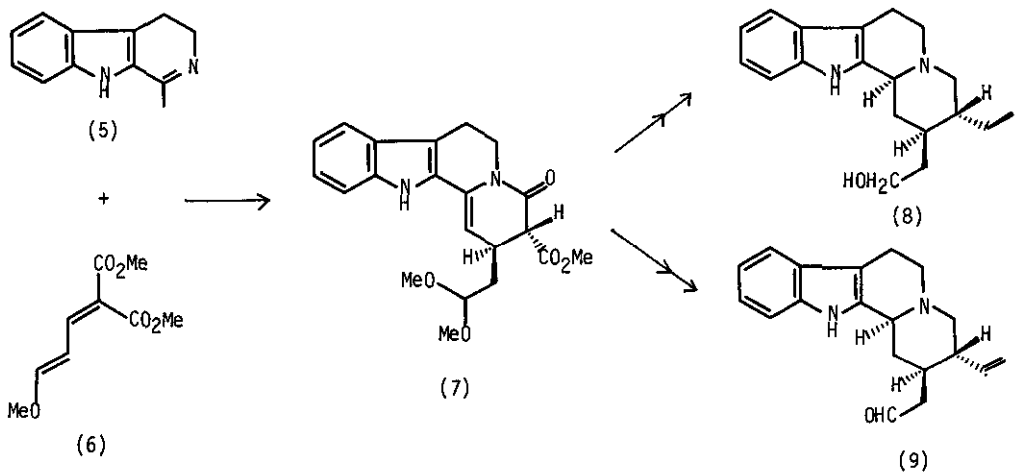
The indoloquinolizidine skeleton is common to a large group of indole alkaloids, and all of four possible diastereomers have been found in nature, such as corynantheine[2] (1), hirsuteine[3] (2), corynantheidine[4] (3), and spciociliatine[5] (4).



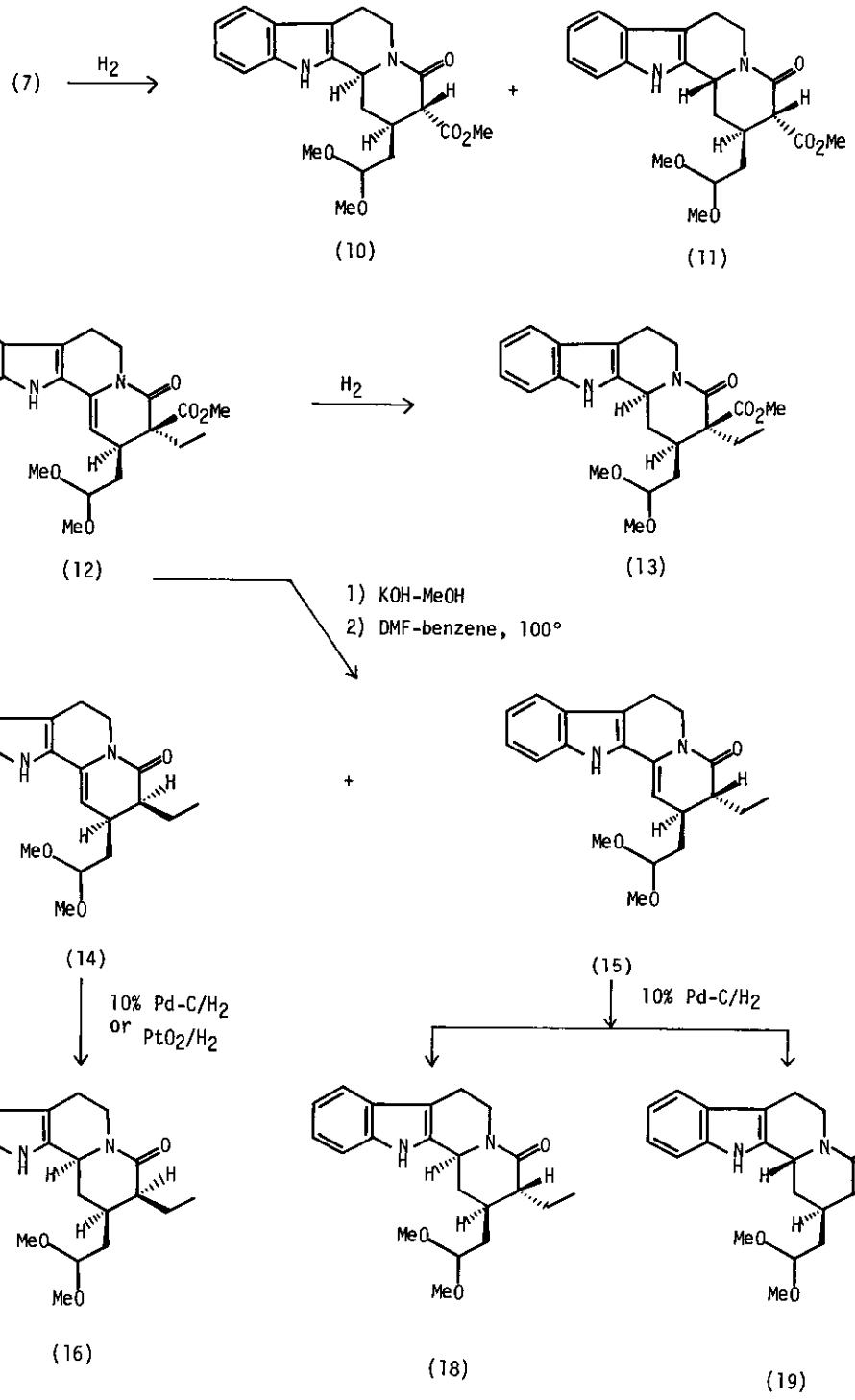
(1) R^1=α-H, R^2=α-CH=CH_2, R^3=H
(2) R^1=β-H, R^2=α-CH=CH_2, R^3=H
(3) R^1=α-H, R^2=β-Et, R^3=H
(4) R^1=β-H, R^2=β-Et, R^3=OMe

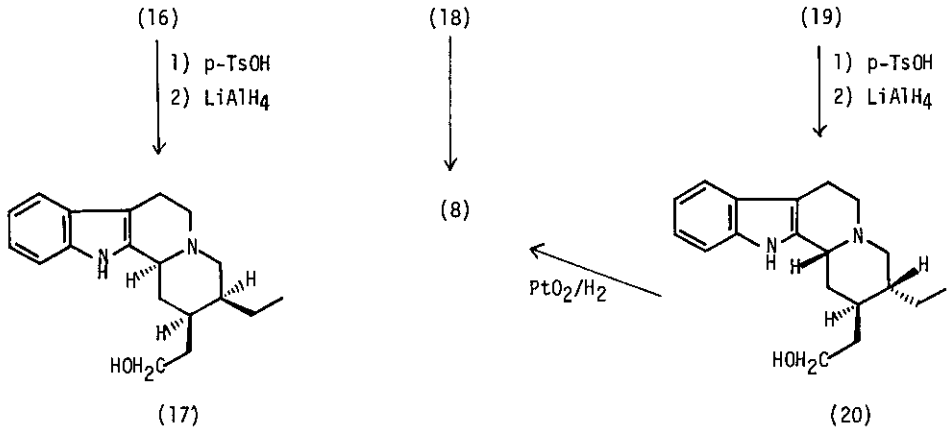
We have recently published the stereoselective synthesis of (±)-dihydrocorynantheol[6] (8) and (±)-corynantheal[7] (9) by application of enamine annelation[8] of 3,4-dihydro-1-methyl-β-carboline (5) with dimethyl 3-methoxyallylidenemalonate (6), as a key reaction, to form the indolo[2,3-a]quinolizine (7). In our continuing program concerned with the synthesis of corynanthe-type indole alkaloids by the application of the above strategy, it is essential to investigate the stereochemistry of hydrogenation products of indolo[2,3-a]quinolizine with appropriate functionality at the C_{15} and C_{20} positions. We noted in advance that the catalytic hydrogenation of the enamide (7) with 10 % palladium-carbon in methanol under 2 atm of hydrogen afforded two stereoisomers (10) and (11) in a ratio of 1 : 1, while hydrogenation

using Adams catalyst gave a mixture of (10) and (11) in a ratio of 1 : 2, both of which had been converted into (±)-corynantheal (9). Moreover the hydrogenation of (12) in the presence of Adams catalyst in methanol furnished the amide (13), exclusively, which had been transformed into (±)-dihydrocorynantheol (8).



In order to synthesise (±)-corynantheidol (17) which has thermodynamically less stable $C_{15/20}$ cis configuration, the known enamide[5] (12) was firstly hydrolysed with methanolic potassium hydroxide and then decarboxylated by heating at 100°C in dimethylfomamide-benzene (1 : 2 v/v) solution to give two stereoisomers (14) and (15) in a ratio of 5 : 3. When the decarboxylation was carried out by heating at 120 - 130°C in dimethylformamide, the ratio of the two stereoisomers (14) and (15) was reversed to 1 : 1.4. Hydrogenation of the former enamide (14) with 10 % palladium-carbon or Adams catalyst in methanol gave the amide (16) as a sole product in 89.5 % yield. Deprotection of (16) with p-toluenesulphonic acid in acetone and subsequent lithium aluminium hydride reduction afforded (±)-corynantheidol (17) [m.p. 160 - 161°(lit.,[9-12] 158 - 162°; 157 - 159°; 158 - 160°)], the spectral data of which were undistinguishable from those of an authentic sample provided by Professor Takano. On the other hand, hydrogenation of $C_{15/20}$ trans isomer (15) in the presence of 10 % palladium-carbon afforded two stereoisomers (18) and (19) in a ratio of 1 : 2, and the stereochemistry of the former amide (18) was deduced from a direct comparison with an authentic sample[13]. Deprotection of the latter amide (19) with p-toluenesulphonic acid, followed by lithium aluminium hydride reduction furnished (±)-hirstinol, whose spectral data were consistent with the structure of (20). Since epimerisation at the C_3-position of the amine (20) with Adams catalyst under 2 atm of hydrogen in

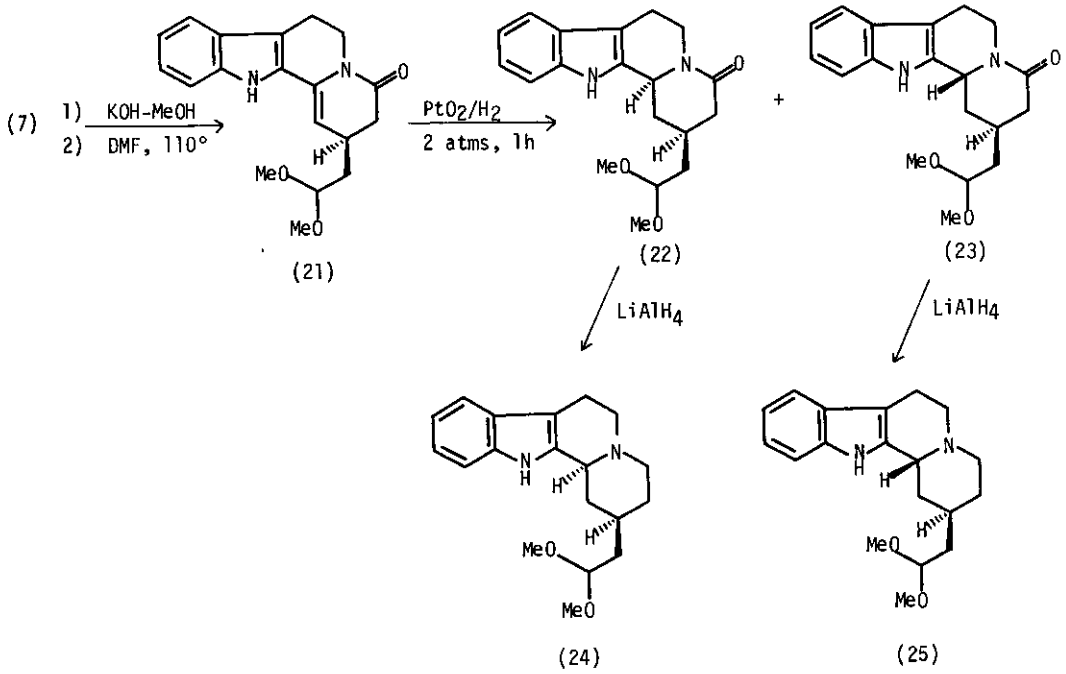

(7)
H2
(10)
(11)
(12)
(13)
1) KOH-MeOH
2) DMF-benzene, 100°
(14)
(15)
10% Pd-C/H2
or PtO2/H2
10% Pd-C/H2
(16)
(18)
(19)



(17) (20)

methanol for 118 h gave (±)-dihydrocorynantheol (8) in 62.5 % yield, the stereochemistry of (20) was assigned to be 3β-hydrogen in addition to $C_{15/20}$ trans configuration unambiguously. Hydrogenation of the enamide (21), prepared from (7) by hydrolysis and subsequent decarboxylation, in the presence of Adams catalyst under 2 atm of hydrogen for 1 h afforded two stereoisomers (22) and (23) in a ratio of 11 : 2, and the latter amide (23) was easily epimerised to the former (22) for a longer reaction time. Both amides were then converted to the corresponding amines (24) and (25) by lithium aluminium hydride reduction, respectively.

As the results of the present work, it can be assumed that the catalytic hydrogenation occurred exclusively from less hindered α-face of the β-substituted enamides at the C_{20} position, such as the enamide (12) and (14). On the contrary, β-face was prefered side in the case of α-substituted enamides at the C_{20} position, such as (7) and (15). Thus the facile synthesis of (±)-corynantheidol (17) was achieved by the adoption of enamine annelation reaction reported by us previously, and four possible stereoisomers of corynanthe-type indole alkaloids would be synthesised by the manipulation of C_{20} functionality, before or after the catalytic hydrogenation.



(21) (22) (23) (24) (25)

EXPERIMENTAL SECTION

Melting points are not corrected. IR spectra were measured with a 215 Hitachi Grating infrared spectrophotometer, NMR spectra with a JEOL JUM-FX100 spectrometer using tetramethylsilane as an internal reference. Mass spectra were taken with a JEOL JMS-D300 spectrometer.

(±)-20β-Ethyl-5,6,15β,20α-tetrahydro-15β-(2,2-dimethoxyethyl)-21-oxoindolo[2,3-a]-quinolizine (14) and (±)-20α-Ethyl Isomer (15) —— Method A: A solution of 12 (470 mg) and 80% potassium hydroxide (200 mg) in methanol-water (30 ml) (5: 1 v/v) was refluxed for 7 h. After evaporation of the solvent, the residue was taken up into water and acidified with acetic acid to pH 6. The acidic solution was extracted with chloroform, and the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded the carboxylic acid as an oil, which without further purification was used in the following reaction. A stirred solution of the above acid in benzene-dimethylformamide (30 ml) (2 : 1 v/v) was heated at 100°C for 2.5 h and then diluted with benzene. The resulting mixture was washed with water. The solvent was dried (Na_2SO_4) and evaporated to leave an oil which was subjected to silica gel column chromatography. Elution with benzene-acetone (97 : 3 v/v) gave 14 (150 mg, 41.8 %) as a reddish oil; NMR ($CDCl_3$)δ: 1.00 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.33 (6H, s, 2 x OCH_3), 4.30 - 4.63 (2H, m, $-CH\overset{O-}{\underset{O-}{\diagup}}$ and C_{20}-H), 5.63 (1H, d, J = 6 Hz, -CH = C$\overset{}{\diagdown}$), 6.96 - 7.60 (4H, m, 4 x ArH), 8.30 (1H, s, NH); MS m/e 354.1927 ($\underline{M}^+$). $C_{21}H_{26}N_2O_3$ requires 354.1942.

Further elution with benzene-acetone (24 : 1 v/v) afforded 15 (120 mg, 25.1 %) as a reddish oil; IR$\nu_{max}^{CHCl_3}$ cm^{-1} : 3475 (NH), 1670 and 1650 (C = O); NMR ($CDCl_3$)δ: 0.96 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.30 (6H, s, 2 x OCH_3), 4.40 - 5.00 (2H, m, $-CH\overset{O-}{\underset{O-}{\diagup}}$ and C_{20}-H), 5.50 (1H, d, J = 6 Hz, -CH = C$\overset{}{\diagdown}$), 7.00 - 7.50 (4H, m, 4 x ArH), 8.53 (1H, s, NH); MS m/e 354.1907 ($\underline{M}^+$). $C_{21}H_{26}N_2O_3$ requires 354.1942.

Method B : A solution of 12 (300 mg) and sodium hydroxide (200 mg) in methanol-water (40 ml) (7 : 1 v/v) was refluxed for 24 h, and and worked up as described above to give the carboxylic acid, whose stirred solution in dimethylformamide (20 ml) was heated at 120 - 130°C for 1 h. After cooling to room temperature, the solution was diluted with benzene, washed with water, and dried (Na_2SO_4). Removal of the solvent afforded a reddish oil, which was chromatographed on silica gel using benzene-acetone (24 : 1 v/v) as eluant to give 14 (49.4 mg, 17.8%) and 15 (70.6 mg, 25.5%), respectively.

(±)-20β-Ethyl-3α,5,6,14,15α,20α-hexahydro-15β-(2,2-dimethoxyethyl)-21-oxoindolo[2,3-a]quinolizine (16) —— A solution of 14 (105 mg) in methanol (30 ml) in the presence

of palladium-charcoal (100 mg) or platinum oxide (20 mg) was shaken at ambient temperature for 30 min under the atmosphere of hydrogen. After removal of the catalyst by filtration, the filtrate was concentrated to the residue, which was then extracted with benzene. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded an oil which was subjected to silica gel column chromatography. Elution with benzene-acetone (94 : 6 v/v) furnished the amide (16) (85 mg, 89.5%) as a yellowish solid, m.p. 175.5 - 176.5°C (from methylene chloride-n-hexane); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 1620 (C = O); NMR ($CDCl_3$) δ : 1.03 (3H, t, J = 7 Hz, $CH_2\underline{CH_3}$), 3.32 (3H, s, OCH_3), 3.35 (3H, s, OCH_3), 4.46 (1H, t, J = 5.7 Hz, $-CH\langle^{O-}_{O-}$), 4.77 (1H, m, C_{20}-H), 5.13 (1H, dd, J = 2.9 and 8.6 Hz, C_3-H), 7.08 - 7.54 (4H, m, 4 x ArH), 7.97 (1H, s, NH); MS m/e 356.2097 (M^+). $C_{21}H_{28}N_2O_3$ requires 356.2098. Anal. calcd for $C_{21}H_{28}N_2O_3 \cdot 0.25\ H_2O$: C, 69.92; H, 7.96; N, 7.77. Found: C, 69.64; H, 7.86; N, 7.65%

(±)-Corynantheidol (17)—— A solution of the amide (16) (80 mg) and a catalytic amount of p-toluenesulphonic acid in acetone (10 ml) was stirred at 0°C for 2 h. After treatment with an excess of crystalline sodium hydrogencarbonate, the solvent was evaporated to leave the residue which was then extracted with chloroform. The chloroform layer was washed with water and dried (Na_2SO_4). Removal of the solvent gave an oil, which was chromatographed on silica gel using methylene chloride-methanol (95 : 5 v/v) as eluant to afford the aldehyde, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715 (C = O). To a stirred solution of lithium aluminium hydride (20 mg) in dry tetrahydrofuran-ether (15 ml) (1 : 2 v/v) was added a solution of the above aldehyde in dry tetrahydrofuran (5 ml) over the period of 30 min at ambient temperature. The mixture was then refluxed for 1 h and the excess of reagent was decomposed with the addition of 10% aqueous sodium hydroxide. After separation of the organic layer by decantation, the aqueous layer was extracted with chloroform and the combined organic lyaer was concentrated to leave the residue, which was taken up into 5% aqueous hydrochloric acid. The acidic layer was washed with ether, basified with saturated aqueous sodium hydrogencarbonate, and extracted with ether. The ethereal layer was washed with water, dried (Na_2SO_4) and evaporated to yield (±)-corynantheidol as colourless plates, m.p. 160 - 161°C (from acetone-ether-n-hexane) (lit., 157 - 159°C[9]; 158 - 160°C[10]; 158 - 162°C[11]); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3475 (NH), 2700 - 2900 (Bohlmann bands); NMR ($CDCl_3$)δ: 0.92 (3H, t, J = 6.3 Hz, $CH_2\underline{CH_3}$), 3.76 (3H, t, J = 7 Hz, $-\underline{CH_2}OH$), 7.05 - 7.49 (4H, m, 4 x ArH), 7.79 (1H, s, NH); MS m/e 298.2023 ($\underline{M}^+$). $C_{19}H_{26}N_2O$ requires 298.2044.

(±)-20α-Ethyl-3α,5,6,14,15α,20β-hexahydro-15β-(2,2-dimethoxyethyl)-21-oxoindolo[2,3-

alquinolizine (18) and (±)-3βH-Isomer (19)—— A mixture of the enamide (15) (117 mg), palladium-charcoal (100 mg) and methanol (30 mg) was shaken at ambient temperature for 1 h in a current of hydrogen. After removal of the catalyst, the filtrate was concentrated to the residue, which was subjected to silica gel column chromatography. Elution with benzene-acetone (24 : 1 v/v) gave the amide (18) (37 mg, 31.4%) as a yellowish solid, which was identical with an authetic sample. Further elution with benzene-acetone (94 : 6 v/v) afforded the 3β-H amide (19) (70 mg, 59.5%) as a colorless oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3470 (NH), 1610 (C=O); NMR ($CDCl_3$) δ: 0.94 (3H, t, J = 7.1 Hz, $CH_2\underline{CH_3}$), 3.35 (3H, s, OCH_3), 3.39 (3H, s, OCH_3), 4.54 (1H, t, J = 5.7 Hz, $\underline{CH}\langle^{O-}_{O-}$), 4.83 (1H, m, C_{20}-H), 5.13 (1H, dd, J = 2.9 and 7.1 Hz, C_3-H), 7.07 - 7.54 (4H, m, 4 x ArH), 7.86 (1H, s, NH); MS m/e 356.2118 ($\underline{M}^+$). $C_{21}H_{28}N_2O_3$ requires 356.2100.

(±)-Hirstinol (20)—— A mixture of 19 (100 mg), a catalytic amount of p-toluenesulphonic acid and acetone (10 ml) was stirred at 0 C° for 2 h. After the usual work-up, the aldehyde obtained was reduced with lithium alminium hydride (25 mg), as described before, to give (±)-hirstinol (20) as an amorphous powder; IR $\nu_{max}^{CHCl_3}$ $^{-1}$: 3450 (NH); NMR ($CDCl_3$) δ : 0.85 (3H, t, J = 7.1 Hz, $CH_2\underline{CH_3}$), 3.76 (2H, t, J = 5.7 Hz, $\underline{CH_2}OH$), 4.00 (1H, m, C_3-H), 7.04 - 7.51 (4H, m, 4 x ArH), 8.10 (1H, s, NH); MS m/e 298.2018 ($\underline{M}^+$). $C_{19}H_{26}N_2O$ requires 298.2044.

Epimerisation of (±)-Hirstinol (20) to (±)-Dihydrocorynantheol (8)—— A mixture of 20 (40 mg), platinum oxide (20 mg) and methanol (20 ml) was shaken at ambient temperature for 118 h under 2 atm of hydrogen. After removal of the catalyst by filtration, the filtrate was evaporated to leave the residue, which was extracted with chloroform. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded an oil which was chromatographed on silica gel using methylene chloride-methanol (93 : 7 v/v) as eluant to give (±)-dihydrocorynantheol (8) (25 mg, 62.5%), which was identical with an authentic sample[6].

5,6,15,20-Tetrahydro-15-(2,2-dimethoxyethyl)-21-oxoindolo[2,3-alquinolizine (21)—— A solution of the enamide (7) (500 mg) and 80% potassium hydroxide (300 mg) in methanol-water (30 ml) (5 : 1 v/v) was refluxed for 1 h. After removal of the solvent, the residue was dissolved in water and acidified with acetic acid to pH 6. The acidic aqueous layer was extracted with chloroform. The organic layer was washed with water, dried (Na_2SO_4) and evaporated to leave the carboxylic acid, which without further purification was used in the following reaction. A stirred solution of the carboxylic acid in dimethylformamide (20 ml) was heated at 110 °C for 1h, and then diluted with benzene. The mixture was washed with water, dried (Na_2SO_4) and evapo-

rated to give an oil, which was chromatographed on silica gel using benzene-acetone (24 : 1 v/v) as eluant to furnish the enamide (21) (240 mg, 56.5 %) as a reddish oil; NMR ($CDCl_3$)δ: 3.30 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 4.30 - 4.63 (1H, m, $CH\langle^{-O-}_{-O-}\rangle$), 5.50 (1H, d, J = 4 Hz, -CH = C⟨), 7.00 - 7.77 (4h, m, 4 x ArH), 8.33 (1H, s, NH); MS m/e 356.1585 ($\underline{M}^+$). $C_{19}H_{22}N_2O_3$ requires 356.1630.

(±)-3α,5,6,14,15α,20-Hexahydro-15β-(2,2-dimethoxyethyl)-21-oxoindolo[2,3-a]quinolizine (22) and (±)-3βH-Isomer (23) —— A mixture of the enamide (21) (100 mg), platinum oxide (20 mg) and methanol (30 ml) was shaken at ambient temperature for 1 h under 2 atm of hydrogen. The catalyst was filtered off and the filtrate was concentrated to the residue which was extracted with benzene. The benzene layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave a yellowish solid which was subjected to silica gel column chromatography. Elution with xhloroform-methanol (98 : 2 v/v) afforded the amide (22) (75.3 mg, 74.9%) as colorless prism, m.p. 196 - 197°C (from benzene-n-hexane); IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3460 (NH), 1625 (C = O); NMR ($CDCl_3$)δ: 3.33 (6H, s, 2 x OCH_3), 4.47 (1H, m, $CH\langle^{-O-}_{-O-}\rangle$), 5.13 (1H, m, C_3-H), 7.00 - 7.53 (4H, m, 4 x ArH), 8.03 (1H, s, NH); MS m/e 328.1786 ($\underline{M}^+$). $C_{19}H_{24}N_2O_3$ requires 328.1786. Anal. calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.53; H, 7.36; N, 8.48%. Further elution with chloroform-methanol (39 : 1 v/v) gave the amide (23) (13.7 mg, 13.7%) as a yellowish oil; NMR ($CDCl_3$)δ: 3.30 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 4.48 (1H, t, J = 5.7 Hz, $CH\langle^{-O-}_{-O-}\rangle$), 4.77 - 5.17 (3H, m, C_{20}-H_2 and C_{15}-H), 7.07 - 7.51 (4H, m, 4 x ArH), 8.26 (1H, s, NH); MS m/e 328.1773 ($\underline{M}^+$). $C_{19}H_{24}N_2O_3$ requires 328.1786.

(±)-3α,5,6,14,15α,20,21-Heptahydro-15β-(2,2-dimethoxyethyl)-indolo[2,3-a]quinolizine (24) —— To a stirred solution of lithium aluminium hydride (20 mg) in dry tetrahydrofuran (10 ml) was added a solution of the amide (22) (46 mg) in dry tetrahydrofuran (5 ml) at ambient temperature over the period of 10 min. The mixture was then refluxed for 1 h and the excess of reagent was decomposed with an addition of 10% aqueous sodium hydroxide. After the separation of the organic layer by decantation, the aqueous layer was extracted with chloroform. The combined organic layer was concentrated to the residue, which was taken up into 5% aqueous hydrochloric acid and washed with ether. The acidic solution was basified with saturated sodium hydrogencarbonate solution and extracted with ether. The ethereal layer was washed with water and dried (Na_2SO_4). Removal of the solvent gave the amine (24) (28 mg, 63.6%) as a yellowish oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3480 (NH), 2700 - 2900 (Bohlmann bands); NMR ($CDCl_3$) δ : 3.33 (6H, s, 2 x OCH_3), 4.53 (1H, t, J = 5.0 Hz, $CH\langle^{-O-}_{-O-}\rangle$), 6.93 - 7.50

(4H, m, 4 x ArH), 7.80 (1H, s, NH); MS m/e 314.1968 (M^+). $C_{19}H_{26}N_2O_2$ requires 314.1993

(±)-3β,5,6,14,15α,20,21-Heptahydro-15α-(2,2-dimethoxyethyl)-indolo[2,3-a]quinolizine (25)— The amide (23) (6 mg) was reduced with lithium aluminium hydride (10 mg) in dry tetrahydrofuran, as described above, to yield the amine (25) (3.5 mg, 61%) as a yellowish oil; IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3480 (NH); NMR ($CDCl_3$) δ : 3.30 (3H, s, OCH_3), 3.33 (3H, s, OCH_3), 3.96 (1H, m, C_3-H), 4.46 (1H, t, J = 5H, $CH\overset{-O-}{\underset{-O-}{}}$), 6.96 - 7.50 (4H, m, 4 x ArH), 7.83 (1H, s, NH); MS m/e 314.1966 (M^+). $C_{19}H_{26}N_2O_2$ requires 314.1992.

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