A Stereoselective Synthesis of Corynantheine-type Alkaloids *via* Enamine Annulation. Total Synthesis of (±)-Dihydrocorynantheol and Formal Total Synthesis of (±)-Corynantheine and (±)-Ajmalicine

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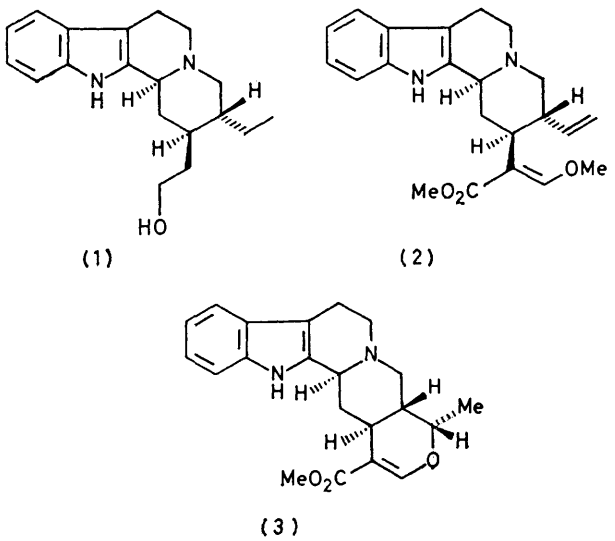
Enamine annulation between 3,4-dihydro-1-methyl-β-carboline (4) and dimethyl 3-methoxyallylidenemalonate (5) yielded 2-(2,2-dimethoxyethyl)-2,3,4,6,7,12-hexahydro-3-methoxycarbonyl-4-oxoindolo[2,3-*a*]quinolizine (6), which was transformed into (±)-dihydrocorynantheol (1). (±)-Corynantheal (19), which is convertible into (±)-*corynantheine* (2) and (±)-*ajmalicine* (3), was stereoselectively synthesised from (6) *via* epimerisations at the angular position using Adams catalyst.

A NUMBER of corynantheine-type alkaloids possess interesting physiological properties such as antihypertensive activity. We have recently developed a facile synthesis of benzo[*a*]quinolizines [1] and indolo[2,3-a]-quinolizines [2] utilizing the enamine character of a 3,4-dihydro-1-methylisoquinoline and 3,4-dihydro-1-methyl-β-carbolines,[3] which led us to the total synthesis of some *ipecac* alkaloids [4] and camptothecins.[5] We further studied the application of this annulation to the synthesis of corynantheine-type alkaloids and here report a total synthesis of (±)-dihydrocorynantheal (1) and a formal total synthesis of (±)-corynantheine (2) and (±)-ajmalicine (3) including epimerisations at the C-12b position with Adams catalyst.[6]



SCHEME 1

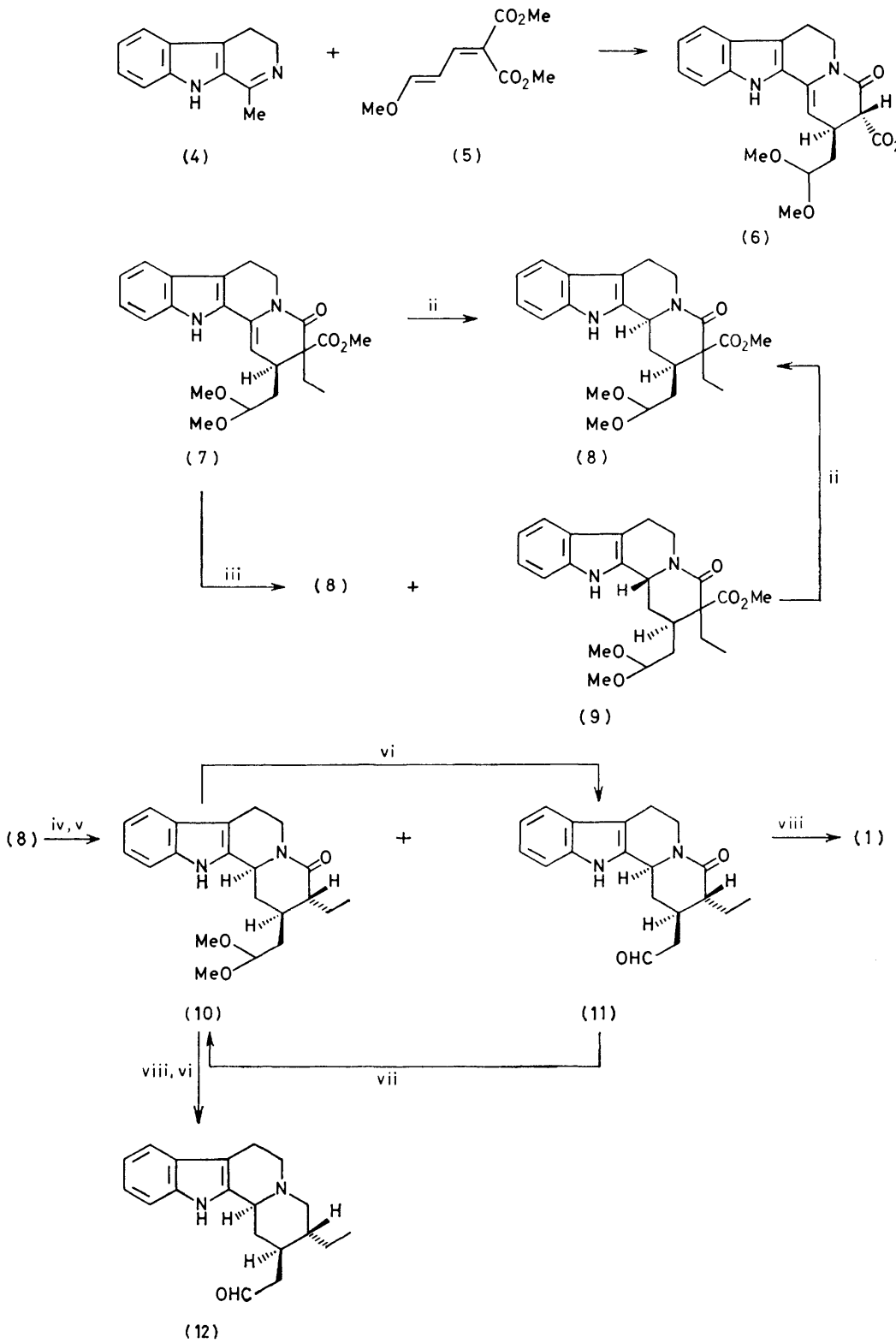
Total Synthesis of (±)-*Dihydrocorynantheol.*—Dihydrocorynantheol (1), first isolated from *Aspidosperma marcgravianum*,[7] was identical with the reduction product of dihydrocorynantheal.[8] A stereoselective synthesis of this alkaloid was achieved by a method similar to our previous synthesis of the *ipecac* alkaloids.[4] The indolo[2,3-*a*]quinolizine having a correct substitution pattern for the synthesis of corynantheine-type alkaloids was effectively synthesised by the enamine annulation. Thus, stirring 3,4-dihydro-1-methyl-β-carboline (4) and dimethyl 3-methoxyallylidenemalonate (5) in methanol for 72 h at room temperature, followed by refluxing the mixture for 24 h, produced the 4-oxoindolo[2,3-*a*]quinolizine (6) in 77% yield with no other stereoisomer being formed. The ^{1}H n.m.r. spectrum of (6) showed signals due to the dimethyl acetal at δ 3.30, the methyl ester group at δ 3.70 and the olefinic hydrogen at δ 5.57 (as a singlet), respectively.

The ethyl group was introduced at the C-3′ position by a reaction with ethyl iodide in the presence of 1 mol equiv. of sodium hydride in dry dimethylformamide at 0 °C to give (7) as single stereoisomer in 89.8% yield. Use of an excess of the reagents caused the further ethylation at the nitrogen of the indole ring.

On hydrogenation of (7) for 2 h in the presence of Adams catalyst under 1.5 atm of hydrogen, the amide (8) was obtained in 95.7% yield as the sole product. When the reduction was carried out for 30 h using 10% palladium–charcoal under 1.5 atm of hydrogen, the amide (8) was produced in 57% yield along with a stereoisomer (9) in 28% yield. Slow conversion of the latter into the former was observed in the presence of Adams catalyst under a hydrogen atmosphere. The stereochemistry of (8) was tentatively assigned as the 12bα-H on the basis of the previous result in the case of the synthesis of the *ipecac* alkaloids [4] and confirmed by the following transformation into the natural product (1).

After hydrolysis of the ester (8) with sodium methoxide in hot aqueous methanol, the resulting carboxylic acid was heated in dimethyl sulphoxide at 160 °C leading to a mixture of the acetal (10) and the aldehyde (11), which on treatment with toluene-*p*-sulphonic acid in acetone at 0 °C produced the pure aldehyde (11) as a single stereoisomer in 92% overall yield. Reduction of the lactam-aldehyde (11) with lithium aluminium hydride furnished, in 54.5% yield, (±)-dihydrocorynantheol (1), m.p. 178.5—180 °C, whose spectral data were consistent with those reported.[7,8] That the three other possible stereoisomers were not formed, *i.e.* that the reaction sequence was stereoselective, was demonstrated by comparison (t.l.c.) of the final reaction product with authentic samples of these isomers.[9]

The acetalisation of the above mixture of (10) and (11)

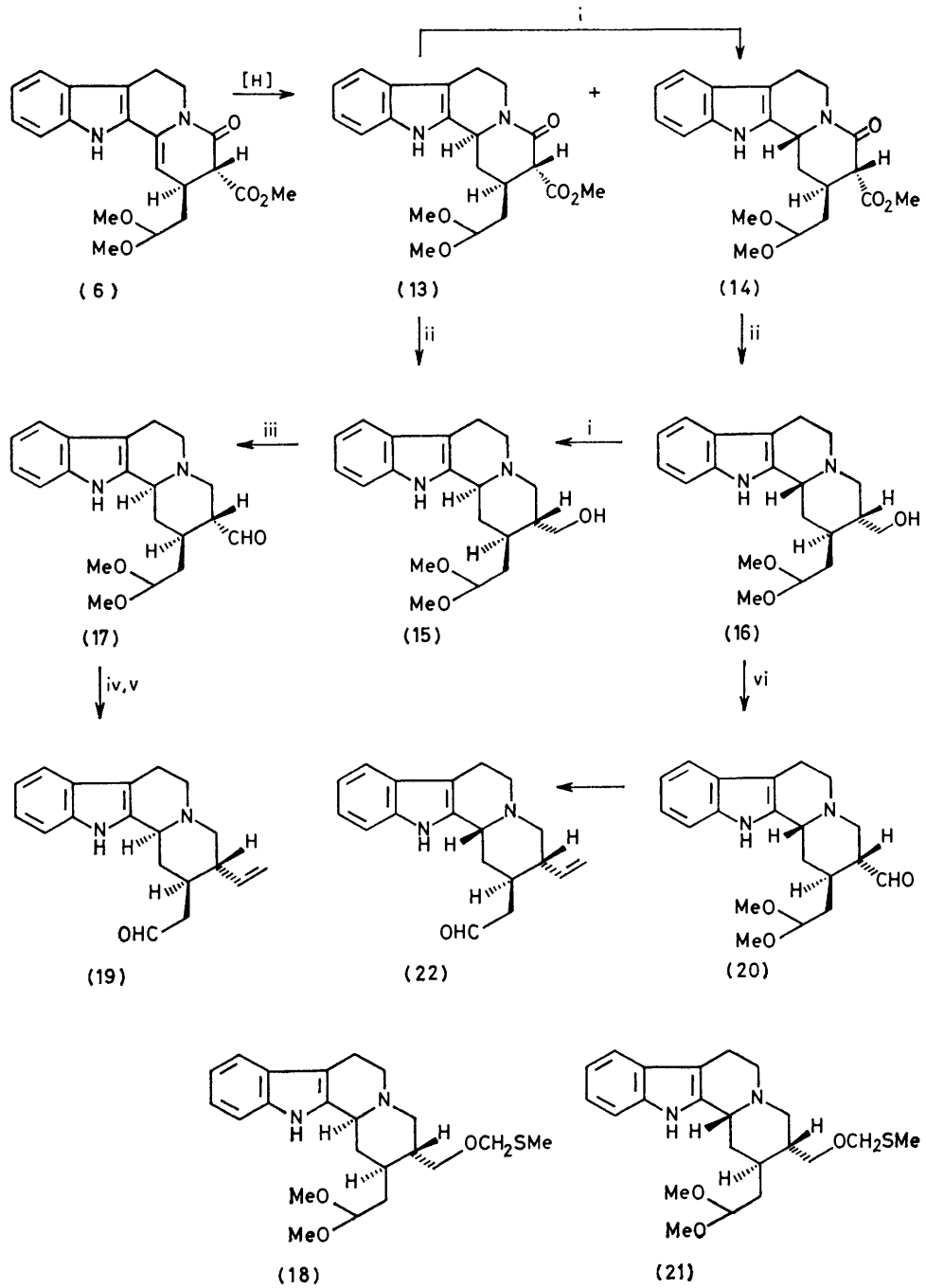


SCHEME 2 *Reagents*: i, EtI, NaH; ii, H_2, PtO_2; iii, H_2, 10% Pd–C; iv, NaOH, MeOH; v, DMSO, 160 °C; vi, TsOH, acetone; vii, TsOH, MeOH; viii, $LiAlH_4$

with toluene-*p*-sulphonic acid in methanol, followed by reduction of the lactam-acetal (10) with lithium aluminium hydride and then deprotection of the acetal group afforded (±)-dihydrocorynantheal (12).[8]

Formal Total Syntheses of (±)-*Corynantheine and* (±)-*Ajmalicine.*—Corynantheine (2) was first isolated along with dihydrocorynantheine as a crystalline mixture from *Pseudocinchona africana*,[10] while the heteroyohimbine alkaloid ajmalicine (3) was found in various plants. Synthesis of both alkaloids had been carried out by several groups,[11,12] including biogenetic-type syntheses by van Tamelen.[13,14] The above indolo[2,3-*a*]quinolizine derivative (6) was transformed, utilizing the carbon atom of the ester group at the C-3 position, into (±)-corynantheal (19) which was convertible into corynantheine and ajmalicine.

The above enamide (6) was completely reduced with 10% palladium–charcoal or Adams catalyst in methanol for 1 h under 2 atm of hydrogen producing two stereoisomers. The faster-moving product (13) on silica gel



SCHEME 3 *Reagents*: i, H_2, PtO_2; ii, $LiAlH_4$; iii, DMSO, DCC, CF_3CO_2H, pyridine; iv, $Ph_3P{=}CH_2$; v, TsOH, acetone; vi, $(CF_3CO)_2O$, DMSO, Et_3N

chromatography showed the dimethyl acetal group at δ 3.26 and 3.35, and the methyl ester group at δ 3.73, whereas the slower-moving product (14), m.p. 206—210 °C, exhibited the dimethyl acetal group at δ 3.37 as a singlet and the methyl ester at δ 3.70 in its n.m.r. spectrum. The formation ratio of the two products depended on the catalysts. For the reaction using 10% palladium–charcoal, (13) and (14) formed in the ratio 1 : 1.2, while hydrogenation using Adams catalyst gave a mixture of (13) and (14) in the ratio 9 : 20. Furthermore, it was observed that the former (13) was slowly convertible into the latter (14) under the conditions used for the Adams catalyst reduction. Thus reduction of (6) with Adams catalyst for 60 h under the same conditions as above gave (13) and (14) in the ratio 1 : 32. The compounds were not interchanged by reaction with sodium hydride in dimethylformamide [4] when only starting materials were recovered. It was therefore assumed that compounds (13) and (14) were stereoisomers at the angular position possessing *trans*-substituents at C-2 and C-3.

Both the lactam and ester groups of (13) and (14) were then reduced with lithium aluminium hydride. The tetracyclic amine (15), formed in 78.2% yield from (13), showed Bohlmann bands at 2 900—2 700 cm^{-1} whereas the product (16), obtained in 81.4% yield from (14), exhibited no *trans*-quinolizidine absorption. At this stage, the latter amine (16) was quantitatively converted into the former (15) by the reaction with Adams catalyst under 2 atm of hydrogen for 3 days. On the basis of the above observations, the stereochemistries of (6) and (13)—(16) were determined as shown in Scheme 3.

It is interesting that catalytic hydrogenation of the 3-monosubstituted enamide (6) in the presence of Adams catalyst predominantly formed the 12bβ-H isomer (14); this contrasts with the 3-disubstituted enamide (7) which gave selectively the 12bα-H isomer (8). Furthermore the 12bβ-H isomer (14) seems to be more thermodynamically stable than the corresponding 12bα-H lactam (13) because treatment of (13) under catalytic hydrogenation conditions using Adams catalyst produced a mixture of (13) and (14) in which (14) was the main component. We had already found that the chirality at the C-1 position of tetrahydroisoquinoline derivatives was changed by treatment using Adams catalyst under hydrogen.[15,*] The exchange of chirality at the angular position using Adams catalyst has been further demonstrated in the case of the indolo[2,3-*a*]-quinolizidines and the corresponding lactams as shown above.

The alcohol (15), which was the sole product from (6) after the above epimerisation procedure, was transformed into (±)-corynantheal (19) as follows. Using dimethyl sulphoxide, dicyclohexylcarbodi-imide, trifluoroacetic acid, and pyridine,[17] the alcohol (15) was oxidised to the aldehyde (17) in 84.6% yield along with a small amount of a methylthiomethyl ether (18). Wittig reaction of (17) using methyltriphenylphosphonium bromide and n-butyl-lithium, followed by deprotection with toluene-*p*-sulphonic acid in acetone, furnished (±)-corynantheal (19) in 51% yield, whose i.r., n.m.r., and mass spectra and t.l.c. behaviour in various solvent systems were identical with those of the authentic (—)-corynantheal.[18] Since corynantheal had already been converted into corynantheine (2) in three steps [11,13,18] and into ajmalicine (3) in four steps,[14,17,19] the formal total synthesis of the racemates of these alkaloids was accomplished in a stereoselective manner.

The stereoisomer (16) of the alcohol was also converted into the epimer (22) of (±)-corynantheal. Oxidation of the alcohol to the corresponding aldehyde (20) by the ordinary Moffatt oxidation [17] resulted in a poor yield and mainly produced a methylthiomethyl ether (21) which was probably due to the more hindered alcohol. The desired aldehyde (20) was synthesised in 78.2% yield by reaction with dimethyl sulphoxide, trifluoroacetic anhydride, and triethylamine,[20] and was then transformed into the epimer (22) in 53.5% yield by the same sequence as above. No Bohlmann bands were observed in the i.r. spectra of (20)—(22) and the hydrogens at the C-12b position of (20)—(22) resonated at δ 4.40—4.50.[21] These results also suggested the *cis*-quinolizidine form for these compounds and confirmed the above stereochemical assignment.

EXPERIMENTAL

I.r. spectra were recorded on a Hitachi 260-10 spectrophotometer, n.m.r. spectra on JEOL JNM-PMX 60 and PS-100 spectrometers, and mass spectra on Hitachi M-52G and JEOL-JMS-01SG-2 spectrometers.

2-(2,2-*Dimethoxyethyl*)-2,3,4,6,7,12-*hexahydro*-3-*methoxycarbonyl*-4-*oxoindolo*[2,3-a]*quinolizine* (6).—A solution of the enamine (4) (3.3 g) and dimethyl 3-methoxyallylidenemalonate (5) (3.9 g) in methanol (150 ml) was stirred for 72 h at room temperature and then refluxed for 24 h under nitrogen. After evaporation of the solution, the residue was chromatographed on silica gel with dichloromethane–methanol (200 : 1 v/v) to give the *enamide* (6) (5.3 g, 77%) as a reddish oil; $\nu_{max.}$ ($CHCl_3$) 3 470 (NH), 1 740 and 1 660 cm^{-1} (C=O); δ ($CDCl_3$) 1.67 [2 H, t, *J* 6 Hz, $CH_2CH(OMe_2)$], 2.83 (2 H, t, *J* 6 Hz, 7-H_2), 3.30 (6 H, s, 2 × OMe), 3.70 (3 H, s, OMe), 4.53 [1 H, t, *J* 6 Hz, $CH(OMe)_2$], 5.57 (1 H, d, *J* 5 Hz, CH=C<), 6.97—7.50 (4 H, m, 4 × ArH), and 8.70 (1 H, s, NH); *m/e* 384 (M^+) (Found: C, 62.35; H, 6.0; N, 6.55. $C_{21}H_{24}N_2O_5 \cdot H_2O$ requires C, 62.65; H, 6.5; N, 6.95%).

2-(2,2-*Dimethoxyethyl*)-3-*ethyl*-2,3,4,6,7,12-*hexahydro*-3-*methoxycarbonyl*-4-*oxoindolo*[2,3-a]*quinolizine* (7).—To a solution of the above compound (6) (1.22 g) in dry dimethylformamide (28 ml), 60% sodium hydride (140 mg) was added with stirring under nitrogen at room temperature. After stirring for 0.5 h at room temperature, ethyl iodide (534 mg) was added dropwise to the above mixture at 0 °C and the resulting mixture was stirred for 2 h. Benzene was added to the reaction mixture, which was then washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give a residue, which was then chromatographed on

* Epimerisation of 3-epidihydrocorynantheol into dihydrocorynantheol during hydrogenation has been observed by Ziegler and Sweeny.[16]

silica gel (15 g) with dichloromethane–methanol (200 : 1 v/v) to afford the *ethyl compound* (7) (1.176 g, 89.8%); δ ($CDCl_3$) 1.00 (3 H, t, *J* 6 Hz, CH_2CH_3), 2.10 [4 H, m, CH_2CH_3 and $CH_2CH(OMe)_2$], 2.90 (2 H, t, *J* 5 Hz, 7-H_2), 3.33 (6 H, s, 2 × OMe), 3.51 (3 H, s, OMe), 5.56 (1 H, d, *J* 3 Hz, C*H*=C<), 7.00—7.50 (4 H, m, 4 × ArH), and 8.76 (1 H, s, NH); *m/e* 412 (M^+) (Found: C, 65.2; H, 6.65; N, 6.4. $C_{23}H_{28}N_2O_5 \cdot 0.5H_2O$ requires C, 65.55; H, 6.95; N, 6.65%).

Reduction of the Ethyl Compound (7).—(*a*) A solution of the above compound (7) (1.0 g) in methanol (100 ml) was shaken for 2 h at room temperature under 1.5 atm of hydrogen in the presence of platinum oxide (145 mg). After removal of the catalyst by filtration, the filtrate was evaporated and then taken up into benzene. The benzene solution was washed with water and dried (Na_2SO_4). Evaporation of the solution afforded (±)-2β-(2,2-*dimethoxyethyl*)-3-*ethyl*-1,2α,3,4,6,7,12,12bα-*octahydro*-3-*methoxycarbonyl*-4-*oxoindolo*[2,3-a]*quinolizine* (8) (961 mg, 95.7%) as a yellowish syrup, which was crystallised from chloroform–hexane to give the lactam as fine needles, m.p. 116.5—118 °C; δ ($CDCl_3$) 0.90 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.37 (6 H, s, 2 × OMe), 3.53 (3 H, s, OMe), 7.00—7.53 (4 H, m, 4 × ArH), and 8.38 (1 H, s, NH); *m/e* 413 ($M^+ - 1$) (Found: C, 66.25; H, 7.1; N, 6.7. $C_{23}H_{30}N_2O_5$ requires C, 66.65; H, 7.3; N, 6.75%).

(*b*) A solution of the ethyl compound (7) (77 mg) in methanol (100 ml) was shaken for 30 h under 1.5 atm of hydrogen in the presence of 10% palladium–charcoal (50 mg). After removal of the catalyst by filtration, the filtrate was evaporated and then taken up into benzene. The benzene extract was washed with water and dried (Na_2SO_4). Evaporation of the solution afforded a yellowish syrup, which was chromatographed on silica gel using benzene–ethyl acetate (85 : 15 v/v) to give the lactam (8) (44 mg, 57%), identical (n.m.r. and mass spectra) with the sample prepared by method (*a*).

Further elution with benzene–ethyl acetate (4 : 1 v/v) gave the 12bβ-H *lactam* (9) (22 mg, 28%) as a solid; δ ($CDCl_3$) 0.53 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.23 (3 H, s, OMe), 3.33 (3 H, s, OMe), 3.72 (3 H, s, OMe), 7.00—7.60 (4 H, m, 4 × ArH), and 8.00 (1 H, s, NH); *m/e* 414 (M^+) (Found: C, 66.0; H, 7.45; N, 6.45. $C_{23}H_{30}N_2O_5 \cdot 0.25H_2O$ requires C, 65.95; H, 7.2; N, 6.7%).

Epimerization of the 12*b*β-*H-Lactam* (9) *with Adams Catalyst*.—A solution of the 12bβ-lactam (9) (5 mg) in methanol (10 ml) was stirred for 6 days under 1.5 atm of hydrogen in the presence of platinum oxide (10 mg). After removal of the catalyst by filtration, the filtrate was evaporated and then taken up into benzene. The organic solution was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded a syrup, which was chromatographed on silica gel using benzene–ethyl acetate (85 : 15 v/v) to give the 12bα-H-lactam (8) (2 mg) whose spectral data were identical with those of the above sample (8).

(±)-3α-*Ethyl*-2β-*formylmethyl*-1,2α,3β,4,6,7,12,12bα-*octahydro*-4-*oxoindolo*[2,3-a]*quinolizine* (11).—A solution of the above lactam (8) (120 mg) in 3% methanolic sodium hydroxide solution (3.3 ml) was refluxed for 3 h and the resulting mixture was evaporated. The residue was taken up into water, acidified to pH 6 with acetic acid, and then extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), and evaporated to dryness. A solution of the residue in dry dimethyl sulphoxide (10 ml) was stirred for 1 h at 160 °C under nitrogen. After addition of benzene, the mixture was washed with water, dried (Na_2SO_4), and evaporated to give a mixture of the acetal (10) and the aldehyde (11) as a syrup. A solution of the above mixture in acetone (6 ml) was stirred for 2 h with ice-cooling in the presence of a catalytic amount of toluene-*p*-sulphonic acid (20 mg). After addition of an excess of crystalline sodium hydrogencarbonate with ice-cooling, followed by evaporation of the solvent, the residue was partitioned between water and chloroform. The organic layer was separated, dried (Na_2SO_4), and then evaporated. The oily residue was chromatographed on silica gel using dichloromethane–methanol (20 : 1 v/v) to give the *aldehyde* (11) (82 mg, 92%) as a yellow solid, which was recrystallised from chloroform–hexane to give prisms, m.p. 210—213 °C; $\nu_{max.}$ ($CHCl_3$) 3 475 (NH), and 1 720 and 1 630 cm^{-1} (C=O); δ ($CDCl_3$) 0.90 (3 H, t, *J* 7 Hz, CH_2CH_3), 7.00—7.53 (4 H, m, 4 × ArH), 8.70, (1 H, s, NH), and 9.70 (1 H, s, CHO), *m/e* 310 (M^+) (Found: C, 72.0; H, 7.05; N, 8.35. $C_{19}H_{22}N_2O_2 \cdot 0.5H_2O$ requires C, 72.5; H, 7.0; N, 8.45%).

(±)-*Dihydrocorynantheol* (1).—To lithium aluminium hydride (20 mg) in a mixture of dry tetrahydrofuran (10 ml) and dry ether (5 ml), a solution of the above aldehyde (11) (42 mg) in dry tetrahydrofuran (5 ml) was added dropwise with stirring for 1 h at 0 °C under nitrogen. The mixture was refluxed for 3.5 h and then cooled with ice. The excess of reagent was decomposed with addition of 15% aqueous sodium hydroxide and the organic layer was separated by decantation. The aqueous layer was extracted with chloroform and the combined organic extracts were evaporated. The residue was taken up into 5% hydrochloric acid, washed with ether, and basified with saturated aqueous sodium hydrogencarbonate. After extraction with ether, the extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give (±)-dihydrocorynantheol (1) (22 mg, 54.5%) as a reddish syrup, which was recrystallised from dichloromethane–n-hexane to give prisms, m.p. 178.5—180 °C (lit.,[16] m.p. 178—180.5 °C); $\nu_{max.}$ ($CHCl_3$) 3 475 (NH) and 2 700—2 900 cm^{-1} (Bohlmann bands); *m/e* 297 ($M^+ - 1$), 298 (M^+), 169, 170, and 156.

(±)-2β-(2,2-*Dimethoxyethyl*)-3α-*ethyl*-1,2α,3,4,6,7,12,12bα-*octahydro*-4-*oxoindolo*[2,3-a]*quinolizine* (10).—A solution of the above mixture of (10) and (11) (47 mg) in methanol (5 ml) was stirred for 2.5 h under ice-cooling in the presence of a catalytic amount of toluene-*p*-sulphonic acid (10 mg). After addition of an excess of crystalline sodium hydrogencarbonate under ice-cooling, followed by evaporation of the solvent, the residue was partitioned between water and chloroform. The organic layer was separated and dried (Na_2SO_4). Evaporation afforded a yellowish oil, which was chromatographed on silica gel using benzene–ethyl acetate (1 : 1 v/v) to give the acetal (10) (46 mg, 86.5%) as a yellow powder; $\nu_{max.}$ ($CHCl_3$) 3 450 (NH) and 1 620 cm^{-1} (C=O); δ ($CDCl_3$) 0.92 (3 H, t, *J* 7 Hz, CH_2CH_3), 3.30 (6 H, s, 2 × OMe), 6.93—7.60 (4 H, m, 4 × ArH), and 8.63 (1 H, s, NH); *m/e* 356 (M^+) (Found: M^+, 356.2114. $C_{21}H_{28}N_2O_3$ requires *M*, 356.2099).

(±)-*Dihydrocorynantheal* (12).—To a mixture of lithium aluminium hydride (20 mg) and dry tetrahydrofuran (20 ml), a solution of the above acetal (10) (40 mg) in dry tetrahydrofuran was added dropwise with stirring for 10 min at room temperature under nitrogen. The mixture was refluxed for 1 h and then cooled with ice. The excess of reagent was decomposed with addition of 15% aqueous sodium hydroxide and the organic layer was separated by

decantation. The aqueous layer was extracted with dichloromethane and the combined organic extracts were washed with water, dried (Na_2SO_4), and evaporated to give a reddish oil. A solution of the residue in acetone (5 ml) was stirred for 2 h under ice-cooling in the presence of a catalytic amount of toluene-*p*-sulphonic acid (20 mg). After addition of an excess of crystalline sodium hydrogencarbonate under ice-cooling followed by evaporation of the solvent, the residue was partitioned between water and chloroform. The organic layer was separated and dried (Na_2SO_4). Evaporation afforded a yellowish oil, which was chromatographed on silica gel using dichloromethane–methanol (50 : 1 v/v) to give (±)-*dihydrocorynantheal* (12) (16 mg, 48%) as a yellowish syrup; $\nu_{max.}$ ($CHCl_3$) 3 475 (NH), 2 700—2 900 (Bohlmann bands), and 1 715 cm^{-1} (C=O); δ ($CDCl_3$) 0.96 (3 H, m, CH_2CH_3), 6.90—7.50 (4 H, m, 4 × ArH), 8.10 (1 H, s, NH), and 9.80 (1 H, s, CHO); *m/e* 296 (M^+) (Found: M^+, 296.1842. $C_{19}H_{24}N_2O$ requires *M*, 296.1887).

Reduction of Indolo[2,3-a]*quinolizine* (6).—(*a*) A solution of the above enamide (6) (140 mg) in methanol (30 ml) was shaken for 60 h at room temperature under 2 atm of hydrogen in the presence of platinum oxide (15 mg). After removal of the catalyst by filtration, the filtrate was evaporated to give a yellowish syrup, which was recrystallised from methanol to give (±)-2β-(2,2-*dimethoxyethyl*)-1,2α,3β,4,6,7,12,12β-*octahydro*-3α-*methoxycarbonyl*-4-*oxoindolo*[2,3-a]*quinolizine* (14) (50 mg) as prisms, m.p. 209—210 °C; δ ($CDCl_3$) 3.26 (3 H, s, OMe), 3.35 (3 H, s, OMe), 3.73 (3 H, s, OMe), 7.20—7.80 (4 H, m, 4 × ArH), and 8.00 (1 H, s, NH); *m/e* 386 (M^+) (Found: C, 65.15; H, 6.65; N, 7.0. $C_{21}H_{26}N_2O_5$ requires C, 65.25; H, 6.8; N, 7.25%).

Evaporation of the filtrate afforded a yellowish oil, which was chromatographed on silica gel using benzene–ethyl acetate (4 : 1 v/v) to give (±)-2β-(2,2-dimethoxyethyl)-1,2α,3β-4,6,7,12,12bα-*octahydro*-3α-*methoxycarbonyl*-4-*oxoindolo*[2,3-a]*quinolizine* (13) (3 mg, 2%) as a light brown syrup; $\nu_{max.}$ ($CHCl_3$) 3 460 (NH), and 1 735 and 1 635 cm^{-1} (C=O); δ ($CDCl_3$) 3.57 (6 H, s, 2 × OMe), 3.70 (3 H, s, OMe), 7.06—7.66 (4 H, m, 4 × ArH), and 8.65 (1 H, s, NH); *m/e* 386 (M^+) (Found: C, 64.8; H, 6.6; N, 7.05. $C_{21}H_{26}N_2O_5 \cdot 0.25H_2O$ requires C, 64.50; H, 6.75; N, 7.15%).

Further elution using benzene–ethyl acetate (7 : 3 v/v) gave the 12bβ-H compound (14) (40 mg, total yield 64%) as a yellow solid.

(*b*) A solution of the above enamide (6) (300 mg) in methanol (100 ml) was shaken for 1 h at room temperature under 2 atm of hydrogen in the presence of 10% palladium–charcoal (200 mg). After work-up as above, the residue was chromatographed on silica gel using benzene–ethyl acetate (4 : 1 v/v) to give the C-12bα-H-lactam (13) (100 mg, 33.2%) as a yellowish syrup, identical (i.r., n.m.r., and mass spectra) with the sample prepared by method (*a*).

Further elution with benzene–ethyl acetate (7 : 3 v/v) gave the C-12bβ-H-lactam (14) (116 mg, 38.5%) as a solid, identical (n.m.r. and mass spectra) with the sample prepared by method (*a*).

Epimerisation of the 12bα-H-*Lactam* (13) *with Adams Catalyst*.—A solution of the 12bα-H-lactam (13) (150 mg) in methanol (30 ml) was shaken for 6 days under 2 atm of hydrogen in the presence of platinum oxide (20 mg). After removal of the catalyst by filtration, the filtrate was evaporated to give a yellowish residue, which was chromatographed on silica gel using benzene–ethyl acetate (4 : 1 v/v) to give the 12bα-H-lactam (13) (40 mg). Further elution with benzene–ethyl acetate (7 : 3 v/v) gave the 12bβ-H-lactam (14) (107 mg).

(±)-2β-(2,2-*Dimethoxyethyl*)-1,2α,3β,4,6,7,12,12bα-*octahydro*-3α-*hydroxymethyl*-4-*oxoindolo*[2,3-a]*quinolizine* (15).—To a mixture of lithium aluminium hydride (200 mg) and dry tetrahydrofuran (10 ml), a solution of the above 12bα-H-lactam (13) (400 mg) in dry tetrahydrofuran (10 ml) was added dropwise with stirring under reflux. The mixture was stirred for 1 h under reflux and then cooled with ice. The excess of reagent was decomposed with addition of 10% aqueous sodium hydroxide and the organic layer was separated by decantation. The aqueous layer was extracted with chloroform and the combined organic extracts were washed with water, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on silica gel using ethyl acetate–methanol (100 : 2 v/v) to give a solid (278 mg, 78.2%), which was recrystallised from benzene to give the *alcoholic amine* (15) as a yellowish solid, m.p. 180—182 °C; $\nu_{max.}$ ($CHCl_3$) 3 460 (NH) and 2 700—2 900 cm^{-1} (Bohlmann bands); δ ($CDCl_3$) 3.30 (6 H, s, 2 × OMe), 3.60 (2 H, d, CH_2OH), 4.50 [1 H, t, $CH(OMe)_2$], 7.16 (4 H, m, 4 × ArH), and 7.93 (1 H, s, NH); *m/e* 344 (M^+) (Found: C, 66.2; H, 7.7; N, 7.5. $C_{20}H_{28}N_2O_3 \cdot H_2O$ requires C, 66.65; H, 7.85; N, 7.75%).

(±)-2β-(2,2-*Dimethoxyethyl*)-3α-*formyl*-1,2α,3β,4,6,7,12,-12bα-*octahydro*-4-*oxoindolo*[2,3-a]*quinolizine* (17).—To a solution of the above alcoholic amine (15) (290 mg) in dry benzene (5 ml) and dry dimethyl sulphoxide (5 ml), dry pyridine (0.24 ml), trifluoroacetic acid (0.12 ml), and dicyclohexylcarbodi-imide (555 mg) were in turn added with stirring for 20 min under nitrogen at room temperature. The resulting mixture was left for 12 h at room temperature. Benzene was then added and the reaction mixture was washed with water. The organic layer was dried (Na_2SO_4) and evaporated to give an oily residue, which was then chromatographed on silica gel using benzene–ethyl acetate (9 : 1 v/v) to give the *aldehyde* (17) (208 mg, 84.6%) as a syrup; $\nu_{max.}$ ($CHCl_3$) 3 475 (NH) and 1 725 cm^{-1} (C=O); δ ($CDCl_3$) 3.33 (6 H, s, 2 × OMe), 4.50 [1 H, t, $CH(OMe)_2$], 7.00—7.60 (4 H, m, 4 × ArH), 7.96 (1 H, s, NH), and 9.70 (1 H, s, CHO); *m/e* 342 (M^+) (Found: M^+, 342.1919. $C_{20}H_{26}N_2O_3$ requires *M*, 342.1941).

Further elution with ethyl acetate gave the *methylthiomethyl ether* (18) (4 mg, 1%); δ ($CDCl_3$) 2.03 (3 H, s, SMe), 3.27 (3 H, s, OMe), 3.33 (3 H, s, OMe), 4.50 (2 H, s, OCH_2S), 6.70—7.50 (4 H, m, 4 × ArH), and 8.73 (1 H, s, NH); *m/e* 404 (M^+) (Found: M^+, 404.2131. $C_{22}H_{32}N_2O_3S$ requires *M*, 404.2132).

(±)-*Corynantheal* (19).—To a suspension of methyltriphenylphosphonium bromide (200 mg) in dry benzene (5 ml) was added 10% (w/v) n-butyl-lithium in hexane solution (0.45 ml) and the mixture was refluxed for 1 h. After cooling, a solution of the aldehyde (17) (100 mg) in dry benzene (3 ml) was added to the resulting solution. The mixture was stirred at room temperature for 1 h under argon. Water was added and the reaction mixture was then extracted with benzene. The extract was washed with brine, dried (Na_2SO_4), and evaporated to give a reddish oil. A solution of the residue in acetone (10 ml) was stirred for 1 h with ice-cooling in the presence of a catalytic amount of toluene-*p*-sulphonic acid (10 mg). After addition of an excess of crystalline sodium hydrogencarbonate with ice-cooling followed by evaporation of the solvent, the residue was partitioned between water and chloroform. The organic layer was separated, dried (Na_2SO_4), and then evaporated to

give a yellowish oil, which was chromatographed on silica gel using benzene–ethyl acetate (4 : 1 v/v) to give a yellowish solid (48.3 mg, 51%), which was recrystallised from benzene–dichloromethane to give (±)-*corynantheal* (19) as prisms, m.p. 190—191.5 °C; $\nu_{max.}$ ($CHCl_3$) 3 460 (NH), 2 700—2 900 (Bohlmann bands), and 1 720 cm^{-1} (C=O); δ ($CDCl_3$), 4.90—5.90 (3 H, m, $CH{=}CH_2$), 6.93—7.60 (4 H, m, 4 × ArH), 7.96 (1 H, s, NH), and 9.77 (1 H, s, CHO); *m/e* 294 (M^+), 293, 184, 170, 169, and 156 (Found: M^+, 294.1710. $C_{19}H_{22}N_2O$ requires *M*, 294.1730). The spectral data and the t.l.c. behaviour in various solvent systems were identical with those of (−)-corynantheal.

(±)-2β-(2,2-*Dimethoxyethyl*)-1,2α,3β,4,6,7,12,12bβ-*octahydro*-3α-*hydroxymethyl*-4-*oxoindolo*[2,3-a]*quinolizine* (16).—To a mixture of lithium aluminium hydride (200 mg) and dry tetrahydrofuran (20 ml), a hot solution of the above 12bβ-H-lactam (14) (400 mg) in dry tetrahydrofuran (15 ml) was added dropwise with stirring under reflux. The mixture was stirred for 1 h under reflux. After work-up as described for the case of (13), the residue was chromatographed on silica gel using ethyl acetate–methanol (20 : 1 v/v) to give a yellow solid, which was recrystallised from benzene to give the *alcoholic amine* (16) (290 mg, 81.4%) as prisms, m.p. 189—190 °C; $\nu_{max.}$ ($CHCl_3$) 3 460 cm^{-1} (NH); δ ($CDCl_3$) 3.30 (6 H, s, 2 × OMe), 4.43 [1 H, m, $CH(OMe)_2$], 6.93—7.43 (4 H, m, 4 × ArH), and 8.06 (1 H, s, NH), *m/e* 344 (M^+) (Found: C, 69.45; H, 8.2; N, 8.05. $C_{20}H_{28}N_2O_3$ requires C, 69.75; H, 8.2; N, 8.15%).

(±)-2β-(2,2-*Dimethoxyethyl*)-3α-*formyl*-1,2α,3β,4,6,7,12,-12bβ-*octahydro*-4-*oxoindolo*[2,3-a]*quinolizine* (20).—To a solution of dry dimethyl sulphoxide (0.5 ml) and dry dichloromethane (5 ml), a solution of trifluoroacetic anhydride (360 mg) in dry dichloromethane (1 ml) was added at −78 °C with stirring under nitrogen. After the mixture had been stirred for 10 min at −78 °C, a solution of the above alcohol (16) (360 mg) in dry dichloromethane (2 ml) and dry dimethyl sulphoxide (0.1 ml) was added dropwise. The resulting mixture was stirred for 50 min at −78 °C, followed by dropwise addition of triethylamine (1 ml). The cooling-bath was then removed and the reaction mixture was allowed to stand at room temperature for 1 h. Water was added to the mixture, which was then extracted with dichloromethane. The extract was evaporated to give a reddish oil, which was extracted with benzene. The organic layer was washed with water and brine, dried (Na_2SO_4), and evaporated to afford a yellowish oil, which was chromatographed on silica gel using benzene–ethyl acetate (1 : 1 v/v) to give the *aldehyde* (20) (280 mg, 78.2%), which was recrystallised from benzene to give fine needles, m.p. 164—166 °C; $\nu_{max.}$ ($CHCl_3$) 3 470 (NH) and 1 720 cm^{-1} (C=O); δ ($CDCl_3$) 3.33 (6 H, s, 2 × OMe), 4.50 [2 H, m, $CH(OMe)_2$ and 12b-H], 6.90—7.60 (4 H, m, 4 × ArH), 7.90 (1 H, s, NH), and 9.66 (1 H, s, CHO); *m/e* 343 (M^+) (Found: C, 69.65; H, 7.8; N, 8.05. $C_{20}H_{26}N_2O_3$ requires C, 70.15; H, 7.7; N, 8.2%).

Further elution with ethyl acetate–methanol (100 : 5 v/v) gave the sulphide (21) (15 mg, 3.6%) as a reddish oil; δ ($CDCl_3$) 2.06 (3 H, s, SMe), 3.26 (3 H, s, OMe), 3.33 (3 H, s, OMe), 4.53 [4 H, m, OCH_2S, $CH(OMe)_2$, and 12b-H], 6.90—7.50 (4 H, m, 4 × ArH), and 7.83 (1 H, s, NH); *m/e* 404 (M^+) (Found: M^+, 404.2163. $C_{22}H_{32}N_2O_3S$ requires *M*, 404.2162).

(±)-*Epicorynantheal* (22).—To a suspension of methyltriphenylphosphonium bromide (175 mg) in dry benzene (5 ml) was added 10% (w/v) n-butyl-lithium in hexane solution (0.4 ml) and the resulting mixture was refluxed for 1 h. After cooling, a solution of the aldehyde (20) (100 mg) in dry benzene (3 ml) was added to the above resulting mixture, and the mixture was stirred at room temperature for 40 min under argon. After the same work-up as the case of (17), a solution of the residue in acetone (20 ml) was stirred for 1 h with ice-cooling in the presence of a catalytic amount of toluene-*p*-sulphonic acid (10 mg). After work-up as above, the residue was chromatographed on silica gel using ethyl acetate–methanol (100 : 3 v/v) to give *epicorynantheal* (22) (46 mg, 53.5%) as a yellowish syrup; $\nu_{max.}$ ($CHCl_3$) 3 450 (NH) and 1 720 cm^{-1} (C=O); δ ($CDCl_3$) 4.30 (1 H, m, 12b-H), 4.80—5.70 (3 H, m, $CH{=}CH_2$), 7.00—7.80 (4 H, m, 4 × ArH), 8.4 (1 H, s, NH), and 9.73 (1 H, s, CHO); *m/e* 294 (M^+) (Found: M^+, 294.1704. $C_{19}H_{22}N_2O$ requires *M*, 294.1730).

Epimerisation of the 12bβ-H-*Alcohol* (16).— A solution of the 12bβ-H-alcohol (16) (50 mg) in methanol (20 ml) was shaken for 118 h at room temperature under 2 atm of hydrogen in the presence of platinum oxide (10 mg). After removal of the catalyst by filtration, evaporation of the filtrate afforded a yellowish oil, which was chromatographed on silica gel using ethyl acetate–methanol (20 : 1 v/v) to give the C-12bα-H-alcohol (15) (43 mg), identical (i.r. and n.m.r. spectra) with an authentic sample.

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