The Synthesis of 9,10-Dimethyl-4,6,6a,7,8,9,10,10a-octahydroindolo[3,4-*gh*]-isoquinoline, the 8,9-Dimethyl-8-aza Analogue† of Ergoline

William H. Hunter *
Royal Holloway and Bedford College, Egham Hill, Surrey TW20 0EX
David E. Tupper
Lilly Research Centre Limited, Eli Lilly and Co., Windlesham, Surrey GU20 6PH

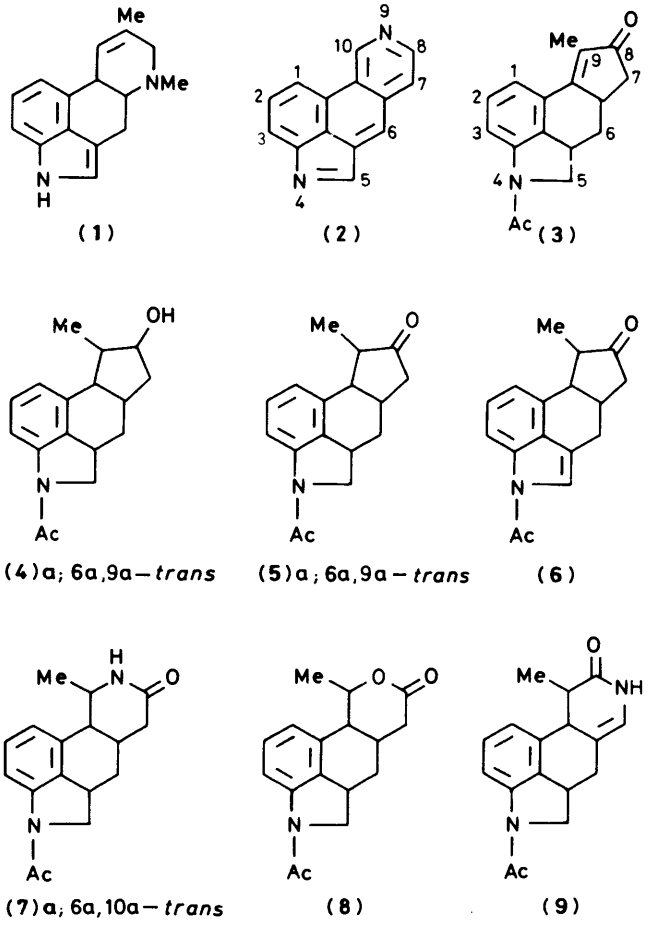
The title compound (**15**) has been synthesised by ring expansion of the cyclopentanone 4-acetyl-9-methyl-4,5,5a,6,6a,7,9,9a-octahydroindeno[6,5.4-*cd*]indol-8-one (**5**) by means of the Schmidt reaction. The stereochemistry at C-6a, -9, and -9a of the starting ketone and at C-6a, -10, and -10a of the four lactams produced by the reaction is established by means of the ^{1}H n.m.r. spectral analysis. Two of these isomeric lactams and the corresponding isomers of the title compound have been isolated and characterised.

The naturally occurring ergot alkaloids are partially hydrogenated derivatives of indolo[4,3-*fg*]quinolines such as agroclavine (**1**). They are therefore the derivatives of ergoline, and we have previously reported the synthesis of several 7-aza analogues.[1] We now report the total synthesis of the isomeric indolo[3,4-*gh*]isoquinoline ring system, structure (**2**), the 8-aza analogue of ergoline.[2] A synthesis of some compounds containing this ring system has been reported[3] but no data or details of the synthesis have been published. As starting material, we used the same benz[*cd*]indole derivative (**3**) that we used for synthesis of the 7-azaergoline isomer. We have previously shown that ring expansion of the cyclopentenone (**3**) gave a lactam that was the precursor for the 7-azaergoline system.[1] Rearrangement of the corresponding cyclopentanone (**5**), however, could be expected to proceed to an 8-azaergoline lactam though this synthetic route was likely to result in formation of a mixture of isomers.

Reduction of the cyclopentenone (**3**)‡ was accomplished over platinum(IV) oxide, the ketone function being reduced simultaneously to give the alcohol (**4**). Examination of the cyclopentanol (**4**) by high-performance liquid chromatography (h.p.l.c.) showed the presence of two components in the ratio 5:1, but the mixture was oxidised directly with pyridinium chlorochromate (PCC) in methylene dichloride. Precipitation of the spent oxidant with ether as recommended by Corey[4] led to loss of product; ethyl acetate proved a more satisfactory precipitant. The ^{1}H n.m.r. spectrum of the ketone (**5**) showed two doublets, at δ 0.70 (*J* 7.5 Hz) and at δ 1.29 (*J* 6.8 Hz), assignable to the 9-methyl substituent, and h.p.l.c. confirmed that compound (**5**) could be separated into two components. The isomerism previously observed in the alcohol (**4**) could not therefore be attributed to a *cis–trans* arrangement of 8-OH and 9-Me substituents.

Since catalytic hydrogenation could be expected to proceed by *cis* addition of hydrogen, then both compounds (**4**) and (**5**) should have a *cisoid* arrangement of the hydrogen atoms at C-9 and C-9a. The mixture of two components in compounds (**4**) and (**5**) is therefore more probably due to the presence of *cis* and *trans* fusion about the ring junction at C-6a–C-9a.

A minor component formed during this oxidation gave a positive reaction as an indole and proved to be the *N*-acetylindole (**6**); it too gave two sets of doublets for the 9-methyl signal.



Fractional crystallisation of the cyclopentanol (**4**) from ethyl acetate gave a major component with the 9-methyl doublet at δ 0.65 (*J* 7.2 Hz), and oxidation of this isomer gave the cyclopentanone (**5a**) with the 9-methyl doublet resonating at δ 0.70 (*J* 7.5 Hz). The 220 MHz ^{1}H n.m.r. spectrum of this isomer (**5a**) showed four low-field aliphatic protons, assignable to 5-H_2 (δ 3.57 and 4.25), 5a-H (δ 3.38), and 9a-H (δ 3.77). The proton 9a-H had two large couplings (8.0 and 8.5 Hz) to 9-H and 6a-H, indicating a *trans* configuration at the ring junction. In order to assist with the stereochemical identification of the mixtures of isomers expected to result from the ring-expansion reaction, this

† Locants describing the *n*-aza analogues refer to the ergoline numbering scheme displayed in structure (**2**) in ref. 1.

‡ The cyclopentenone (**3**) is itself a mixture of four stereoisomers arising from the asymmetry at C-5a and C-6a.

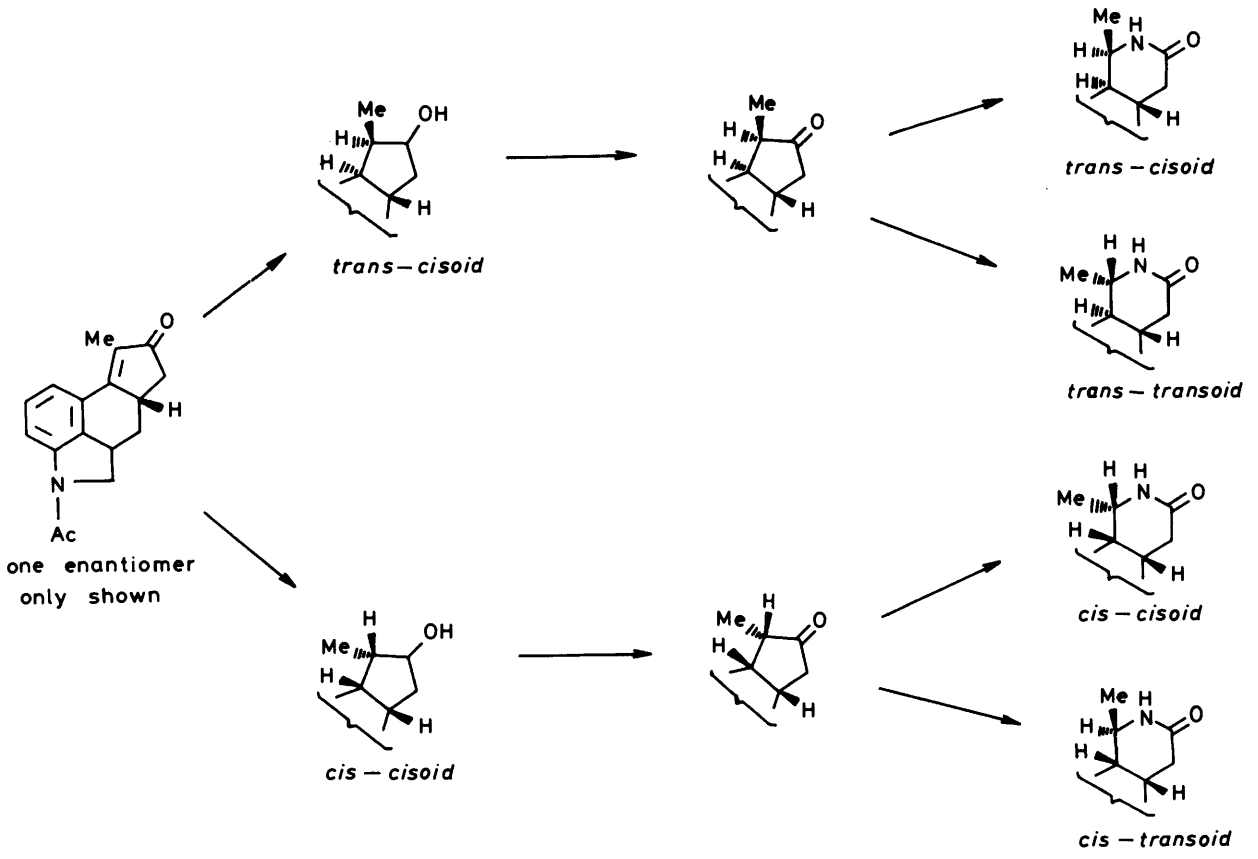


Figure 1.

was conducted with both the mixed isomers of (**5**) and with the *trans* compound (**5a**) described above. The ring expansion of the mixed isomers of (**5**), achieved *via* the Schmidt reaction, gave a mixture of at least three, possibly four, lactams of structure (**7**), the ^{1}H n.m.r. spectrum of the product showing sets of doublets for the 10-methyl group at δ 0.95 (20%), 1.11 (10%), 1.33 (60%), and 1.20 (< 10%). The *trans*-compound (**5a**), however, gave a mixture of two lactams only, (**7a**) with 10-methyl doublets at δ 0.95 (30%) and 1.33 (70%).

Figure 1 shows diagrammatically how two cyclopentanols and two cyclopentanones could give rise to four lactams as described.

The Schmidt reaction gave also a small proportion (~ 5%) of the lactone (**8**) formed presumably by a carbonium ion pathway rather than the concerted mechanism expected for the formation of the lactams.

With such a complex mixture resulting from the ring expansion, the possibility of formation of some indolo[4,3-*fg*]-isoquinoline could not be dismissed, and so, as an aid to structure assignment, the unsaturated lactams (**9**)[1] and (**10**)[1] were hydrogenated to give compounds (**11**) and (**12**) respectively. The lactam (**11**) appeared to be a single component on t.l.c. in a variety of solvents, and had a 10-methyl doublet at δ 1.02 (*J* 7.2 Hz). The lactam (**12**), however, was a mixture of at least two components in the ratio 3:1, separable by t.l.c., and with 10-methyl doublet signals at δ 1.13 (*J* 7.0 Hz) and 1.00 (*J* 7.5 Hz). T.l.c. experiments showed that neither of the components of compound (**12**) nor the single isomer of (**11**) was identical with any of the compounds in the mixture (**7**), the product of the ring-expansion reaction whose components [apart from the lactone (**8**)] could not be separated by t.l.c. The n.m.r. spectra of the mixture (**7**) and of the *trans*-isomer (**7a**) were, however, sufficiently different from that of the two-component mixture (**12**) to make it extremely unlikely that any 7-azaergoline lactam was formed during the Schmidt reaction in more than trace amounts.

The mixture of lactams (**7**) could not be alkylated under the phase-transfer conditions used previously,[1] but methylation by sodium hydride in dimethylformamide (DMF) with methyl iodide gave the 9,10-dimethyl compound (**13**) in high yield. The n.m.r. spectrum of the product suggested that it apparently contained 90% of the isomer with the 10-methyl doublet at δ 1.48 (*J* 7.0 Hz). Deacetylation and aromatisation of the crude product (**13**) gave the indole (**14**), which still clearly contained four components, giving four separate 10-methyl signals at δ 0.78 (25%), 1.16 (12.5%), 1.40 (12.5%), and 1.48 (50%) and two *N*-methyl singlets at δ 2.94 and 3.03.

N-Methylation of the two-component mixture (**7a**) gave compound (**13a**) with 10-methyl doublets at δ 0.93 (15%) and 1.47 (85%); deacetylation and aromatisation of this mixture gave the *trans*-isomer (**14a**) with 10-methyl doublets at δ 0.78 (15%) and 1.48 (85%).

T.l.c. of the four-component mixture of indoles represented by structure (**14**) and of the two-component mixture (**14a**) in 10% ethanol in ethyl acetate showed only two components, the more polar of which was the *trans*-isomer mixture. Separation of these two components by preparative t.l.c. (p.l.c.) gave the less polar *cis*-mixture (**14b**) with 10-methyl doublets at δ 1.16 (20%) and 1.40 (80), and the more polar *trans*-isomers (**14a**), identical with the (**14a**) *trans*-isomers described above (δ 0.78 and 1.48). The appearance of two distinct signals (at δ 2.94 and 3.03) for the *N*-methyl group in the *trans*-isomers (**14a**) is due presumably to the occurrence of either *cisoid* or *transoid* stereochemistry around C-10–C-10a in a *trans*-fused ring system.

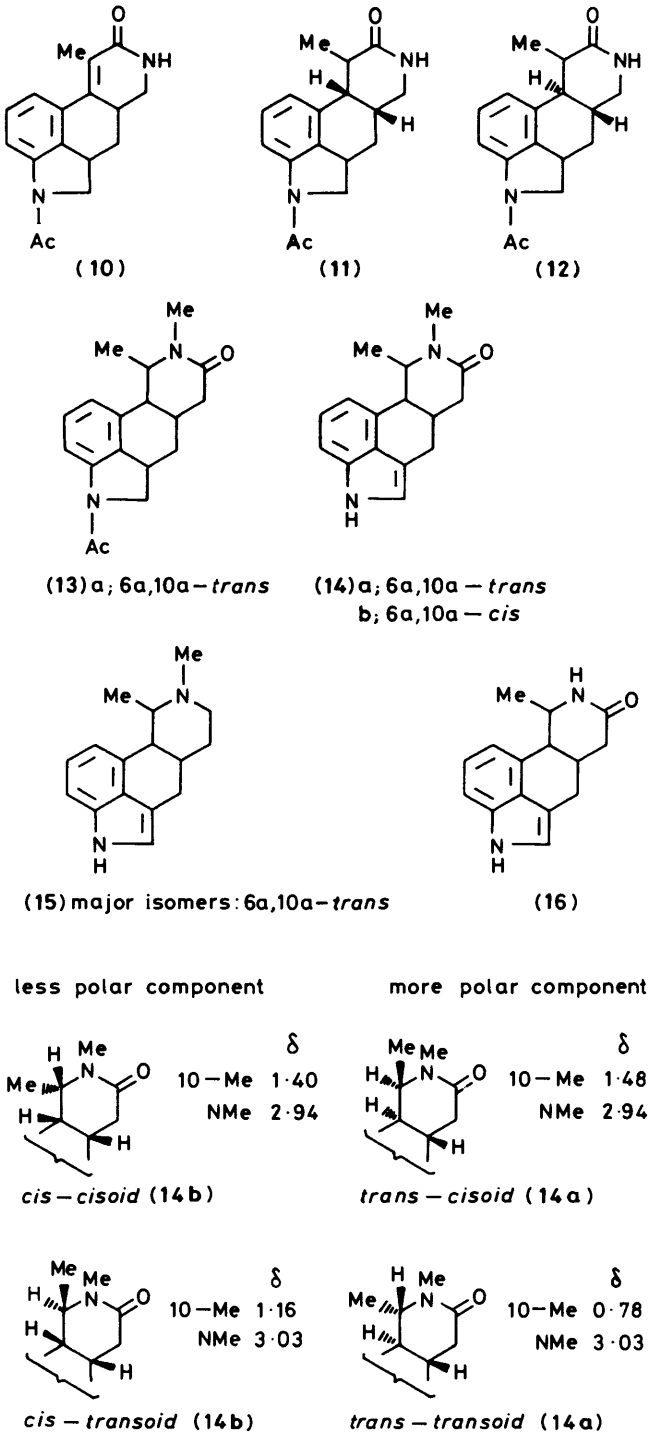


Figure 2.

A diagrammatic representation of the relationship between these pairs is shown in Figure 2 in which the assignments *cisoid* and *transoid* are tentative and may need to be reversed.

Reduction of the four-component mixture (**14**) with Red-Al gave a mixture of D-ring amines (**15**) which, by t.l.c., could be shown to consist of four components, two major and two minor. The two major components were isolated by h.p.l.c. and showed 10-methyl doublet signals at δ 1.18 and 0.67 (*J* 6.2 and 7.4 Hz), while the *N*-methyl signals were at δ 2.35 and 2.45 respectively.

Reduction of the two-component *trans* mixture (**14a**) gave the same two amines (**15**); they are therefore the *trans–cisoid* and *trans–transoid* isomers corresponding to the amides of Figure 2. We could not isolate a sufficient quantity of the minor component from the reduction to identify the two other isomers which are, in all probability, the *cis–cisoid* and *cis–transoid* isomers.

The study of the biological activity of these isomers is in progress to compare the properties of the naturally occurring ergolines with those of the 7-, 8-, and 9-aza analogues.

Experimental

M.p.s were determined on a Kofler–Reichert micro heating stage and are uncorrected. I.r. and u.v. spectra were recorded on a Perkin-Elmer P.E. 297 and a Pye Unicam SP.800 spectrophotometer respectively. ^{1}H N.m.r. spectra were recorded on either a Varian EM 360 (60 MHz) or a Varian FT 80A (79.5 MHz) spectrometer. T.l.c. was conducted with Merck 60F/254 precoated silica gel plates, and p.l.c. with 20 × 20 cm (2.5 mm thickness) plates of the same type. Two spray reagents were used to visualise t.l.c. plates. Indole derivatives showed as intense red or brown spots when sprayed with a cerium(IV)-based reagent at room temperature.* *N*-Protected indolines were not visualised under these conditions but required that the plate be gently warmed to produce the blue spots characteristic of this reagent. Indole derivatives were detected by Allport and Cockings reagent [5] which gave blue spots at room temperature. Column chromatography was conducted with Crosfield Sorbsil U30 silica gel (referred to as silica gel) or Florisil. Extracts were dried over anhydrous magnesium sulphate unless otherwise stated.

4-*Acetyl*-9-*methyl*-5,5a,6,6a,7,8,9,9a-*octahydro*-4H-*indeno*-[6,5,4-cd]*indol*-8-*ol* (**4**).—To a suspension of the enone (**3**) [1] (5.0 g, 0.019 mol) in ethanol (100 ml) was added platinum(IV) oxide (2.5 g). The mixture was hydrogenated at 60 p.s.i. for 18 h. T.l.c. (10% ethanol–ethyl acetate) showed that some starting material remained. Further platinum(IV) oxide (1 g) was added and the hydrogenation was continued for another 6 h. The catalyst was removed by filtration and the solution was evaporated to dryness under reduced pressure to give the title compound (**4**) as a mixture of isomers (81:16 by h.p.l.c.). Crystallisation from ethyl acetate gave the *major component* (**4a**) (1.5 g, 30%), m.p. 234—236 °C; $\lambda_{max.}$(MeOH) 217 (ε 30 000), 256 (15 200), 280 (5 500), and 290 nm (5 000); $\nu_{max.}$(KBr) 3 380 (OH) and 1 640 cm^{-1} (COMe); δ($CDCl_3$) 0.65 (3 H, d, 9-Me), 1.0—1.7 (2 H, m, 6-H_2), 2.0—2.8 (4 H, m, 6a-H, 7-H_2, and 9-H), 2.22 (3 H, COMe), 3.0—3.5 (2 H, m, 5a- and 9a-H), 3.60 (1 H, m, 5-H), 4.25 (1 H, m, 5-H), 4.45 (1 H, m, 8-H), 6.7—7.3 (2 H, m, 1- and 2-H), and 7.85 (1 H, d, 3-H); *m/z* 271 (M^+) (Found: C, 75.2; H, 7.6; N, 5.0. $C_{17}H_{21}NO_2$ requires C, 75.24; H, 7.80; N, 5.16%).

4-*Acetyl*-9-*methyl*-4,5,5a,6,6a,7,9,9a-*octahydroindeno*[6,5,4-cd]*indol*-8-*one* (**5**).—To the stirred solution of the mixture of isomers of compound (**4**) (7.0 g, 0.026 mol) in dry AnalaR methylene dichloride (150 ml) was added PCC (6.2 g, 0.027 mol). After 4 h the reaction mixture was diluted with ethyl acetate (150 ml), filtered through a pad of Celite, and evaporated under reduced pressure to give a light brown oil. The product was chromatographed on silica gel (eluant chloroform) and two components were isolated: (a) 4-*acetyl*-9-*methyl*-4,6,6a,7,9,9a-*hexahydroindeno*[6,5,4-cd]*indol*-8-*one* (**6**) (0.2 g, 3%), m.p. 157—159 °C; $\lambda_{max.}$(MeOH) 242 (20 900), 296 (6 600), and 306 nm (7 620); $\nu_{max.}$(KBr) 1 735 (ketone CO) and 1 700 cm^{-1} (amide CO); δ($CDCl_3$) 1.12 and 1.26 (3 H, 2 d, ratio

* The Ce^{IV}-based reagent is made by dissolving cerium(IV) sulphate (1%) and molybdic acid (2.5%) in sulphuric acid (10%) in water.

2:1, *J* 7.5 and 6.9 Hz, 9-Me), 2.62 (3 H, s, COMe), 1.9—3.5 (7 H, m, skeletal aliphatics), 6.9—7.5 (3 H, m, 1-, 2-, and 5-H), and 8.1 (1 H, d, 3-H); *m/z* 267 (M^+) (Found: C, 76.7; H, 6.7; N, 5.0. $C_{17}H_{17}NO_2$ requires C, 76.38; H, 6.41; N, 5.24%); and (b) compound (**5**) (4.7 g, 68%), m.p. 170—175 °C (from ethyl acetate); δ($CDCl_3$) 0.7 and 1.28 (3 H, 2 d, ratio 3:2, *J* 7.2 and 6.8 Hz, 9-Me), 2.20 (3 H, s, COMe), 1.0—4.5 (10 H, m, skeletal aliphatics), 6.65—7.3 (2 H, m, 1- and 2-H), and 7.85 (1 H, d, 3-H).

trans-*Isomers* (**5a**).—The crystalline alcohol (**4a**) (9,9a-*trans*) (1.05 g, 0.0039 mol) was oxidised in the same manner to give *isomer* (**5a**) (0.8 g, 77%), m.p. 194—196 °C (from ethyl acetate); $\lambda_{max.}$(MeOH) 217 (23 100), 261 (14 200), 280 (4 300), and 289 nm (3 800); $\nu_{max.}$(KBr) 1 725 (ketone CO) and 1 655 cm^{-1} (amide CO); δ($CDCl_3$) 0.70 (3 H, d, *J* 7.2 Hz, 9-Me), 1.25 (1 H, m, 6-H), 2.23 (3 H, s, COMe), 2.0—3.0 (5 H, m, 6-H, 6a-H, 7-H_2, and 9-H), 3.0—3.9 (3 H, m, 5-, 5a-, and 9a-H), 4.25 (1 H, m, 5-H), 6.75—7.35 (2 H, m, 1- and 2-H), and 7.90 (1 H, d, 3-H); *m/z* 269 (M^+) (Found: C, 75.95; H, 7.1; N, 5.2. $C_{17}H_{19}NO_2$ requires C, 75.81; H, 7.11; N, 5.20%).

4-*Acetyl*-10-*methyl*-4,5,5a,6,6a,9,10,10a-*octahydroindolo*[3,4-gh]*isoquinolin*-8(7H)-*one* (**7**).—A solution of compound (**5**) (4.7 g, 0.0174 mol) in glacial acetic acid (50 ml) was stirred and warmed to 30 °C. Sodium azide (1.4 g, 0.02 mol) was added, followed by conc. sulphuric acid (4.0 ml) dropwise during 10 min while the temperature was kept between 35 and 40 °C. One further addition of sodium azide and conc. sulphuric acid was made to ensure complete conversion of the starting material. The reaction mixture was poured onto a mixture of ice–saturated aqueous sodium hydrogen carbonate, and extracted into chloroform, and the extract was washed with water, dried, and evaporated to afford a white solid. Chromatography on silica gel [solvent (gradient) chloroform—2% methanol–chloroform] gave two components: (a) 4-*acetyl*-10-*methyl*-4,5,5a,6,6a,7,10,10a-*octahydro*[2]*benzopyrano*[6,7,8-*cd*]indol-8-one (**8**) (0.3 g, 6.0%), m.p. 214 °C (from acetonitrile); $\lambda_{max.}$(MeOH) 216 (24 800) and 255 nm (14 400); $\nu_{max.}$(KBr) 1 740 (ketone CO) and 1 650 cm^{-1} (amide CO); δ($CDCl_3$) 1.52 (3 H, d, *J* 6.5 Hz, 10-Me), 2.24 (3 H, s, COMe), 1.95—3.85 (9 H, m, skeletal aliphatics), 4.35 (1 H, m, 10-H), 6.85—7.4 (2 H, m, 1- and 2-H), and 7.95 (1 H, d, 3-H); *m/z* 285 (M^+) (Found: C, 71.7; H, 6.0; N, 5.3. $C_{17}H_{19}NO_3$ requires C, 71.55; H, 6.71; N, 4.91%); and (b) compound (**7**) (2.7 g, 56%), m.p. 224—226 °C (after trituration with n-hexane); δ($CDCl_3$) 0.95, 1.11, 1.20, and 1.33 (3 H, 4 d, proportions 20:10:10:60, 10-Me), 2.24 (3 H, s, COMe), 1.0—3.0 (5 H, m, 6-H_2, 6a-H, and 7-H_2), 3.2—3.8 (4 H, m, 5-, 5a-, 10-, and 10a-H), 4.25 (1 H, m, 5-H), 5.6 (1 H, br s, exchanged in D_2O, NH), 6.75—7.35 (2 H, m, 1- and 2-H), and 7.95 (1 H, d, 3-H).

trans-*Isomer* (**7a**).—The *trans*-isomers (**5a**) (0.7 g, 0.0026 mol) were subjected to the same ring-expansion conditions and gave isomers (**7a**) (0.45 g, 61%), m.p. 236—238 °C; $\lambda_{max.}$(MeOH) 216 (24 700) and 256 nm (14 000); $\nu_{max.}$(KBr) 3 190 (NH) and 1 660 cm^{-1} (amide COs); δ($CDCl_3$) 0.95 and 1.33 (3 H, 2 d, ratio 30:70, *J* 7.0 and 6.5 Hz, 10-Me); *m/z* 284 (M^+) (Found: C, 71.6; H, 7.0; N, 9.6. $C_{17}H_{20}N_2O_2$ requires C, 71.80; H, 7.09; N, 9.85%).

6a,10a-cis-4-*Acetyl*-10-*methyl*-5,5a,6,6a,7,8,10,10a-*octahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (**11**).—To a solution of compound (**9**)[1] (0.1 g) in ethyl acetate (100 ml) was added platinum(IV) oxide (50 mg). The mixture was hydrogenated at 60 p.s.i. for 18 h. Removal of the catalyst by filtration, evaporation to dryness under reduced pressure, and crystallisation of the result from ethyl acetate gave the *dihydro derivative* (**11**) (20 mg, 20%), m.p. 214—216 °C; $\lambda_{max.}$(MeOH) 214 (30 900) and 254 nm (16 500); $\nu_{max.}$(KBr) 3 200 and 3 070 (NH) and 1 665 cm^{-1} (C=O); δ($CDCl_3$) 1 02 (3 H, d, *J* 7.2 Hz, 10-Me), 2.20 (3 H, s, COMe), 1.5—3.7 (8 H, m, skeletal aliphatics), 4.35 (1 H, m, 5-H), 5.9—6.0 (1 H, br s, exchanged in D_2O, NH), 6.6—7.4 (2 H, m, 1- and 2-H), and 7.9 (1 H, d, 3-H); *m/z* 284 (M^+) (Found: C, 72.0; H, 7.1; N, 9.8. $C_{17}H_{20}N_2O_2$ requires C, 71.80; H, 7.09; N, 9.85%).

6a,10a-trans-4-*Acetyl*-10-*methyl*-5,5a,6,6a,7,8,10,10a-*octahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (**12**).—To a solution of compound (**10**)[1] (0.5 g) in ethyl acetate (100 ml) was added platinum(IV) oxide (0.5 g). The mixture was hydrogenated at 60 p.s.i. for 18 h. Removal of the catalyst by filtration, evaporation to dryness under reduced pressure, and crystallisation of the residue from ethyl acetate gave the *dihydro derivative* (**12**) (0.4 g, 80%), m.p. 260—262 °C; $\lambda_{max.}$(MeOH) 216 (26 500), 257 (15 300), 282 (4 470), and 291 nm (3 830); $\nu_{max.}$(KBr) 3 300—3 050 (NH) and 1 660 cm^{-1} (amide C=O); δ($CDCl_3$) 1.00 and 1.13 (3 H, 2 d, ratio 1:3, *J* 7.5 and 7.0 Hz, 10-Me), 1.40 (1 H, m, 6-H), 2.23 (3 H, s, COMe), 2.0—2.5 (2 H, m, 6- and 6a-H), 2.8—3.7 (6 H, m, skeletal aliphatics), 4.25 (1 H, m, 5-H), 6.03 (1 H, br s, exchanged in D_2O, NH), 6.7—7.3 (2 H, m, 1- and 2-H), and 7.90 (1 H, d, 3-H); *m/z* 284 (M^+) (Found: C, 72.0; H, 7.3; N, 10.0%).

4-*Acetyl*-9,10-*dimethyl*-4,5,5a,6,6a,9,10,10a-*octahydroindolo*-[3,4-gh]*isoquinolin*-8(7H)-*one* (**13**).—To a stirred solution of compound (**7**) (2.7 g, 0.0095 mol) in anhydrous DMF (20 ml) maintained at 60 °C was added sodium hydride (50% dispersion in mineral oil; 0.8 g, 0.016 mol). The mixture was stirred for 30 min, and was then cooled to 10 °C. Methyl iodide (1.5 ml) was added and the solution was allowed to warm at room temperature during 1 h whilst being stirred. The reaction mixture was diluted with water, extracted with chloroform, and the extract was washed with water, dried, and evaporated to afford a white solid. Chromatography of the residue on silica gel (eluant 1% methanol–methylene dichloride) and crystallisation from ethyl acetate gave *compound* (**13**) (2.4 g, 85%), m.p. 184—186 °C; $\lambda_{max.}$(MeOH) 218 (26 700) and 255 nm (14 300); $\nu_{max.}$(KBr) 1 640 cm^{-1} (amide COs); δ($CDCl_3$) 1.25 (1 H, m, 6-H), 1.48 (3 H, d, *J* 7.0 Hz, 10-Me), 2.22 (3 H, s, COMe), 2.90 (3 H, s, NMe), 2.0—3.1 (5 H, m, 6-H, 6a-H, 7-H_2, and 10a-H), 3.0—3.7 (3 H, m, 5-, 5a-, and 10-H), 4.25 (1 H, m, 5-H), 6.7—7.3 (2 H, m, 1- and 2-H), and 7.90 (1 H, d, 3-H); *m/z* 298 (M^+) (Found: C, 72.8; H, 7.4; N, 9.7. $C_{18}H_{22}N_2O_2$ requires C, 72.45; H, 7.43; N, 9.39%).

trans-*Isomers* (**13a**).—The mixed *trans*-isomers (**7a**) (0.4 g, 0.0014 mol) were *N*-methylated in the same manner to give *trans*-(**13a**) (0.3 g, 71%), δ($CDCl_3$) 0.93 and 1.48 (3 H, 2 d, ratio 15:85, 10-Me).

9,10-*Dimethyl*-4,6,6a,9,10,10a-*hexahydroindolo*[3,4-gh]*isoquinolin*-8(7H)-*one* (**14**).—A solution of compound (**13**) (2.2 g, 0.0074 mol) in a mixture of glacial acetic acid (20 ml) and conc. hydrochloric acid (20 ml), kept under nitrogen, was heated at reflux for 3 h. The cooled solution was poured into ice–water and made basic with 50% aqueous sodium hydroxide. The product was extracted into chloroform, the extract was washed with water, then dried, and the solvent was evaporated off under reduced pressure. The crude indoline was immediately dissolved in acetone (200 ml) and the solution was vigorously stirred whilst MnO_2–C (22 g)[1] was added during 6 h, and the mixture was then stirred for a further 2 h. The MnO_2–C was removed by filtration and washed well with acetone (3 × 50 ml). The combined filtrates were evaporated to afford a white solid, which was purified by chromatography on Florisil (eluant 1% methanol–methylene dichloride). Fractions containing the product were evaporated to give compound (**14**) as a white solid (1.2 g, 64%), m.p. 230—232 °C (after trituration with ethyl

acetate); δ($CDCl_3$) 0.78, 1.16, 1.40, and 1.48 (3 H, 4 d, proportions approx. 2:1:1:4, 10-Me), 2.94 and 3.03 (3 H, 2 s, ratio 2:3, NMe), 2.3—4.0 (7 H, m, skeletal aliphatics), 6.92 (1 H, s, 5-H), 7.0—7.3 (3 H, m, ArH), and 8.00 (1 H, br s, exchanged in D_2O, NH).

trans-*Isomer* (**14a**).—*trans*-Isomer (**13a**) (0.3 g, 0.001 mol) was deacylated and aromatised in the same manner to give *isomer* (**14a**) 0.15 g, 59%), m.p. 250—252 °C; $\lambda_{max.}$(MeOH) 226 (25 900) and 282 nm (6 550); $\nu_{max.}$(KBr) 3 160 (NH) and 1 620 cm^{-1} (amide CO); δ($CDCl_3$) 0.78 and 1.48 (3 H, 2 d, ratio 15 : 85, 10-Me); *m/z* 254 (M^+) (Found: C, 75.9; H, 7.25; N, 11.2. $C_{16}H_{18}N_{20}$ requires C, 75.56; H, 7.13; N, 11.02%).

The four-component mixture (**14**) was compared with the mixture of *trans*-isomers (**14a**) by t.l.c. (developer 10% ethanol–ethyl acetate). The *trans*-isomers appeared as a single spot (R_F 0.38), whereas the mixture also contained a second, minor component at R_F 0.44. The two components were separated by p.l.c. (developer as above) and crystallised from ethyl acetate to give (a) *cis*-(**14b**) (R_F 0.44), δ($CDCl_3$) 1.16 and 1.40 (3 H, 2 d, ratio *ca.* 20:80, $J_{1.40}$ 6.9 Hz, 10-Me); and (b) *trans*-(**14a**) (R_F 0.38), δ($CDCl_3$) 0.78 and 1.48 (3 H, 2 d, ratio *ca.* 15:85, $J_{1.48}$ 6.4 Hz, 10-Me).

6a,10a-trans-9,10-*Dimethyl*-4,6,6a,7,8,9,10,10a-*octahydroindolo*[3,4-gh]*isoquinoline* (**15**).—To a stirred suspension of compound (**14**) (0.1 g) in dry benzene (10 ml) was added Red-Al (1 ml). After 2 h the reaction mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to dryness. T.l.c. [diethyl ether–methylene dichloride–methanol–0.880 ammonia (50:30:20:0.2)] showed two major components (R_F 0.26 and 0.19) and two minor components (R_F 0.39 and 0.21). The two major components were separated by p.l.c. (developer as for t.l.c.) and were crystallised from ethyl acetate to give *component* (a) (R_F 0.26), m.p. 220—222 °C; $\lambda_{max.}$(MeOH) 229 (22 900) and 285 nm (6 200); $\nu_{max.}$($CHCl_3$), 3 490 cm^{-1} (NH); δ($CDCl_3$) 1.18 (3 H, d, *J* 6.2 Hz, 10-Me), 2.35 (3 H, s, NMe), 1.6—3.55 (9 H, m, skeletal aliphatics), 6.87 (1 H, s, 5-H), 6.8—7.3 (3 H, m, ArH), and 7.85 (1 H, br s, exchanged in D_2O, NH); *m/z* 240 (M^+) (Found: C, 80.4; H, 8.6; N, 11.1. $C_{16}H_{20}N_2$ requires C, 79.96; H, 8.39; N, 11.66%); and component (b) (R_F 0.19), $\lambda_{max.}$(MeOH) 227 (25 700) and 285 nm (6 100); $\nu_{max.}$(KBr) 3 200—3 100 cm^{-1} (NH); δ($CDCl_3$) 0.67 (3 H, d, *J* 7.4 Hz, 10-Me), 2.45 (3 H, s, NMe), 2.4—3.6 (9 H, m, skeletal aliphatics), 6.87 (1 H, s, 5-H), 6.8—7.3 (3 H, m, ArH), and 7.85 (1 H, br s, exchanged in D_2O, NH); *m/z* 240 (M^+).

10-*Methyl*-4,6,6a,9,10,10a-*hexahydroindolo*[3,4-gh]*isoquinolin*-8(7H)-*one* (**16**).—A solution of the mixed isomers (**7**) (0.6 g, 0.0021 mol) in a mixture of glacial acetic acid (10 ml) and conc. hydrochloric acid (10 ml), kept under nitrogen, was heated at reflux for 4 h. The cooled solution was poured into ice–water and made basic with 50% aqueous sodium hydroxide. The product was extracted into chloroform, the extract was washed with water, then dried, and the solvent was evaporated off under reduced pressure. The crude indoline was dissolved in acetone (50 ml) and the solution was vigorously stirred while MnO_2–C (6 g) was added during 3 h, and the mixture was then stirred for a further 18 h. The MnO_2–C was removed by filtration and washed well with acetone (3 × 50 ml). The combined filtrates were evaporated to dryness, and the residue was purified by chromatography on Florisil (eluant 1% methanol–methylene dichloride). Crystallisation from ethyl acetate gave *compound* (**16**) (0.3 g, 59%), m.p. 242—250 °C; $\lambda_{max.}$(MeOH) 227 (30 700) and 283 nm (11 400); $\nu_{max.}$(KBr) 3 200—3 350 (NHs) and 1 660 cm^{-1} (amide CO); δ($CDCl_3$) 1.17 and 1.28 (3 H, 2 d, ratio 2:1, *J* 6.6 and 6.2 Hz, 10-Me), 2.0—4.0 (7 H, m, skeletal aliphatics), 5.8 and 6.5 (1 H, 2br s, exchanged in D_2O, CONH), 6.92 (1 H, s, 5-H), 7.0—7.4 (3 H, m, ArH), and 8.0 (1 H, br s, exchanged in D_2O, indole NH); *m/z* 240 (M^+) (Found: C, 75.0; H, 6.6; N, 11.45. $C_{15}H_{16}N_2O$ requires C, 74.97; H, 6.71; N, 11.66%).

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