The Synthesis of 8-Methyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]-isoquinoline, the 9,10-Didehydro-7-methyl-7-aza Analogue [a] of Ergoline

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The title compound has been synthesised by ring expansion of the cyclopentenone 4-acetyl-4,5,5a,6,6a,7-hexahydro-8*H*-indeno[6,5,4-*cd*]indol-8-one (5c). Compound (5c) was prepared from the readily available 1-benzoyl-2,2a-3-4-tetrahydrobenz[*cd*]indol-5(1*H*)-one (3). An unexpected isomerisation was observed on *N*-methylation of the 7-aza lactam, the double bond having migrated from $\Delta^{9,10}$ to $\Delta^{5,6}$. Hydrogenation of the $\Delta^{9,10}$ lactam (7c) and the $\Delta^{5,6}$ lactam (8a) gave rise to different dihydro derivatives whose configurations are discussed on the basis of their 360 MHz ^{1}H n.m.r. spectra.

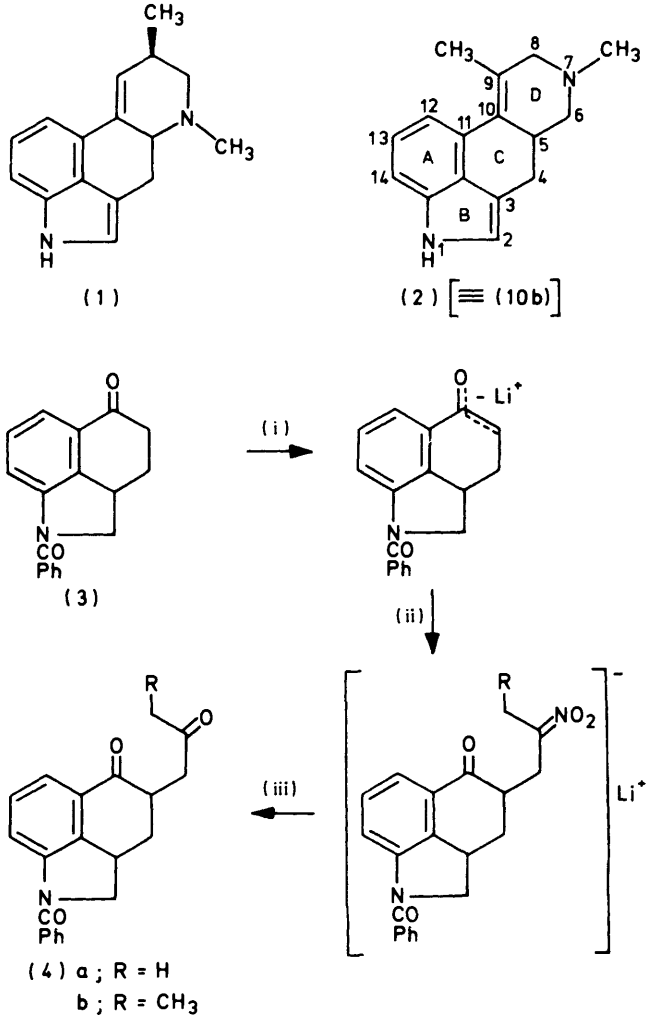
The ergot alkaloids are metabolic products of various species of fungi and plants and were first isolated from the parasitic fungus genus *Claviceps* (calvicipitales). These alkaloids have been the subject of intensive research for over seventy years. Numerous reviews are available detailing the chemistry and complex pharmacological actions of this intriguing group of compounds.[1]

The naturally occurring alkaloids are partially hydrogenated indolo[4,3-*fg*]quinolines, exemplified by lysergine (1). We now report the total synthesis of the novel isomeric indolo-[4,3-*fg*]isoquinoline ring system as in structure (2).†‡

The starting material chosen for this synthesis was the benz[*cd*]indole derivative (3) used by Kornfeld and Woodward as the key intermediate in the total synthesis of lysergic acid,[2] and by Rastogi for the synthesis of 'nor-7-deazalysergic acid'[3] (de-*N*-methyl-6-carbalysergic acid).‡[3] The tricyclic ketone (3) is prepared from commercially available indole-3-propionic acid.[2]

Reaction of the ketone (3) with mesityl-lithium [4] (from the action of t-butyl-lithium on mesityl bromide) in tetrahydrofuran (THF) at −50 °C gave the corresponding enolate. Reaction of this enolate with 2-nitropropene [5] gave a nitronate anion which, on hydrolysis *in situ* with 70% perchloric acid, gave the 1,4-diketone (4a) as a white crystalline solid (yield 45%) (Scheme 1). The diketone (4b) was similarly formed in 66% yield when 2-nitrobut-1-ene [5] was used as the electrophile. Cyclisation of these two diketones with sodium hydroxide in boiling ethanol gave the cyclopentenones (5a, b) with simultaneous loss of the *N*-benzoyl protecting group. Acylation with acetic anhydride as part of the work-up procedure gave the cyclopentenones (5c) (64%) and (5d) (57%). Alternatively, the crude indoline (5b) could be aromatised to the indole derivative (6) (Scheme 2).

Aromatisation was achieved using manganese dioxide on activated carbon, prepared by the method of Carpino.[6] We have found this reagent of particular use for the aromatisation of indolines to give indoles in this series. Its main advantage over the more commonly used Attenburrow's material [7] lies in its ease of preparation and filtration and the consistency of the product on repeat preparations. It was found that if the whole of the MnO_2–C (used at a rate of 10 g per 1 g of substrate) were

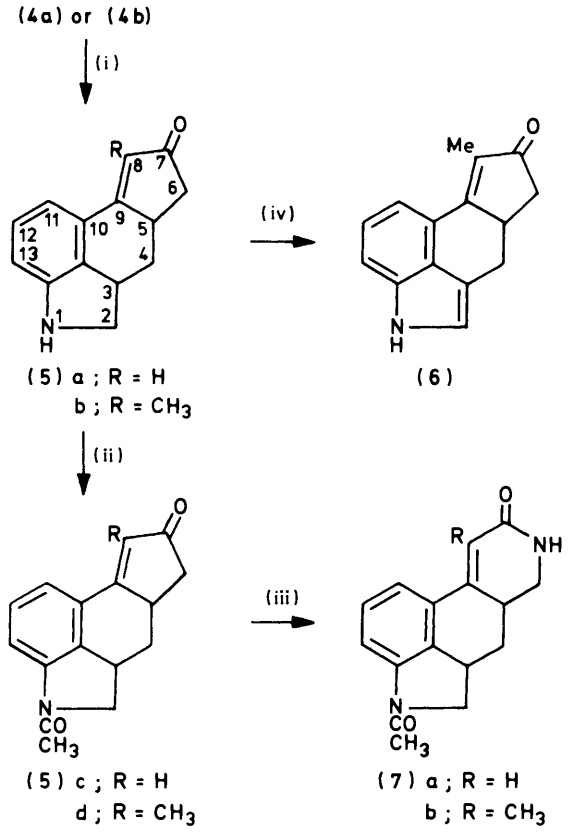


Scheme 1. *Reagents:* (i) Mesityl-lithium, THF; (ii) $H_2C{=}C(NO_2)$-CH_2R; (iii) 70% $HClO_4$

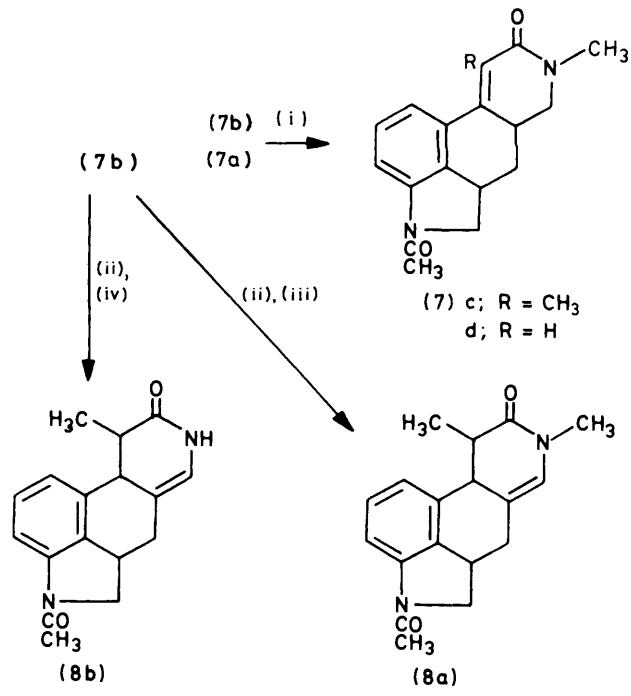
[a] Ergoline-type numbering.

† During the course of this work the synthesis of some indolo[3,4-*gh*]quinoline derivatives was reported (J. M. Cassady, Joint Central Great Lakes regional meeting of the American Chemical Society, Balter University, 1978). We shall publish our total synthesis of the indolo[3,4-*gh*]isoquinoline system separately.

‡ Conventional ergot-type numbering as shown in structures (2) and (5) is used throughout this paper except for the systematic names and certain n.m.r. data (indicated) in the Experimental section.



Scheme 2. *Reagents:* (i) NAOH, EtOH, heat; (ii) Ac_2O; (iii) NaN_3, H_2SO_4, AcOH; (iv) MnO_2–C. Ergoline-type numbering scheme shown



Scheme 3. *Reagents:* (i) NaH, DMF, CH_3I; (ii) $AcN\bar{C}H_3$ Na^+, $AcNHCH_3$, heat; (iii) CH_3I; (iv) H_2O

added in one portion the reaction stopped before completion. To avoid this a Normag solid-addition funnel was used and the reagent was added gradually over several hours. This greatly improved the consistency of the reaction. The yield of compound (6) from (3) was 30%, which compares favourably with the yields of (5c) and (5d).

The indole derivative (6) was intensely fluorescent under 254 and 350 nm u.v. irradiation. The carbonyl stretching frequency was 1 670 cm^{-1}, compared with 1 695 cm^{-1} for the *N*-acetylcyclopentenone (5d). As might be expected from these data the carbonyl group of the indole (6) was very unreactive. Thus an oxime could only be formed on prolonged heating with hydroxylamine in n-propanol (18 h). The ketone was also found to be inert to the action of hydrazoic acid at temperatures which did not cause complete destruction of the molecule.

Ring expansion of the cyclopentenones (5c) and (5d) by means of the Schmidt reaction [8] was achieved by generating hydrazoic acid *in situ* from concentrated sulphuric acid and sodium azide in glacial acetic acid.[9] A temperature of 60—65 °C was found to be necessary for this conversion. The lactams (7a) and (7b) were obtained in yields of 85 and 89%, respectively. No trace of the isomeric 8-aza lactam could be detected. The initial assignment of the lactams as the required 7-aza isomers was based on the n.m.r. spectrum of (7a) compared with that of (5c). The position of 9-H at δ 6.5 for (7a) compared favourably with that of 8-H for (5c) (δ 6.44), implying a similar environment adjacent to a carbonyl group. In (5c) there are methylene groups adjacent to both nitrogen and carbonyl functions and the aliphatic integration was distributed between δ 1.3 and 4.5. For (7a) the bulk (5 H) of the integration assignable to skeletal alipahtic protons was grouped between δ 2.8 and 3.85, indicating that the ring-D methylene group was adjacent to a nitrogen rather than a carbonyl function, which it was in the starting material or as it would be if the lactam were the 8-aza isomer. The structural assignment was subsequently confirmed by the ^{13}C n.m.r. and the 360 MHz ^1H n.m.r. spectra of the *N*-methylated lactam (7c).

The lactams (7a) and (7b) were *N*-methylated using sodium hydride and methyl iodide in dimethylformamide (DMF) at room temperature (Scheme 3). Yields were generally *ca.* 50%. When the reaction was attempted at elevated temperatures (60 °C for 2.5 h), t.l.c. examination of the reaction mixture (10% ethanol–ethyl acetate) revealed considerable conversion of compound (7b) into a less polar product (8a) (R_F 0.28) instead of the expected product (7c) (R_F 0.12). The new product was found to be isomeric with (7c). The structures of compounds (7c) and (8a) were assigned on the basis of their spectral characteristics, particularly the 360 MHz ^1H n.m.r. spectra (Table 1).

Little difference could be seen in the carbonyl stretching region of the i.r. spectra of compound (7c) and (8a) owing to the masking effect of the *N*-acetyl group. The u.v. spectrum of (8a) had $\lambda_{max.}$ 262 nm (ε 20 100) whereas that of (7c) had $\lambda_{max.}$ 295 nm (ε 17 300), clearly showing the absence of the $\Delta^{9,10}$ double bond in (8a). The 360 MHz ^1H n.m.r. spectrum of (8a) had a doublet at δ 0.81 (*J* 7.2 Hz) arising from the 9-methyl substituent; this assignment was confirmed by decoupling from 9-H, which gave a sharp doublet (*J* 5.5 Hz). This coupling (to 10-H) was good evidence for a *syn*-arrangement of 9- and 10-H. Further decoupling experiments by irradiation at δ 4.01 (10-H) and δ 3.37 (3-H) confirmed the remaining assignments.

The 360 MHz ^1H n.m.r. spectrum of (7c) showed one high-field proton at δ 1.30 having two large couplings (*J* 11.5 and 12.6 Hz) assigned to 4-H_{ax} which is abnormally shielded. The

Table 1. 360 MHz ^{1}H n.m.r. spectra of (8a) and (7c) in $CDCl_3$

	(8a)			(7c)		
H [a]	δ	J (H$_3$)		δ	J (H$_3$)	
2_{ax}	3.66	$J_{2ax,2eq}$	10.1,	3.65	$J_{2ax,2eq}$	10.1,
		$J_{2ax,3}$	11.0		$J_{2ax,3}$	9.4
2_{eq}	4.30	$J_{2eq,3}$	10.1	4.33	$J_{2eq,3}$	9.4
3	3.37			3.45		
4_{ax}	2.19	$J_{3,4ax}$	12.6,	1.30	$J_{4ax,4eq}$	11.5,
		$J_{4ax,4eq}$	13.0		$J_{4ax,3\text{ or }5}$	12.6
4_{eq}	2.77	$J_{4eq,5}$	4.7	2.18	$J_{4eq,5}$	5.0 *,
					$J_{3,4eq}$	4.0 *
5				3.00		
6_{ax}	6.08			3.35	$J_{6ax,6eq}$	12.6,
					$J_{5,6ax}$	5.4
6_{eq}				3.27	$J_{5,6eq}$	14.0
9	2.96	$J_{9,10}$	5.5			
10	4.01					
9-CH_3	0.81	$J_{9,9\text{-}CH_3}$	6.5	2.41	$J_{5,9\text{-}CH_3}$	2.9
12	6.86			7.57		
13	7.24			7.30		
14	7.91			8.06		
$COCH_3$	2.25			2.25		
NCH_3	3.11			3.12		

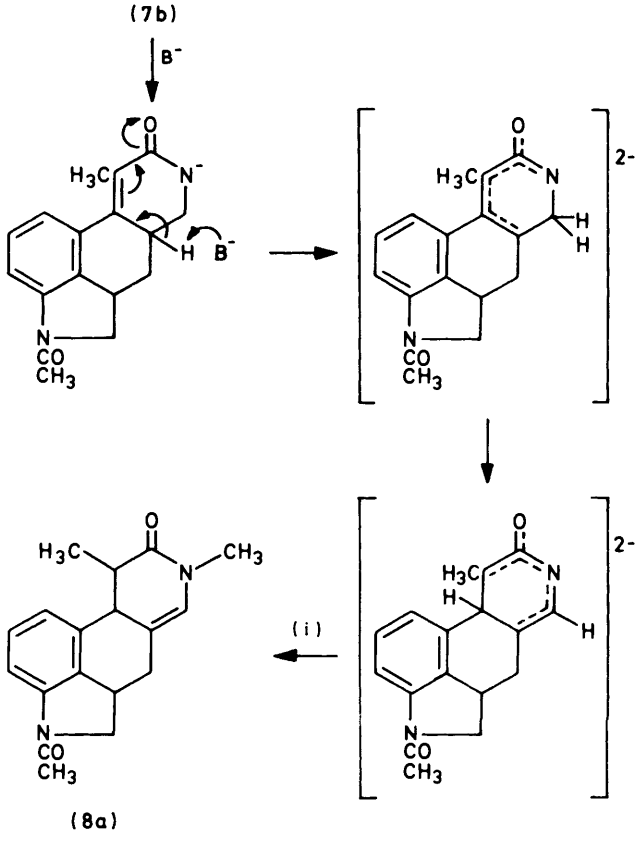
[a] Ergoline-type numbering system. * Assignments may be reversed.

remaining assignments are as shown in Table 1. The ^{13}C n.m.r. spectrum of (7c) * was of particular interest in confirming that the 7-aza lactam had been obtained. The off-resonance spectrum of (7b) showed a low-field aliphatic triplet at δ 45.1 p.p.m. which was assigned to C-6 but which could have been due to a methylene group next to either NH (as in the 7-aza series) or CO (as in the 8-aza series). In the ^{13}C spectrum of (7c) this signal has moved to δ 52.6 p.p.m. which is consistent with methylation on an adajcent N-atom.

Replacing sodium hydride with the sodium salt of *N*-methylacetamide gave a much cleaner reaction in which the yield of (8a) was 40%. Quenching the rearranged anion with water instead of methyl iodide gave the secondary enamide (8b). It can be rationalised that at low temperatures only the proton on nitrogen is removed to give the monoanion which undergoes alkylation to give (7c). At higher temperatures, however, 5-H is also removed giving a resonance-stabilised dianion (Scheme 4). Protonation of this dianion at C-9 would give the $\Delta^{5,10}$ compound and the dianion from this could be protonated at C-10 to form the $\Delta^{5,6}$ compound. Monoalkylation and protonation of the amide enolate on work-up could then produce the observed product (Scheme 4). The analogous production of a resonance-stabilised dianion by treatment of 4-methylcarbostyril (2-hydroxy-4-methylquinoline) with n-butyl-lithium has been reported.[10] The migration of olefinic double bonds to give enamines under basic conditions is also well documented.[11]

Deacylation of (7d) and (7c) to the indolines (7e and f) proceeded smoothly on heating at reflux for 1 h in a 1 : 1 mixture of glacial acetic acid and concentrated hydrochloric acid. The relatively unstable indolines were not characterised but were converted directly into the more stable indole derivatives (9a) and (9b) (Scheme 5). Yields for the overall deacylation–aromatisation steps were *ca.* 50—70%. The D-ring amide carbonyl gave a sharp band at 1 640 cm^{-1} for (9a) and 1 630 cm^{-1} for (9b) in the absence of the masking *N*-acetyl group. The peaks at 360 nm (ε 8 000) and 353 nm (ε 8 800) in the u.v. spectra confirm the extended conjugation present in these molecules.

* The ^{13}C n.m.r. spectra of compounds in this series will be published separately.



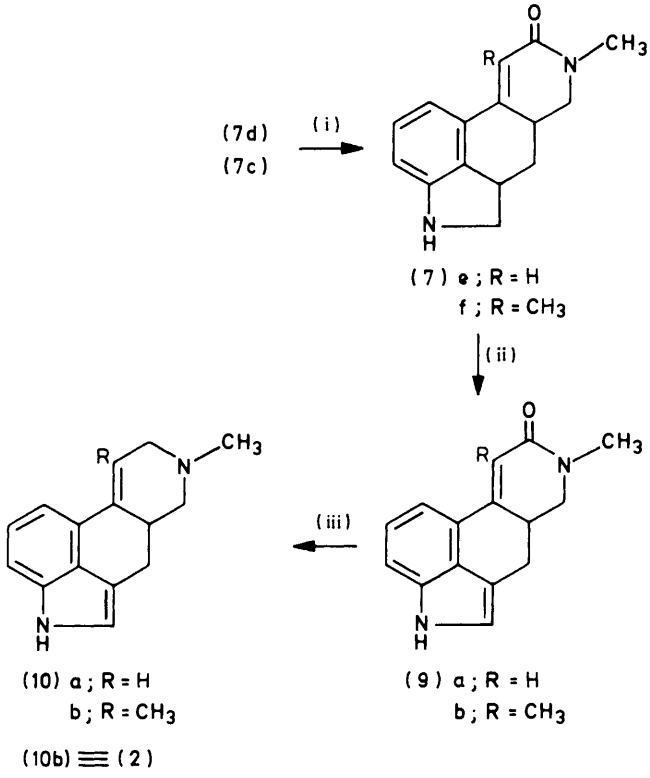
Scheme 4. *Reagents:* (i) CH_3I

The D-ring amide carbonyl was reduced using sodium bis-(2-methoxyethoxy)aluminium hydride (Red-Al) at room temperature to give the amines (10a) and (10b) [– (2)] in high yield. The u.v. spectra showed a maximum at 311 (ε 10 700) and 309 nm (ε 10 100), respectively, which compares favour-

Table 2. 360 MHz ^{1}H n.m.r. spectra of (14) and (13) in [$^2H_5$]pyridine

	(14)			(13)		
H [a]	δ	J (H_3)		δ	J (H_3)	
2	7.20			7.20		
4_{ax}	2.90	$J_{4ax.4eq}$	15.9,	2.51	$J_{4ax.4eq}$	12.0,
		$J_{4ax.5}$	7.9		$J_{4ax.5}$	11.6,
4_{eq}	2.99	$J_{4eq.5}$	5.5	3.00	$J_{4eq.5}$	4.3
5	2.50	$J_{5.10}$	3.7-	2.44	$J_{5.10}$	9.8,
		$J_{5.6ax}$	5.5,		$J_{5.6ax}$	not measured,
		$J_{5.6eq}$	5.5		$J_{5.6eq}$	4.9
6_{ax}	3.07	$J_{6ax.6eq}$	12.2	2.95	$J_{6ax.6eq}$	11.6
6_{eq}	3.37			3.23		
9	3.01	$J_{9.9\text{-}CH_3}$	7.3,	3.57	$J_{9.9\text{-}CH_3}$	7.3,
		$J_{9.10}$	6.1		$J_{9.10}$	4.9
9-CH_3	1.36			1.27		
10	3.48			3.27		
12	7.12			6.97		
13	7.20			7.29		
14	7.39			7.38		
NH	—			—		
NCH_3	2.81			2.96		

[a] Ergoline-type numbering system.



Scheme 5. *Reagents:* (i) HCl, AcOH, heat; (ii) MnO_2–C; (iii) Red-Al

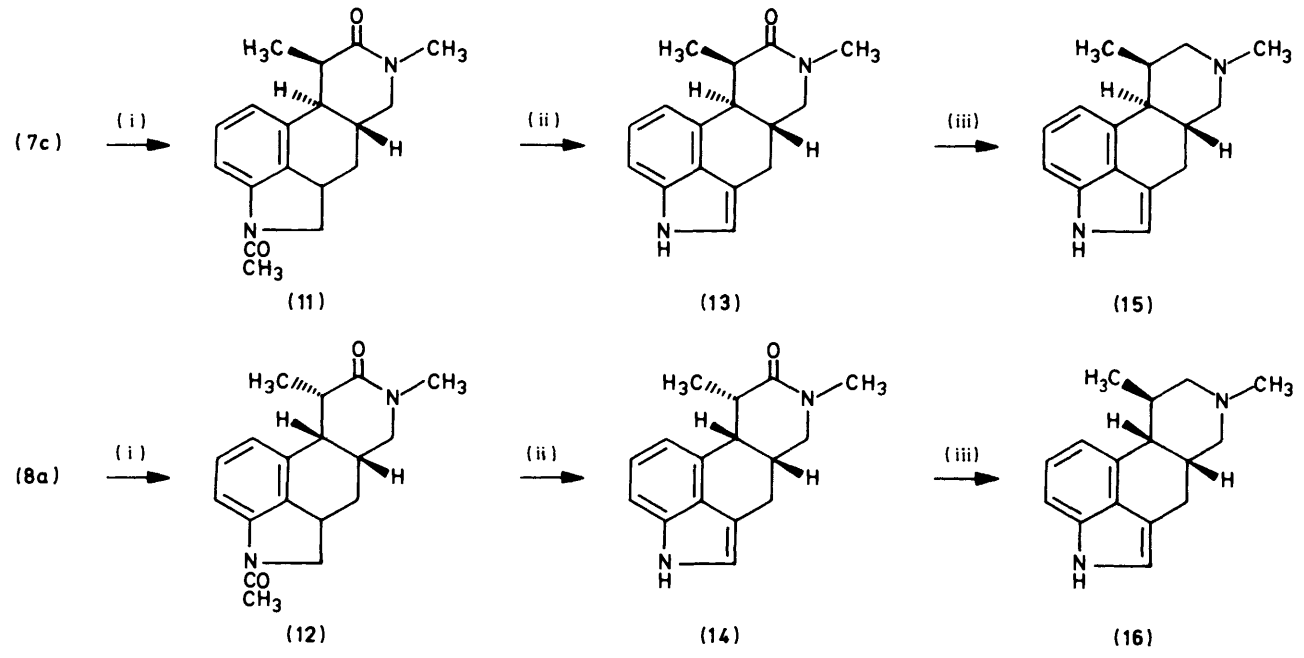
ably with that found for lysergine (1) at 309 nm (ε 8 500).[12] This hypsochromic shift from the maximum found for the amides (9a) and (10b) indicates that the carbonyl group is involved in conjugation with the indole ring as a vinylogous amide rather than as a lactam. This may explain the ease of alkylation of N-7.

As an extension of our work with this series of compounds we required the compounds in which the D-ring double bond was absent. To this end both compounds (7c) and (8a) were reduced by catalytic hydrogenation using platinum(IV) oxide at 60 lb in^{-2} to give compounds (11) and (12), respectively (Scheme 6). Both products appeared to be a single homogeneous compound but differed slightly on t.l.c. Deacylation and aromatisation as previously described gave two indole derivatives (13) and (14) which were clearly different. The 360 MHz ^{1}H n.m.r. spectra of these two diastereoisomeric amides have been recorded. Table 2 gives the chemical-shift assignments and coupling constants for the two isomers. For compound (13) the large coupling of 5-H to 4-H_{ax} (11.6 Hz) shows 5-H to be in an axial position. The coupling of 5-H to 10-H, 9.8 Hz, indicates an axial position for 10-H. Compound (13) can, therefore, be assigned the *trans-syn* stereochemistry. The value of 9.8 Hz is, however, rather low for a typical axial–axial relationship and suggests some strain in the C and D rings. The coupling of 9-H to 10-H (4.9 Hz) is indicative of a *syn* relationship between these two protons (dihedral angle *ca.* 40°). Compound (14) is assigned the C/D-*cis* stereochemistry on the basis of the 3.7 Hz coupling between 5-H and 10-H. The relationship between 9-H and 10-H, having already been established as *syn* from the $J_{9,10}$ 5.5 Hz coupling observed for compound (8a) confirms compound (14) as the *cis-syn* isomer. The assignment of compound (13) as *trans-syn* and (14) as *cis-syn* has been confirmed by *X*-ray studies.* Compounds (13) and (14) were each reduced to the isomeric D-ring amines (15) and (16) as previously described. A comparison of the chemical, physical, and biological properties of these novel isomers with those of naturally occurring ergoline derivatives is under way.

Experimental

M.p.s were determined on a Kofler–Reichart micro heating stage and are uncorrected. I.r. and u.v. spectra were recorded on a Perkin-Elmer PE 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. ^{13}C N.m.r. spectra were recorded with the Varian FT 80A (20 MHz). 360 MHz Spectra (where

* The full data from this study are not yet available and will be published separately.



Scheme 6. *Reagents:* (i) H_2, PtO_2; (ii) HCl, AcOH; then NaOH; then MnO_2–C; (iii) Red-Al. Only one enantiomer is shown for compounds (11)—(16)

indicated) were recorded using a Bruker WH 360 instrument. Column chromatography was carried out using Crosfield's Sorbsil U30 silica gel (referred to as silica gel) or Florisil. Extracts were dried over anhydrous magnesium sulphate unless otherwise stated.

All experiments involving the use of alkyl-lithium reagents were carried out in clean, dry, three-necked flasks under nitrogen. Nitrogen and all reagents were introduced through rubber septa by means of Aldrich stainless steel needles with Leur fittings. Small quantities of reagent were transferred by means of a syringe. Larger quantities (*i.e.* solutions of alkyl-lithium reagents) were blown under nitrogen pressure directly from an Aldrich Sure-seal bottle into a dried measuring cylinder sealed with a septum, and from there directly into the reaction vessel. A double-ended stainless steel needle was used for these transfers. THF was freshly distilled from $LiAlH_4$.

1-*Benzoyl*-4-(2-*oxopropyl*)-2,2a,3,4-*tetrahydrobenz*(*cd*)*indol*-5(1H)-*one* (4a).—To the yellow solution formed on adding t-butyl-lithium (10.25 ml of a 15% solution in pentane, 0.024 mol) to THF (50 ml) at −75 °C (acetone–solid CO_2 bath) was added mesityl bromide (2.4 g, 0.012 mol) whilst the temperature was kept below −65 °C. During the addition a dense white precipitate formed; as the last of the mesityl bromide was added the yellow colour was discharged. The suspension of mesityl-lithium was stirred for 10 min. A solution of compound (3) (2.77 g, 0.01 mol) in THF (30 ml) was added as rapidly as possible whilst the temperature was kept below −50 °C and the solution was then stirred for 15 min at between −50 and −60 °C. The dark brown solution of the enolate was cooled to −75 °C and 2-nitropropene (1.0 g, 0.01 mol) added dropwise. The temperature was allowed to rise to −30 °C at which time a dense yellow precipitate formed. After 1 h the suspension was cooled to −70 °C and 70% aqueous perchloric acid (2 ml) was added. The mixture was allowed to attain room temperature and was then stirred for 28 h. Cool water was added and the product extracted with chloroform. The extract was washed with water, dried, and evaporated under reduced pressure. The gummy residue was purified by chromatography on silica gel (eluant 50% ethyl acetate–hexane) and those fractions containing the product were combined, evaporated under reduced pressure and crystallised from methanol to give the *dione* (4a) (1.5 g, 45%), m.p. 117—119 °C; $\lambda_{max.}$ (MeOH) 237 (ε 24 200) and 326 nm (ε 4 600); $\nu_{max.}$ (KBr) 1 715 (aliphatic C=O), 1 680 (aromatic C=O), and 1 640 cm^{-1} (amide C=O); δ ($CDCl_3$) 2.24 (3 H, s, $COCH_3$), 1.9—4.5 (8 H, m, skeletal aliphatics), and 7.0—7.8 (8 H, m, ArH); *m/z* 333 (M^+) (Found: C, 75.4; H, 5.55; N, 4.2. $C_{21}H_{19}NO_3$ requires C, 75.65; H, 5.75; N, 4.2%).

1-*Benzoyl*-4-(2-*oxobutyl*)-2,2a,3,4-*tetrahydrobenz*[cd]*indol*-5(1H)-*one* (4b).—This was similarly formed using 2-nitrobut-1-ene. Short-path distillation at 120 °C and 0.05 mmHg gave the dione (4b) as a non-crystallisable gum (2.3 g, 66%), $\lambda_{max.}$ (MeOH) 237 (ε 24 200), and 326 nm (ε 4 600); δ * ($CDCl_3$) 1.09 (3 H, t, CH_2CH_3), 1.5—2.0 (1 H, m, 3-H), 2.1—3.3 (6 H, m, $CH_2COCH_2CH_3$, 3-H, and 4-H), 3.4—3.9 (2 H, m, 2- and 2a-H), 4.4 (1 H, m, 2-H), and 7.0—7.6 (8 H, m, ArH); *m/z* 347 (M^+).

4-*Acetyl*-4,5,5a,6,6a,7-*hexahydro*-8H-*indeno*[6,5,4-cd]indol-8-*one* (5c).—To a solution of the dione (4a) (1.3 g, 0.004 mol) in ethanol (100 ml) under nitrogen was added sodium hydroxide (2.0 g). The reaction mixture was stirred and slowly warmed to a gentle reflux. After 15 min the mixture was cooled to 10 °C and diluted with ice–water. The product was extracted into chloroform and the extract was washed with water, dried, and acetic anhydride (1 ml) was added. After 10 min the solvent was removed under reduced pressure and the semi-solid residue was dissolved in ethyl acetate, from which the *enone* (5c) crystallised (0.6 g, 64%), m.p. 180—182 °C; $\lambda_{max.}$ (MeOH) 236 (ε 31 900) and 294 nm (ε 26 200); $\nu_{max.}$ (KBr) 1 705 (ketone) and 1 665 cm^{-1} (amide); δ ($CDCl_3$) 2.26 (3 H, s, $COCH_3$), 1.3—4.5 (8 H, m, skeletal aliphatics), 6.44 (1 H, d,

* Systematic numbering scheme.

J 1.6 Hz, 8-H), 7.2—7.5 (2 H, m, 11- and 12-H), and 8.09 (1 H, d, 13-H); *m/z* 253 (M^+) (Found: C, 75.65; H, 5.9; N, 5.75. $C_{16}H_{15}NO_2$ requires C, 75.85; H, 5.95; N, 5.55%).

4-*Acetyl*-9-*methyl*-4,5,5a,6,6a,7-*hexahydro*-8H-*indeno*[6,5,4-cd]*indol*-8-*one* (5d).—From compound (4b) (2.3 g, 0.0066 mol) after a reflux time of 2 h there was obtained, in similar manner, the *enone* (5d) (1.0 g, 57%), m.p. 223—224 °C; $\lambda_{max.}$ (MeOH) 261 (ε 27 600) and 293 nm (ε 26 700); $\nu_{max.}$ (KBr) 1 695 (ketone) and 1 660 cm^{-1} (amide); δ ($CDCl_3$) 2.05 (3 H, d, *J* 1.0 Hz, 8-CH_3), 2.22 (3 H, s, $COCH_3$), 1.0—4.4 (8 H, m, skeletal aliphatics), 6.95—7.68 (2 H, m, 11- and 12-H), and 8.05 (1 H, d, 13-H); *m/z* 267 (M^+) (Found: C, 76.15; H, 6.4; N, 5.50. $C_{17}H_{17}NO_2$ requires C, 76.35; H, 6.4; N, 5.25%).

9-*Methyl*-4,6,6a,7-*tetrahydro*-8H-*indeno*[6,5,4-cd]*indol*-8-*one* (6).—Compound (3) (5.5 g, 0.02 mol) was treated as in the previous preparation of (5d) until the work-up after the sodium hydroxide cyclisation. Instead of the chloroform extract being treated with acetic anhydride it was evaporated to dryness under reduced pressure and the residue was redissolved in acetone (200 ml). MnO_2–C [6] (50 g) was added slowly during 6 h and the mixture was stirred for a further 18 h. The MnO_2–C was removed by filtration and well washed with acetone (3 × 50 ml). The combined filtrate and washings were evaporated under reduced pressure to give a red oil which was purified by chromatography on silica gel (eluant chloroform). Crystallisation from chloroform–ethyl acetate then gave the *enone* (6) (1.3 g, 30%), m.p. 257—259 °C; $\lambda_{max.}$ (MeOH) 212 (ε 21 300), 262 (ε 17 000), and 359 nm (ε 9 800); $\nu_{max.}$ (KBr) 3 320 (NH) and 1 670 cm^{-1} (C=O); δ ($CDCl_3$–[$^2H_6$]DMSO) * 2.07 (3 H, d, *J* 1.0 Hz, 8-CH_3), 1.9—3.55 (5 H, m, skeletal aliphatics), 6.98 (1 H, d, singlet in D_2O, 2-H), 7.0—7.58 (3 H, m, ArH), and 10.28 (1 H, br s, exchanged slowly in D_2O, NH); *m/z* 223 (M^+) (Found: C, 80.7; H, 6.05; N, 6.35. $C_{15}H_{13}NO$ requires C, 80.7; H, 5.85; N, 6.25%).

4-*Acetyl*-5,5a,6,6a,7,8-*hexahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (7a).—A solution of compound (5c) (2.2 g, 0.0087 mol) in glacial acetic acid (20 ml) was stirred and warmed to 60 °C. Sodium azide (0.6 g, 0.0087 mol) was added, followed by concentrated sulphuric acid (2 ml) dropwise during 5 min. The reaction mixture was stirred at 60—65 °C until effervescence ceased. Two further additions of sodium azide and concentrated sulphuric acid (same quantities as above) were made to complete the conversion of all starting material. The reaction mixture was poured onto ice-saturated aqueous sodium hydrogen carbonate and extracted into chloroform. The extract was washed with water, dried, and evaporated to dryness. Crystallisation from methanol gave the *lactam* (7a) (1.7 g, 85%), m.p. 300—305 °C; $\lambda_{max.}$ (MeOH) 256 (ε 34 300), and 296 nm (ε 17 200); $\nu_{max.}$ (KBr) 3 250 (NH) and 1 675 and 1 660 cm^{-1} (amide C=O); δ ($CDCl_3$) 1.5 and 2.3 (each 1 H, m, 4-H), 2.24 (3 H, s, $COCH_3$), 2.8—4.3 (6 H, m, remaining skeletal aliphatics), 6.0 (1 H, s, exchanged in D_2O, NH), 6.5, (1 H, d, *J* 2.0 Hz, 9-H), 7.0—7.5 (2 H, m, 12- and 13-H), and 8.0 (1 H, d, 14-H); *m/z* 268 (M^+) (Found: C, 71.5; H, 5.9; N, 10.2. $C_{16}H_{16}H_2O_2$ requires C, 71.6; H, 6.0; N, 10.45%).

4-*Acetyl*-10-*methyl*-5,5a,6,6a,7,8-*hexahydroindolo*[4,3-fg]-*isoquinolin*-9(4H)-*one* (7b).—From compound (5d) (10.7 g, 0.04 mol) there was similarly obtained the *lactam* (7b) (10.1 g, 89%), m.p. 214—216 °C (from methanol); $\lambda_{max.}$ (MeOH) 255 (ε 30 800) and 292 nm (ε 17 300); $\nu_{max.}$ (KBr) 3 220 (NH) and 1 650 cm^{-1} (amide C=O); δ ($CDCl_3$) 1.0—1.7 (1 H, m, 4-H), 2.27 (3 H, s, $COCH_3$), 2.42 (3 H, s, 9-CH_3), 1.7—4.8 (7 H, m, remaining skeletal aliphatics), 7.0 (1 H, br s, exchanged in D_2O, NH), 7.28 (1 H, t, 13-H), 7.58 (1 H, d, 12-H), and 8.07 (1 H, d, 14-H); *m/z* 282 (M^+) (Found: C, 72.4; H, 6.25; N, 9.7. $C_{17}H_{18}N_2O_2$ requires C, 72.3; H, 6.4; N, 9.9%).

4-*Acetyl*-8,10-*dimethyl*-5,5a,6,6a,7,8-*hexahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (7c).—To a stirred solution of compound (7b) (0.14 g, 0.005 mol) in anhydrous DMF (10 ml) maintained at 20 °C was added sodium hydride (50% dispersion in mineral oil) (30 mg). The mixture was stirred for a further 30 min and the solution was then cooled to 10 °C. Methyl iodide (0.1 g) was added and the red-brown colour of the solution disappeared immediately. The mixture was allowed to warm to room temperature and was then stirred for 1 h before dilution with water. The mixture was extracted with chloroform and the extract washed with water, dried, and evaporated under reduced pressure to give a brown oil. Crystallisation from 10% ethanol–ethyl acetate gave the *lactam* (7c) (110 mg, 75%), m.p. 210—212 °C; $\lambda_{max.}$ (MeOH) 253 (ε 33 500) and 295 nm (ε 17 300); $\nu_{max.}$ (KBr) 1 640 cm^{-1} (amide C=O); 360 MHz n.m.r. spectrum, see Table 1 (Found: C, 72.8; H, 6.7; N, 9.2. $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.8; N, 9.45%).

4-*Acetyl*-8-*methyl*-5,5a,6,6a,7,8-*hexahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (7d).—From compound (7a) (2.7 g, 0.01 mol) there was similarly obtained the *lactam* (7d) (1.3 g, 48%), m.p. 250—255 °C; $\lambda_{max.}$ (MeOH) 255 (ε 32 400) and 297 nm (ε 14 900); $\nu_{max.}$ (KBr) 1 650 cm^{-1} (amide C=O); δ ($CDCl_3$) 2.24 (3 H, s, $COCH_3$), 3.06 (3 H, NCH_3), 1.5 and 2.4 (each 1 H, m, 4-H), 2.5—4.5 (6 H, m, remaining skeletal aliphatics), 6.5 (1 H, d, *J* 1.0 Hz, 9-H), 7.0—7.5 (2 H, m, 12- and 13-H), and 8.0 (1 H, d, 14-H); *m/z* 282 (M^+) (Found: C, 72.9; H, 6.7; N, 9.65. $C_{17}H_{18}N_2O_2$ requires C, 73.3; H, 6.4; N, 9.9%).

4-*Acetyl*-8,10-*dimethyl*-5,5a,6,8,10,10a-*hexahydroindolo*-[4,3-fg]*isoquinolin*-9(4H)-*one* (8a).—The reaction was conducted, as in the previous experiment, with compound (7b) (2.8 g, 0.01 mol) except that the mixture was heated at 60 °C for 2.5 h. On work-up the product was found by t.l.c. (eluant 10% ethanol–ethyl acetate) to consist predominantly of a less polar spot [R_F 0.28 compared with R_F 0.12 for (7c)]. The new product was purified by chromatography on silica gel (eluant 1% methanol–methylene dichloride) and crystallisation from acetonitrile to give the *lactam* (8a) (1.0 g, 34%), m.p. 233—235 °C; $\lambda_{max.}$ (MeOH) 213 (ε 31 200) and 262 nm (ε 20 100); $\nu_{max.}$ (KBr) 1 660 cm^{-1} (amide C=O); 360 MHz n.m.r. spectrum, see Table 1; *m/z* 296 (M^+) (Found: C, 72.7; H, 6.7; N, 9.55. $C_{18}H_{20}N_2O_2$ requires C, 72.95; H, 6.8; N, 9.45%).

4-*Acetyl*-10-*methyl*-5,5a,6,8,10,10a-*hexahydroindolo*[4,3-fg]-*isoquinolin*-9(4H)-*one* (8b).—To a solution of the sodium salt of *N*-methylacetamide, made by treating sodium hydride (0.3 g, 0.006 mol) with *N*-methylacetamide (10 ml), was added the lactam (7b) (0.5 g, 0.0018 mol). The mixture was heated at 60 °C for 2 h and poured into ice–water. The product was extracted with chloroform and the extract was washed with water, dried, and evaporated under reduced pressure to give a brown oil. Chromatography on silica gel (eluant chloroform) and crystallisation from ethyl acetate gave the rearrangement *product* (8b) (0.2 g, 40%), m.p. 244—245 °C; $\lambda_{max.}$ (MeOH) 214 (ε 24 700) and 261 nm (ε 20 900); $\nu_{max.}$ (KBr) 3 250, 3 125 (amide NH), and 1 680 and 1 650 cm^{-1} (amide C=O); δ ($CDCl_3$) 0.85 (3 H, d, *J* 7.1 Hz, 9-CH_3), 2.26 (3 H, s, $COCH_3$),

* DMSO is dimethyl sulphoxide.

1.0—4.5 (7 H, m, skeletal aliphatics), 6.11 (1 H, s, 6-H), 6.8—7.3 (2 H, m, 12- and 13-H), and 7.9 (1 H, d, 14-H); *m/z* 282 (M^+) (Found: C, 72.45; H, 6.15; N, 9.65. $C_{17}H_{18}N_2O_2$ requires C, 72.3; H, 6.4; N, 9.9%).

8-*Methyl*-6,6a,7,8-*tetrahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (9a).—A solution of compound (7d) (0.45 g, 0.0016 mol) in a mixture of glacial acetic acid (10 ml) and concentrated hydrochloric acid (10 ml), kept under nitrogen, was heated at reflux for 1 h. The cooled solution was poured into ice–water and made basic with 50% aqueous sodium hydroxide. The product was extracted into chloroform and the extract was washed with water, dried, and the solvent was evaporated off under reduced pressure. The crude indoline (7e) was immediately dissolved in acetone (50 ml) and the solution was vigorously stirred. MnO_2–C (5 g) was added during 2 h and the mixture was then stirred a further 18 h. The MnO_2–C was removed by filtration and well washed with acetone (3 × 50 ml). The combined filtrate and washings were evaporated to leave a grey solid which was purified by chromatography on Florisil (eluant chloroform). Crystallisation from ethyl acetate gave the *indole* (9a) (0.2 g, 59%), m.p. 245—250 °C; $\lambda_{max.}$ (MeOH) 211 (ε 17 800) 256 (ε 15 000), and 360 nm (ε 8 000); $\nu_{max.}$ (KBr) 3 200 (indole NH) and 1 640 cm^{-1} (amide C=O); δ ($CDCl_3$) 3.08 (3 H, s, NCH_3), 2.5—3.55 (5 H, m, skeletal aliphatics), 6.67 (1 H, d, *J* 1.3 Hz, 9-H), 6.97 (1 H, s, 2-H), 7.2—7.5 (3 H, m, ArH), and 8.0 (1 H, br s, exchanged in D_2O, NH); *m/z* 238 (M^+) (Found: C, 75.4; H, 5.8; N, 11.9. $C_{15}H_{14}N_2O$ requires C, 75.6; H, 5.9; N, 11.75%).

8,10-*Dimethyl*-6,6a7,8-*tetrahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (9b).—From the indoline (7c) (1.5 g, 0.0052 mol) there was similarly obtained the *indole* (9b) (0.95 g, 74%), m.p. 237—239 °C (from acetonitrile); $\lambda_{max.}$ (MeOH) 210 (ε 22 500), 244 (ε 16 900), and 353 nm (ε 8 800); $\nu_{max.}$ 3 190 (indole NH) and 1 630 cm^{-1} (amide C=O); δ ($CDCl_3$) 2.55 (3 H, s, 9-CH_3), 3.2 (3 H, s, NCH_3), 2.8—3.8 (5 H, m, skeletal aliphatics), 7.1 (1 H, s, 2-H), 7.3—7.7 (3 H, m, ArH), and 8.3 (1 H, br s, exchanged in D_2O, NH); *m/z* 252 (M^+) (Found: C, 76.1; H, 6.25; N, 11.25. $C_{16}H_{16}N_2O$ requires C, 76.15; H, 6.4; N, 11.1%).

8-*Methyl*-4,6,6a,7,8,9-*hexahydroindolo*[4,3-fg]*isoquinoline* (10a).—To a stirred suspension of compound (9a) (0.35 g, 0.0015 mol) in dry benzene (30 ml) was added Red-Al (70% solution in toluene, 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 give an off-white solid (0.3 g, 91%) which was recrystallised from acetonitrile to afford the *amine* (10a), m.p. 235—237 °C; $\lambda_{max.}$ (MeOH) 266 (ε 23 300), 243 (ε 23 500), and 311 nm (ε 10 700); $\nu_{max.}$ ($CHCl_3$) 3 490 cm^{-1} (indole NH); δ ($CDCl_3$) 2.43 (3 H, s, NCH_3), 1.8—3.6 (7 H, m, skeletal aliphatics), 6.4 (1 H, s, 9-H), 6.85 (1 H, s, 2-H), 7.0—7.3 (3 H, m, ArH), and 8.0 (1 H, br s, exchanged in D_2O, NH); *m/z* 224 (M^+) (Found: C, 80.6; H, 6.85; N, 12.25. $C_{15}H_{16}N_2$ requires C, 80.3; H, 7.2; N, 12.5%).

8,10-*Dimethyl*-4,6,6a,7,8,9-*hexahydroindolo*[4,3-fg]*isoquinoline* (10b)[(⁻ 2)].—From the lactam (9b) (0.72 g, 0.00285 mol) there was similarly obtained the *amine* (10b) (0.58 g, 85%), m.p. 211—213 °C (from acetonitrile); $\lambda_{max.}$ (MeOH) 237 (ε 20 200) and 309 nm (ε 10 100); $\nu_{max.}$ ($CHCl_3$) 3 490 cm^{-1} (indole NH); δ ($CDCl_3$) 2.09 (3 H, s, 9-CH_3), 2.47 (3 H, s, NCH_3), 1.9—3.5 (7 H, m, skeletal aliphatics), 6.85 (1 H, s, 2-H), 7.0—7.3 (3 H, m, ArH), and 7.82 (1 H, br s, exchanged in D_2O, NH); *m/z* 238 (M^+) (Found: C, 80.35; H, 7.45; N, 11.5. $C_{16}H_{18}N_2$ requires C, 80.65; H, 7.6; N, 11.75%).

(6aR*,10R*,10aR*)-4-*Acetyl*-8,10-*dimethyl*-5,5a,6,6a,7,8,-10,10a-*octahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (11).—To a suspension of compound (7c) (1.1 g, 0.0037 mol) in ethyl acetate (100 ml) was added platinum(IV) oxide (1.1 g). The mixture was hydrogenated at 60 lb in^{-2} for 18 h. The catalyst was removed by filtration and the solvent was evaporated off under reduced pressure to give a white solid. Crystallisation from ethyl acetate gave the *reduced lactam* (11) (0.7 g, 64%), m.p. 189—191 °C; $\lambda_{max.}$ (MeOH) 218 (ε 26 300) and 257 nm (ε 15 500); $\nu_{max.}$ 1 650 and 1 640 cm^{-1} (amide C=O); δ ($CDCl_3$) 1.12 (3 H, d, *J* 7.1 Hz, 9-CH_3), 2.23 (3 H, s, $COCH_3$), 2.99 (3 H, s, NCH_3), 0.7—4.25 (10 H, m, skeletal aliphatics), 6.83 (1 H, d, 12-H), 7.22 (1 H, t, 13-H), and 7.88 (1 H, d, 14-H); *m/z* 298 (M^+) (Found: C, 72.4; H, 7.6; N, 9.2. $C_{18}H_{22}N_2O_2$ requires C, 72.45; H, 7.45; N, 9.4%).

(6aR*,10S*,10aS*)-4-*Acetyl*-8,10-*dimethyl*-5,5a,6,6a,7,8,-10,10a-*octahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (12).—To a solution of compound (8a) (0.55 g, 0.0019 mol) in ethanol (50 ml) was added platinum(IV) oxide (50 mg). The solution was hydrogenated at 60 lb in^{-2} until hydrogen uptake ceased. The catalyst was removed by filtration and the solution was evaporated to dryness under reduced pressure. Crystallisation of the residue from ethyl acetate gave the *reduced lactam* (12) (0.47 g, 85%), m.p. 204—206 °C; $\lambda_{max.}$ (MeOH) 214 (ε 31 200), 255 (ε 14 800), 280 (ε 4 750), and 290 nm (ε 4 220); $\nu_{max.}$ (KBr) 1 655 and 1 645 cm^{-1} (both amide C=O); δ ($CDCl_3$) 1.0 (3 H, d, *J* 7.1 Hz, 9-CH_3), 2.21 (3 H, s, $COCH_3$), 3.0 (3 H, s, NCH_3), 1.9—4.3 (10 H, m, skeletal aliphatics), 6.7—7.4 (2 H, m, 12- and 13-H), and 7.9 (1 H, d, 14-H); *m/z* 298 (M^+) (Found: C, 72.75; H, 7.3; N, 9.5. $C_{18}H_{22}N_2O_2$ requires C, 72.45; H, 7.45; N, 9.4%).

(6aR*,10R*,10aR*)-8,10-*Dimethyl*-6,6a,7,8,10,10a-*hexahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (13).—A solution of the indoline (11) (1.05 g, 0.0035 mol) in glacial acetic acid (20 ml) and concentrated hydrochloric acid (20 ml), kept under nitrogen, was refluxed for 2 h. The cooled solution was poured into ice–water and made basic with 50% aqueous sodium hydroxide. The product was extracted with chloroform (3 × 50 ml) and the combined extracts were washed with water, dried, and evaporated to dryness to give a white solid. The crude deacetylated indoline was dissolved in acetone (150 ml) and the solution was vigorously stirred. MnO_2–C (11 g) was added slowly during 4 h and the mixture was stirred for a further 8 h. The MnO_2–C was removed by filtration and well washed with acetone (3 × 50 ml). The combined filtrate and washings were evaporated to dryness to give to a grey solid which was purified by chromatography on silica gel (eluant 1% methanol–methylene dichloride). Crystallisation from ethyl acetate gave the *indole* (13) (0.4 g, 45%), m.p. 278—279 °C; $\lambda_{max.}$ 228 (ε 28 700) and 284 nm (ε 6 760); $\nu_{max.}$ 3 220 (NH) and 1 610 cm^{-1} (amide C=O); 360-MHz n.m.r. spectrum, see Table 2 (Found: C, 75.5; H, 7.0; N, 11.3. $C_{16}H_{18}N_2O$ requires C, 75.55; H, 7.15; N, 11.0%).

(6aR*,10S*,10aS*)-8,10-*Dimethyl*-6,6a,7,8,10,10a-*hexahydroindolo*[4,3-fg]*isoquinolin*-9(4H)-*one* (14).—From the indoline (12) (0.3 g, 0.001 mol) there was similarly prepared the *indole* (14) which was crystallised from ethyl acetate (0.1 g, 39%), m.p. 217—219 °C; $\lambda_{max.}$ (MeOH) 226 (ε 30 300) and 284 nm (ε 7 500); $\nu_{max.}$ (KBr) 3 200 (NH) and 1 620 cm^{-1} (amide C=O); 360 MHz n.m.r. spectrum, see Table 2; *m/z* 254 (M^+) (Found: C, 75.3; H, 6.9; N, 10.85. $C_{16}H_{18}N_2O$ requires C, 75.55; H, 7.15; N, 11.0%).

(6aR*,10R*,10aS*)-8,10-*Dimethyl*-4,6,6a,7,8,9,10,10a-*octahydroindolo*[4,3-fg]*isoquinoline* (15).—To a stirred solution

of the lactam (13) (50 mg) in dry benzene (10 ml) was added Red-Al (0.1 ml). After 2 h the mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to dryness. Crystallisation from ethyl acetate gave the *amine* (15) (30 mg, 63.5%), m.p. 230—232 °C; $\lambda_{max.}$ 228 (ε 29 300) and 285 nm (ε 7 050); $\nu_{max.}$ ($CHCl_3$) 3 490 cm^{-1} (NH); δ ($CDCl_3$) 1.1 (3 H, d, *J* 6.7 Hz, 9-CH_3), 2.35 (3 H, s, NCH_3), 1.7—3.5 (9 H, m, skeletal aliphatics), 6.84 (1 H, s, 2-H), 6.8—7.3 (3 H, m, ArH), and 7.85 (1 H, s, exchanged in D_2O, NH); *m/z* 240 (M^+) (Found: C, 79.65; H, 8.25; N, 11.9. $C_{16}H_{20}N_2$ requires C, 79.95; H, 8.4; N, 11.65%).

(6aR*,10S*,10aR*)-8,10-*Dimethyl*-4,6,6a,7,8,9,10,10a-*octahydroindolo*[4,3-fg]*isoquinoline* (16).—To a stirred solution of the lactam (14) (30 mg) in dry benzene (10 ml) was added Red-Al (0.1 ml). After 2 h the mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to dryness. Crystallisation from ethyl acetate gave the *amine* (16) (20 mg, 42%), m.p. 170—173 °C; $\lambda_{max.}$ 226 (ε 16 000), 284 (ε 3 330), and 294 nm (ε 2 870); $\nu_{max.}$ (KBr) 3 400 cm^{-1} (indole NH); δ ($CDCl_3$) 0.85 (3 H, d, *J* 6.3 Hz, 9-CH_3), 2.28 (3 H, s, NCH_3), 2.0—3.3 (9 H, m, skeletal aliphatics), 6.86 (1 H, s, 2-H), 7.0—7.3 (3 H, m, ArH) and 7.85 (1 H, br s, exchanged in D_2O, NH); *m/z* 240 (M^+) (Found: C, 80.0, H, 8.25; N, 11.7. $C_{16}H_{20}N_2$ requires C, 79.95; H, 8.4; N, 11.65%).

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