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BENZOMORPHAN RELATED COMPOUNDS. XXII.[1]
REDUCTION OF 3-(TETRAHYDROPYRIDYL)INDOLES TO INDOLINES. SYNTHESIS OF A NEW TYPE OF INDOLOMORPHAN[2]

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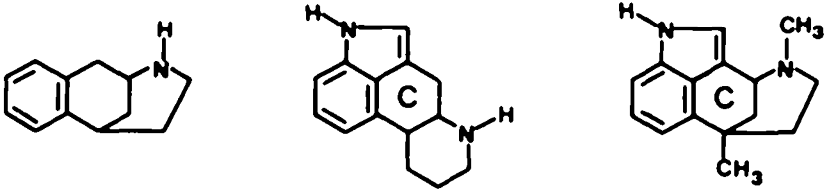
Abstract – The first synthesis of an indolo[4,3-*fg*]morphan system has been achieved through a route involving the acid-catalyzed cyclization of a 3-(tetrahydro-2-pyridyl)indoline. A procedure for the reduction of 3-(tetrahydropyridyl)indoles to the corresponding indolines, consisting in the formation of the tetrahydropyridine-borane complex followed by treatment with ethanolic hydrochloric acid, is established.

The known pharmacological properties of benzomorphans[3] and ergoline related compounds,[4] which are modified structures of morphine and ergot alkaloids, respectively, have stimulated much synthetic activity in these areas. However there are no works about the synthesis of analogues simultaneously related to both structural types.

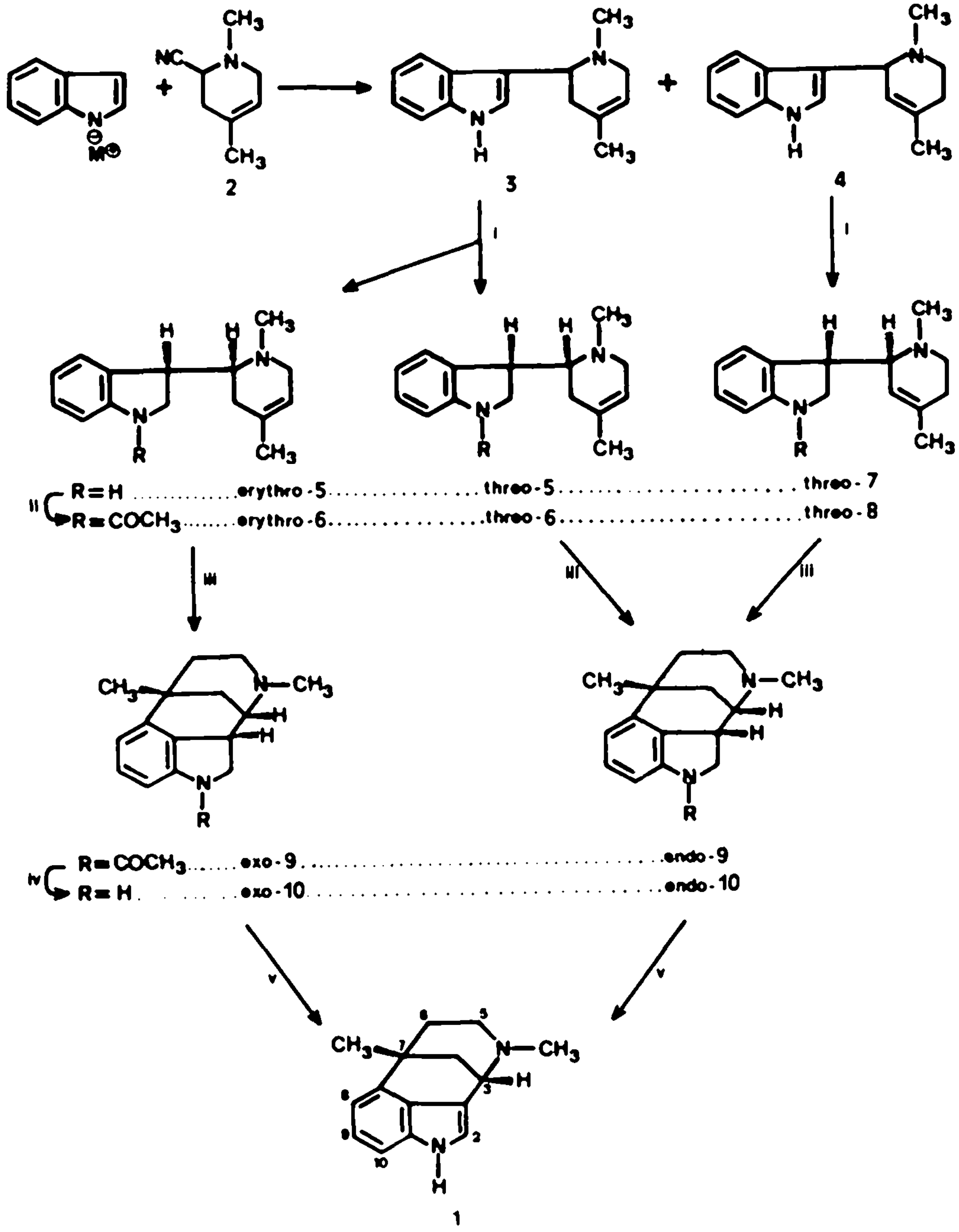
We now report the synthesis of tetracyclic base 1 which constitutes a new type of benzomorphan, having an additional pyrrole ring, and also a modified structural type of ergoline derivative in which the quinoline ring is replaced by a bridged morphan nucleus.



6,7-BENZOMORPHAN **ERGOLINE** **1**

Scheme 1

The strategy employed in the synthesis of indolo[4,3-*fg*]morphan 1[5] implies the formation of the carbocyclic ring C in the key step by electrophilic cyclization on the indole 4-position of an appropriate *N*-protected 3-(tetrahydro-2-pyridyl)indoline. This protocol was proposed taking into account the previous work on the synthesis of ergoline derivatives, although in these syntheses the closure of ring C is normally done before the elaboration of piperidine ring.[6,7] Accordingly, the requisite indoline would be prepared by condensation of a suitable 2-cyanotetrahydropyridine 2 with indolyl-lithium, followed by reduction of the indole nucleus and further acylation. After Friedel-Crafts cyclization, the deprotection and aromatization of the indoline ring should give rise the target molecule 1.



Scheme 2. (i) $NaBH_4$(THF), BF_3-Et_2O; then 6N HCl-EtOH; (ii) Ac_2O; (iii) $AlBr_3$, CS_2; (iv) 6N HCl; (v) MnO_2, $CHCl_3$.

RESULTS AND DISCUSSION

Reduction of 3-(tetrahydropyridyl)indoles to indolines

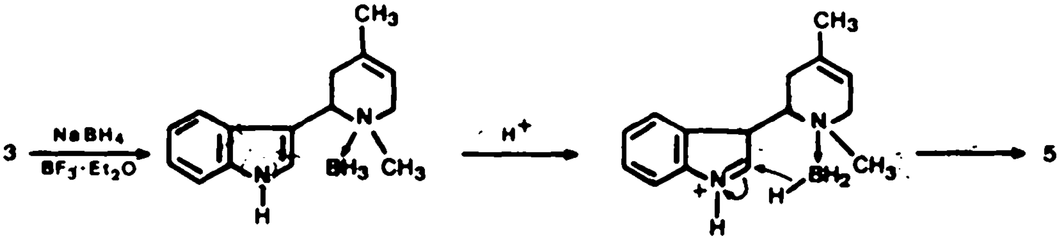
According to our synthetic plan, cyclization upon the indole 4-position required the previous chemoselective reduction of the indole nucleus to indoline, without affecting the tetrahydropyridine double bond. The reduction of indoles to indolines has been widely studied during the last years,[8] especially in the case of indoles containing a basic nitrogen in a side chain, which has received particular attention.[9]

The required 3-(tetrahydro-2-pyridyl)indole **3** was prepared as previously reported,[10] by condensation of 2-cyanotetrahydropyridine **2** with the indole Grignard reagent. A mixture (3:1 ratio) of the expected condensation product **3** (Δ^4 isomer) and the isomeric 3-(1,2,5,6-tetrahydro-2-pyridyl)indole **4** (Δ^3 isomer) was obtained.[11] However, it is worth mentioning that this Δ^3 isomer is synthetically equivalent to the Δ^4 isomer because it can also be further elaborated to the tetracyclic base **1** (see later). Alternatively, the indole compound **3** was obtained as a sole product (60% yield) by reaction of the same 2-cyanotetrahydropyridine **2** with indolyl-lithium.[12]

Our first attempts on the reduction of 3-(tetrahydropyridyl) indole **3**, using pyridine-borane[9d] or sodium cyanoborohydride[9c] in TFA, or sodium borohydride in HCl, gave scarcely satisfactory results since the expected indoline **5**[14] was never formed in yield higher than 35%, the starting indole **3** being recovered in all cases in a variable percentage depending on the reactions conditions.[15]

These results can be explained in the light of the mechanism proposed for the reduction[8d] and by considering that, under the acidic reaction conditions, the amine nitrogen atom is protonated. Consequently, further protonation at the indole 3-position to give a 3*H*-indolenium cation is disfavoured,[9d] and reduction to indoline by *intermolecular* hydride attack competes with destruction of the reducing agent by the acid.[9f]

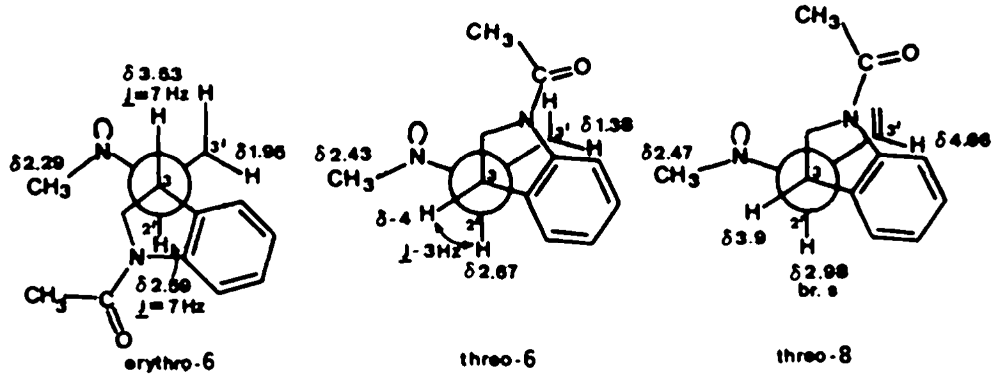
In a previous work we had observed the formation of an indoline derivative during the acid hydrolysis of the pyridine-borane complex derived from a 2-(2-pyridylmethyl)indole.[16] The reduction presumably takes place since the preformed pyridine-borane adduct delivers hydride *intramolecularly* to the 3*H*-indolenium salt formed by protonation of indole. Subsequently, the acid would hydrolyze the amine-borane complex. This observation prompted us to effect a similar reduction from 3-(tetrahydropyridyl)indole **3**.[17] In order to avoid hydroboration of the tetrahydropyridine carbon-carbon double bond, the amine-borane complex was preformed by treating **3** with diborane generated internally[18] from sodium borohydride and *one* equivalent of borontrifluoride etherate.[9h] Further treatment with ethanolic hydrochloric acid afforded in excellent yield (87%) the indolines **5** as an epimeric mixture that could not be separated.



Scheme 3

The stereochemical result of the process, which is governed by the protonation of the indole nucleus, was investigated from the *N*-acetyl indolines **6**. These indolines were obtained by reaction of **5** with acetic anhydride and separated by column chromatography. However, separation of the two diastereomers is not necessary from a synthetic standpoint since their stereochemical difference is lost during the final oxidative step of the synthesis to give a sole azocinoindole **1**.

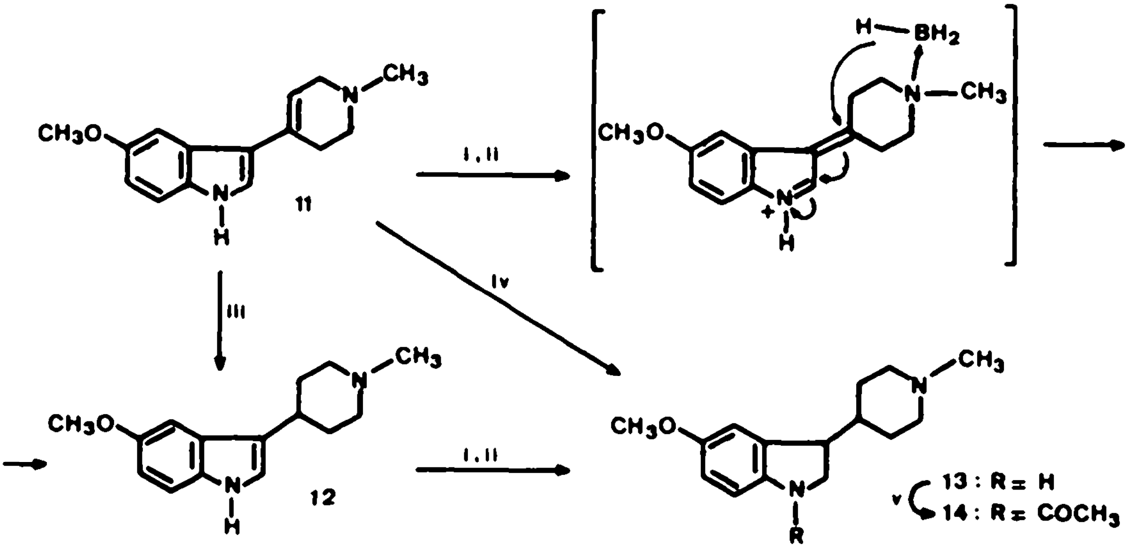
The IR spectra of isomers **6** showed a strong absorption at ~1650 cm^{-1} for the amide carbonyl group, whereas the most significant signals in the ^{1}H NMR spectra were two singlets due to acetamide and *N*-methyl groups and two broad singlets corresponding to the vinyl proton and the methyl group attached to the tetrahydropyridine double bond. The most deshielded signal in both isomers was assigned to 7-H, because this proton falls within the deshielding zone of the amide carbonyl,



Scheme 4

which exists fully as the *endo* rotamer.[19] The relative configuration of *erythro* and *threo* isomers was inferred from the ^{1}H-NMR data (200 MHz), by assuming the preferred conformations depicted in Scheme 4.[20] The chemical shift and multiplicity of indoline and tetrahydropyridine methine protons as well as the shielding of the equatorial proton on the tetrahydropyridine 3-position in *threo*-6, caused by the benzene ring, are consistent with the proposed stereochemistry. This stereochemical assignment was confirmed once *erythro*-6 and *threo*-6 were cyclized to the tetracyclic derivatives *exo*-9 and *endo*-9, respectively (see later).

The satisfactory result of the above reduction prompted us to study the extension of the procedure to other (tetrahydropyridyl)indoles such as the Δ^3 isomer 4 and the 3-(tetrahydro-4-pyridyl)indole 11. As could be expected, in the first case the reduction took place again in excellent yield (92%) and was even stereoselective: the indoline *threo*-7 was obtained as a single diastereomer. The stereochemical assignment was effected, as above, from the ^{1}H-NMR spectrum of the corresponding acetyl derivative *threo*-8. The most significant data were the small value for the coupling constant between indoline 3-H and tetrahydropyridine 2-H, and the strong shielding of the vinyl proton (δ4.66)[21] (see Scheme 4).



Scheme 5. (i) $NaBH_4$(THF), BF_3-Et_2O; (ii) 6N HCl-EtOH; (iii) H_2-PtO_2; (iv) H_2-PtO_2, 3N HCl; (iv) Ac_2O.

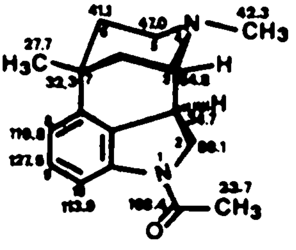
Surprisingly, when (tetrahydropyridyl)indole 11 was submitted to the same reductive process, the 3-(piperidyl)indole 12 was obtained in 85% yield instead of the expected (tetrahydropyridyl)indoline. This result can be explained by considering that the initial protonation occurs at the carbon-carbon double bond of the tetrahydropyridine ring, which is conjugated with the indole nucleus. Further intramolecular hydride transfer, as illustrated in Scheme 5, and hydrolysis of amine-borane complex by the acid, accounts for the observed result. On the other hand, the indole 12 certainly underwent reduction to the indoline 13 (93% yield) when it was resubmitted to sodium borohydride and boron trifluoride-etherate treatment followed by refluxing in ethanolic hydrogen chloride.

Alternatively, the 3-(tetrahydropyridyl)indole 11 was converted either to the piperidylindole 12 or to the piperidylindoline 13 by catalytic hydrogenation over platinum dioxide, under neutral or acidic conditions, respectively. In the first case the yield was similar (82%) to that obtained by diborane reduction, whereas in the second one it was considerably lower (45%).

Synthesis of indolo[4,3-fg]*morphan* 1

Cyclization of *erythro-* and *threo-*(tetrahydropyridyl)indolines 6 was accomplished by using aluminium tribromide. The anticipated tetracyclic indolines *exo*-9 and *endo*-9, respectively, were obtained in good yield. On the other hand, the isomer *endo*-9 was the product obtained by aluminium tribromide cyclization of indoline *threo*-8. These results not only confirm that the constitutional isomers *threo*-6 (a Δ^4-tetrahydropyridine) and *threo*-8 (a Δ^3-tetrahydropyridine) have the same relative configuration but also corroborate the above stereochemical assignment of indolines 6 and 8.

The planar structure of isomers 9 was evident from their spectroscopic data. Thus, the IR spectra showed a strong absorption at ∿1650 cm^{-1} due to the amide carbonyl group, whereas the most noteworthy features in the ^{1}H-NMR spectra of these tetracyclic bases, which clearly indicated that cyclization had occurred, were i) the absence of absorption attributable to a vinyl proton, ii) the presence of a singlet at δ 1.3 due to the methyl group attached to a quaternary carbon, and iii) the presence of a triplet and two doublets in the aromatic region, corresponding to three protons in a vicinal relative position, one of them being strongly deshielded by the amide carbonyl group. The ^{13}C-NMR spectrum of *exo*-9 is in full agreement with the established structure, and the observed chemical shift values have an excellent correlation with those reported for 6,7-benzomorphans,[22] *N*-acetylindoline,[23] and 2-azabicyclo[3.3.1]nonanes.[24]



exo-9

The relative stereochemistry of *exo-* and *endo*-9 was deduced taking into account that the geometry of *endo* isomer implies the axial disposition of *N*-methyl group to avoid the serious steric hindrance between this substituent and the methylene group of the indoline ring.[25] This feature was evident by the deshielding of *N*-methyl group in the NMR spectrum (∿0.2 ppm with respect to the *exo* isomer) and by the chemical shift of C-5 methylene protons, since both resonate at δ 2.37, whereas in the *exo* isomer, having the nitrogen lone pair located axially, 5-Heq resonates at lower field (δ2.59) than 5-Hax (δ2.20). Moreover, in the *endo* isomer the relative *synperiplanar* disposition of C_{2a}-H and C_{11}-Heq bonds induces a long-range shielding, clearly observable in the last proton (δ0.95) as compared with the *exo* isomer (δ1.4).

Hydrolysis of acetyl derivatives *exo*- and *endo*-9 to the corresponding *N*-unsubstituted indolines 10 proceeded smoothly by heating in 6N hydrochloric acid. Finally, treatment either of *exo*-10 or *endo*-10 with activated manganese dioxide[26,27] gave the target indolomorphan 1. The most significant signal in the ^{1}H-NMR spectrum of 1 was that corresponding to the 3-H methine proton, which appears at δ 3.9, as could be expected in a compound having an aromatic ring fused to the *g* side of the morphan nucleus.[28]

As a last point, it is worth commenting upon the unsuccessful attempts to cyclize with mercuric acetate the protected piperidylindoline 14, which was obtained by acetylation of 13, to an indolo[3,4-*fg*]morphan system.[29] Under the usual acidic conditions (aqueous 5% acetic acid) a mixture of the starting indoline 14 and small amounts of piperidylindoline 12, coming from hydrolysis of acetyl group and subsequent oxidation of the indoline nucleus, was obtained. When oxidation was carried out at pH 7-8 in the presence of EDTA.2Na (see Experimental), 1-acetyl-5-methoxy-3-(1-methyl-2-oxo-4-piperidyl)indoline (15) was isolated in 56% yield.[30] The failure of this cyclization, in contrast with the successful cyclization of (tetrahydropyridyl)indolines 6 and 8 reported above, can be rationalized taking into account the lower electrophilic character of an iminium salt (a stabilized carbocation) as compared with a carbocation generated by protonation of a carbon-carbon double bond.

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Perkin-Elmer R-24B (60 MHz) instrument or, when indicated, on a Varian XL-200 spectrometer using TMS as internal standard. The ^{13}C-NMR spectrum was determined on a Varian XL-200 spectrometer. The chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were taken with a Perkin Elmer 577 spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. GLC was run isothermally on a Perkin-Elmer F-11 chromatograph fitted with a flame ionization detector. A 2 m glass column, 6.4 mm in diameter was used, packed with 2.5% OV.225 on 100-120 mesh chromosorb WHP. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate powder. TLC and column chromatography were carried out on SiO_2 (silica gel 60, Merck, 0.063-0.200 mm), and the spots were located with UV light or iodoplatinate reagent. Microanalyses were performed by Instituto de Química Bio-Orgànica, Barcelona.

3-(1,4-Dimethyl-1,2,3,6-tetrahydro-2-pyridyl)indole(3) was prepared from 2-cyanotetrahydropyridine 2[31] and indolyl-lithium in a 0.08 mol scale in 60% yield by the published procedure.[12]

3-(1,4-Dimethyl-1,2,5,6-tetrahydro-2-pyridyl)indole(4) was obtained as a minor product (15% yield) in the condensation between indolylmagnesium bromide and 2-cyanotetrahydropyridine 2[31] operating in a 0.24 mol scale by the published procedure.[10] The indole derivative 3 was the major product (45% yield); NMR: 1.7 (br s, 3H, CH_3), 2.2 (s, 3H, NCH_3), 4.0 (br, 1H, NCH), 5.4 (br, 1H, =CH), 6.8-7.4 (m, 4H, ArH), 7.7 (m, 1H, ArH), 8.5 (br, 1H, NH). The hydrochloride melted at 210-212°C (acetone). (Found: C, 68.73; H, 7.36; N, 10.70; Cl, 13.90. Calcd. for $C_{15}H_{19}ClN_2$: C, 68.57; H, 7.23; N, 10.66; Cl, 13.50).

3-(1,4-Dimethyl-1,2,3,6-tetrahydro-2-pyridyl)indoline(5)

Method A. To a solution of indole 3 (3.3 g, 14.6 mmol) in freshly distilled THF (150 ml) was added sodium borohydride (2.7 g, 71 mmol) under nitrogen. The mixture was warmed to reflux and then was added boron trifluoride-etherate (1.8 ml, 14.2 mmol). The reflux was maintained for 45 min until formation of the amine-borane complex was completed (monitored by TLC). The THF was evaporated *in vacuo* and the residue was taken up in 6N HCl-EtOH (250 ml) and refluxed for 1 h. At this time, disappearance of the amine-borane complex was evident by TLC ($CHCl_3$/MeOH, 85:15). After removal of ethanol, the residue was basified with concentrated aqueous sodium hydroxide and extracted with chloroform. Evaporation of the dried extracts gave a mixture of indolines 5 (2.9 g, 87%). The crude product showed only one spot by TLC and was directly used in the next reaction.

Method B. Sodium borohydride (3.32 g, 88 mmol) was added portionwise under nitrogen to a solution of the indole 3 (2 g, 8.8 mmol) in freshly distilled THF (100 ml). The mixture was refluxed for 1 h 50 min and cooled. Then, ethereal 1.9 N hydrogen chloride (100 ml) was added. The mixture was refluxed for 50 min, and the solvent was evaporated *in vacuo*. The residue was taken up in water (200 ml) and 2N hydrochloric acid (5 ml). After being refluxed for 40 min, the solution was basified with aqueous 30% sodium hydroxide and extracted with ether. The extracts were dried and evaporated to give an oil which was chromatographed. On elution with 98:2 chloroform-methanol, the indoline *erythro*-5 (600 mg, 30%) was obtained; IR (NaCl): 3380 (NH), 1610 (ar); NMR: 1.6 (br s, 3H, CH_3), 1.8-2.1 (m, 2H, 3'-H), 2.35 (s, 3H, NCH_3), 2.7 (m, 1H, 2'-H), 3.1 (m, 2H, 6'-H), 3.25-3.9 (m, 3H, 3-H and 2-H), 5.3 (br, 1H, =CH), 6.4-7.3 (m, 4H,ArH). The dihydrochloride melted (with decomposition) at 230-231°C (acetone-ethanol). (Found: C, 59.47; H, 7.36; N, 9.04. Calcd. for $C_{15}H_{21}Cl_2N_2$: C, 59.80; H, 7.36; N, 9.29). On elution with 95:5 chloroform-methanol, 200 mg of the starting indole were recovered.

(3RS)-1-Acetyl-3[(2SR)-1,4-dimethyl-1,2,3,6-tetrahydro-2-pyridyl]indoline (erythro-6) and *(3RS)-1-Acetyl-3[(2RS)-1,4-dimethyl-1,2,3,6-tetrahydro-2-pyridyl] indoline*(threo-6). A solution of indolines 5 (2.9 g, 12.7 mmol) in acetic anhydride (23 ml) was stirred at room temperature for 2 h. The mixture was poured into ice-water, stirred for 4 h, and then kept on standing overnight at 6°C. The solution was made alkaline with concentrated ammonium hydroxide and extracted with chloroform. The extracts were washed with water, dried over anhydrous potassium carbonate, and evaporated to left a residue which was chromatographed. Elution with 99:1 chloroform-methanol gave isomer *erythro*-6: 1.2 g (36%); mp 155-156°C (ether); IR (KBr): 1650 (CO), 1590 (Ar); NMR (200 MHz): 1.63 (s, 3H, CH_3), 1.95 (br, 2H, 3'-H), 2.22 (s, 3H, $COCH_3$), 2.29 (s, 3H, NCH_3), 2.59 (apparent q, *J*= 7 Hz, 1H, 2'-H), 3.04 and 3.21 (2dm, *J*= 15 Hz, 1H each, 6'-H), 3.52 (ddd, *J*=10, 7, 4.5 Hz, 1H, 3-H), 4.02 (apparent t, *J*= 10 Hz, 1H, 2-H), 4.21 (dd, *J*=10, 4.5 Hz, 1H, 2-H), 5.32 (br s, 1H, =CH), 6.99 (t, *J*= 7.5 Hz, 1H, 5-H), 7.18 (d, *J*=7.5 Hz, 1H, 4-H), 7.21 (t, *J*= 7.5 Hz, 1H, 6-H), 8.20 (d, *J*= 7.5 Hz, 1H, 7-H). (Found: C, 75.44; H, 8.49; N, 10.31. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36). Elution with 98:2 chloroform-methanol gave isomer *threo*-6: 1.85 g (54%); mp 140-142°C (ether); IR (KBr): 1655 (CO), 1600 (Ar); NMR (200 MHz): 1.38 (dm, *J*= 15 Hz, 1H, 3'-He), 1.54 (s, 3H, CH_3), 1.76 (m, 1H, 3'-Ha), 2.24 (s, 3H, $COCH_3$), 2.43 (s, 3H, NCH_3), 2.67 (m, 1H, 2'-H), 2.87 and 3.28 (2 dm, *J*= 15 Hz, 1H each, 6'-H), 3.97-4.16 (m, 3H, 2-H and 3-H), 5.34 (br s, 1H, =CH), 7.03 (t, *J*=7.5 Hz, 1H, 5-H), 7.15 (d, *J*=7.5 Hz, 1H, 4-H), 7.24 (t, *J*=7.5 Hz, 1H, 6-H), 8.25 (d, *J*=7.5 Hz, 1H, 7-H). (Found: C, 75.82; H, 8.36; N, 10.37. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36).

(3RS)-1-Acetyl-3-[(2RS)-1,4-dimethyl-1,2,5,6-tetrahydro-2-pyridyl]indoline (threo-8). Operating as in the above Δ^4 series (method A), the indole 4 (1.4 g, 6.19 mmol) was reduced to the indoline *threo*-7 (1.3 g, 92%); IR (NaCl): 3380 (NH), 1610 (Ar); NMR: 1.6 (s, 3H, CH_3), 1.7-3.8 (m, 9H), 2.4 (s, 3H, NCH_3), 4.85 (s, 1H, =CH), 6.3-7.2 (m, 4H, ArH). This indoline was converted, as above, to the corresponding acetyl deriavtive *threo*-8 (1.32 g, 80%); mp 131-132°C (ether); IR (KBr): 1655 (CO), 1590 (Ar); NMR (200 MHz): 1.58 (s, 3H, CH_3), 1.84 (td, *J*=11, 2 Hz, 1H, 5'-Ha), 2.14 (s, 3H, $COCH_3$), 2.2-2.4 (m, 2H, 5'-He and 6'-Ha), 2.47 (s, 3H, NCH_3), 2.84 (m, 1H, 6'-He), 2.98 (br s, 1H, 2'-H), 3.86 (s, 3H, 2-H and 3-H), 4.66 (br s, 1H, =CH), 7.01 (t, *J*=7.5 Hz, 1H, 5-H), 7.13 (d, *J*=7.5 Hz, 1H, 4-H), 7.21 (t, *J*=7.5 Hz, 1H, 6-H), 8.19 (d, *J*=7.5 Hz, 1H, 7-H). (Found: C, 75.74; H, 8.39; N, 10.52. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36).

(2aRS,3SR,7RS)-1-Acetyl-4,7-dimethyl-2a,3,4,5,6,7-hexahgdro- 2H -3,7-methanoazocino[3,4,5-cd]indole(exo-9). Aluminium tribromide (2.1 g, 7.8 mmol) was added in small portions to a cold mixture of acetyl indoline *erythro*-6 (680 mg, 2.5 mmol) in carbon disulfide (15 ml). The mixture was stirred at reflux temperature for 2 h 30 min, cooled, poured into ice-water, basified with concentrated ammonium hydroxide, and extracted with chloroform. The evaporation of the dried extracts gave *exo*-9 (470 mg, 69%). An analytical sample melted at 177-178°C (ether); IR (KBr): 1650 (CO); NMR (200 MHz): 1.31 (s, 3H, CH_3), 1.40 (br d, *J*=12 Hz, 1H, 11-He), 1.8 (masked, 1H, 6-He), 1.86 (dd, *J*=12, 2.5 Hz, 1H, 11-Ha), 1.97 (td, *J*=13, 13, 5 Hz, 1H, 6-Ha), 2.20 (td, *J*=13, 13, 4 Hz, 1H, 5-Ha), 2.23 (s, 3H, $COCH_3$), 2.41 (s, 3H, NCH_3), 2.59 (dd, *J*=13, 5 Hz, 1H, 5-He), 3.18 (br s, 1H, 3-H), 3.36 (qd, *J*=12, 10, 1 Hz, 1H, 2a-H), 3.62 (dd, *J*=12, 10 Hz, 1H, 2-H), 4.11 (apparent t, *J*= 12 Hz, 1H, 2-H), 6.99 (d, *J*= 7.5 Hz, 8-H), 7.16 (t, *J*=7.5 Hz, 1H, 9-H), 7.83 (d, *J*=7.5 Hz, 1H, 10-H). (Found: C, 75.22; H, 8.17; N, 10.18. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36).

(2aRS,3RS,7SR)-1-Acetyl-4,7-dimethyl-2a,3,4,5,6,7-hexahydro-2H-3,7-methanoazocino[3,4,5-cd]indole(endo-9). Operating as above, from acetyl indoline *threo*-8 (200 mg, 0.74 mmol) the isomer *endo*-9 was isolated (100 mg, 50%); IR (KBr): 1655 (CO); NMR (200 MHz): 0.96 (br d, *J*=13 Hz, 1H, 11-He), 1.37 (s, 3H, CH_3), 1.68 (m, 2H, 6-H), 1.96 (dd, *J*=13, 4 Hz, 1H, 11-Ha), 2.20 (s, 3H, $COCH_3$), 2.37 (m, 2H, 5-H), 2.57 (s, 3H, NCH_3), 3.20 (br s, 1H, 3-H), 3.45 (m, 1H, 2a-H), 4.05 (m, 2H, 2-H), 6.84 (d, 1H, 8-H), 7.12 (t, 1H, 9-H), 7.80 (d, 1H, 10-H). The oxalate melted with decomposition at 196-197°C (ethanol). (Found: C, 60.41; H, 7.07; N, 7.48. Calcd.

for $C_{19}H_{24}N_2O_5.H_2O$: C, 60.30; H, 6.87; N, 7.40).

When the cyclization was effected from a mixture of acetyl indolines *erythro*- and *threo*-**6** (4.2 g, 15.5 mmol) in a 2:3 ratio (observed by GLC), a mixture of cyclized products **9** was obtained and separated by column chromatography. Elution with 98:2 chloroform-methanol gave the isomer *endo* -**9** (1.1 g) whereas elution with 97:3 chloroform-methanol afforded the isomer *exo*-**9** (0.9 g). Overall yield, 47%.

(2aRS,3SR,7RS)-4,7-Dimethyl-2a,3,4,5,6,7-hexahydro-2H-3,7-methanoazocino[3,4,5-cd]indole(exo-**10**). A solution of acetyl indoline *exo*-**9** (1.38 g, 5.1 mmol) in aqueous 6N hydrochloric acid (21 ml) was refluxed for 15 min. The cooled solution was poured into ice-water, made basic with ammonium hydroxide, and extracted with ether. The extracts were dried and evaporated to give indoline *exo*-**10** (800 mg, 70%) as a solid, mp 143-144°C (ether); IR (KBr): 3230 (NH), 1600 (Ar); NMR (200 MHz): 1.31 (s, 3H, CH_3), 1.42 (br d, *J*=13 Hz, 1H, 11-He), 1.74 (dm, *J*=13 Hz, 1H, 6-He), 1.84 (br d, *J*= 13 Hz, 1H, 11-Ha), 1.95 (td, *J*=13, 13, 5 Hz, 1H, 6-Ha), 2.28 (td, *J*=13, 13, 4 Hz, 1H, 5-Ha), 2.44 (s, 3H, NCH_3), 2.59 (dm, *J*=13 Hz, 1H, 5-He), 3.13 (t, *J*=2 Hz, 2H, 2-H), 3.18 (t, *J*=2.5 Hz, 1H, 3-H), 3.55 (apparent t, *J*=2 Hz, 1H, 2a-H), 6.55 (d, *J*=7.5 Hz, 1H, 10-H), 6.71 (d, *J*=7.5 Hz, 1H, 8-H), 7.01 (t, *J*=7.5 Hz, 1H, 9-H). (Found: C, 79.06; H, 8.88; N, 11.90. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27).

(2aRS,3RS,7SR)-4,7-Dimethyl-2a,3,4,5,6,7-hexahydro-2H-3,7-methanoazocino[3,4,5-cd]indole(endo-**10**). Operating as above, acetyl indoline *endo*-**9** (1.38 g, 5.1 mmol) was hydrolyzed to the indoline *endo*-**10** (770 mg, 67%); IR ($CHCl_3$): 3390 (NH), 1600 (Ar); NMR: 1.0 (m, 1H, 11-He), 1.3 (s, 3H, CH_3), 1.6-1.9 (m, 3H, 6-H and 11-Ha), 2.3 (m, 2H, 5-H), 2.5 (s, 3H, NCH_3), 3.0-3.6 (m, 4H, 2-, 2a-, 3-H), 4.1(br, 1H, NH), 6.45 (d, 1H, 10-H), 6.5 (d, 1H, 8-H), 6.9 (t, 1H, 9-H). The dioxalate melted at 177-179°C (ethanol). (Found: C, 56.28; H, 6.06; N, 6.67. Calcd. for $C_{19}H_{24}N_2O_8$: C,55.88; H, 5.92; N, 6.86).

4,7-Dimethyl-4,5,6,7-tetrahydro-3H-3,7-methanoazocino[3,4,5-cd]indole(**1**). A mixture of indoline *exo*-**10** (680 mg, 3 mmol) and activated manganese dioxide (4.55 g) in chloroform (225 ml) was stirred at room temperature under nitrogen for 30 h (completion of the reaction was monitored by TLC). The mixture was filtered through Celite and the residue was washed with hot chloroform. The combined filtrate and washings were evaporated to give indole **1** (600 mg, 87%) as a solid which melted with decomposition at 245-247°C (acetone); NMR (DMSO-d_6): 1.5 (s, 3H, CH_3), 1.2-2.6 (m, 6H), 2.15 (s, 3H, NCH_3), 3.9 (s, 1H, 3-H), 6.7-7.2 (m, 4H, ArH). (Found: C, 79.97; H, 8.25; N, 12.11. Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.01; N, 12.37).

When the reaction was effected from the indoline *endo* -**10** (140 mg, 0.6 mmol) the indole **1** (90 mg, 65%) was also obtained.

5-Methoxy-3-(1-methyl-1,2,3,6-tetrahydro-4-pyridyl)indole(**11**). By a modification of the Freter's procedure,[12] by using a 6 molar excess of 1-methyl-4-piperidone (100 ml, 0.85 mol) with respect to 5-methoxyindole[13] (21 g, 0.14 mol), 3-(tetrahydropyridyl)indole **11** was obtained in 65% yield, and 4,4-bis (5-methoxy-3-indolyl)-1-methylpiperidine, an usual byproduct of this reaction, was not detected.

5-Methoxy-3-(1-methyl-4-piperidyl)indole(**12**)

Method A. Following the reductive procedure A, as described for indole **3**, the tetrahydropyridine **11** (3 g, 12.4 mmol) was converted to piperidine **12** (2.54 g, 85%); mp 154-156°C (ether); IR ($CHCl_3$): 3480 (NH); NMR: 1.9-2.3 (m, 6H), 2.4 (s, 3H,NCH_3), 2.5-3.1 (m, 3H), 3.8 (s, 3H, OCH_3), 6.7-7.3 (m, 4H, ArH), 8.5 (br, 1H, NH). (Found: C, 73.51; H, 8.30; N, 11.32. Calcd. for $C_{15}H_{20}N_2O$: C, 73.77; H, 8.19; N, 11.47).

Method B. A solution of tetrahydropyridine **11** (9.3 g, 38 mmol) in ethanol-methanol (200 ml) was hydrogenated over platinum oxide (935 mg) at 50-60°C and atmospheric pressure until one equivalent of hydrogen was absorbed. The catalyst was filtered off and the solution was evaporated to give piperidine **12** (7.7 g, 82%) as a solid.

5-Methoxy-3-(1-methyl-4-piperidyl)indoline(**13**)

Method A. Indole **12** (7.2 g, 29 mmol) was allowed to react, as the above indole derivative **3**, with sodium borohydride (6 g, 0.16 mol) and boron trifluoride etherate (7 ml, 55.4 mmol). After the usual treatment with ethanolic 6N hydrogen chloride (540 ml, reflux, 3 h), the solution was evaporated. In order to completely destroy the amine-borane complex, the residue was dissolved in aqueous 2N hydrochloric acid (200 ml) and refluxed for 1 h. The solution was basified with ammonium hydroxide and extracted with chloroform. Evaporation of the dried extracts afforded indoline **13** (6.95 g, 96%): bp 210°C/0.7 mm Hg; IR (NaCl): 3360 (NH); NMR: 1.4-2.1 (m, 7H), 2.2 (s, 3H, NCH_3), 2.7-3.6 (m, 6H), 3.8 (s, 3H, OCH_3), 6.5-6.7 (m, 3H, ArH). The dioxalate melted at 164-166°C (ethanol). (Found: C, 53.52; H, 6.33; N, 6.53. Calcd. for $C_{19}H_{26}N_2O_9$: C, 53.52; H, 6.10; N, 6.57).

Method B. A solution of indole **11** (2 g, 8.2 mmol) in aqueous 3N hydrochloric acid (40 ml) was hydrogenated at 50-60°C and atmospheric pressure in the presence of platinum dioxide (200 mg). When the absorption ceased, the catalyst was filtered off. The filtrate was basified with ammonium hydroxide and extracted with chloroform. The organic extracts were dried and evaporated to give indoline **13** (1.2 g, 45%) as a dark oil.

1-Acetyl-5-methoxy-3-(1-methyl-4-piperidyl)indoline(**14**). Indoline **13** (3.6 g, 14 mmol) was allowed to react, as described for indolines **5**, with acetic anhydride (32 ml). After the usual work up, the acetyl derivative **14** was obtained (3.8 g,90%); IR ($CHCl_3$): 1635 (CO); NMR: 1.2-2.0 (m, 7H), 2.15 (s, 3H, $COCH_3$), 2.2 (s, 3H, NCH_3), 2.65-3.4 (m, 3H), 3.8 (s, 3H, OCH_3), 3.8-4.1 (m, 2H, 2-H), 6.6-6.75 (m, 2H), 8.15 (d, 1H, 7-H). The hydrochloride melted at 233-235°C (acetone). (Found: C, 60.79; H, 7.71; N, 8.25. Calcd. for $C_{17}H_{25}ClN_2O_2 . 1/2H_2O$: C, 61.16; H, 7.85; N, 8.38).

Attempted cyclization of piperidyl indoline **14**

A solution of mercuric acetate (4.45 g, 14 mmol) and $EDTA.Na_2.2H_2O$ (6.25 g, 16.8 mmol) in water (65 ml) was stirred under nitrogen for 20 min. The mixture was adjusted to pH 7-8 with aqueous 6N sodium hydroxide and heated until it boiled. Then, acetyl indoline **14** (360 mg, 1.25 mmol) was added, and the resulting mixture was refluxed for 40 min. The solution was cooled and poured into a solution of excess of sodium borohydride in methanol. The precipitate was filtered and washed with methanol. The combined filtrate and washings were concentrated to half its volume and extracted with methylene chloride. The extract was dried and evaporated to give *1-acetyl-5-methoxy-3-(1-methyl-2-oxo-4-piperidyl)indoline* (**15**, 210 mg,56%): mp 139-140°C (acetone); IR (NaCl): 1630 (CO); NMR: 1.2-2.5 (m, 5H), 2.2 (s, 3H, $COCH_3$), 2.85 (s, 3H, NCH_3), 3.1-3.5 (m, 3H), 3.6-4.1 (m, 2H, 2-H), 3.8 (s, 3H, OCH_3), 6.65 (m, 2H), 8.05 (d, 1H). (Found: C, 67.53; H, 7.27; N, 9.24. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.55; H, 7.28; N, 9.27).

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REFERENCES

1. For part 21, see: J. Bosch, M. Rubiralta, M. Moral, and J. Ariño, *J. Chem. Soc. Perkin Trans. 1*, **1986**, 1533.
2. This work was presented in a preliminary form at the XVIII Reunión Bienal de la Real Sociedad Española de Química, Burgos, Spain, 1980.
3. a) D. C. Palmer and M. J. Strauss, *Chem. Rev.* **1977**, *77*, 1; b) E. L. May, *J. Med. Chem.* **1980**, *23*, 225.
4. a) E. Campaigne and D. R. Knapp, *J. Pharm. Sci.* **1971**, *60*, 809; b) J. M. Cassady, G. S. Li, E. B. Spitzner, H. G. Floss, and J. A. Clemens, *J. Med. Chem.* **1974**, *17*, 300; c) H. G. Floss, *Tetrahedron* **1976**, *32*, 873; d) J. C. Craig and S.D. Hurt, *J. Org. Chem.* **1979**, *44*, 1113; e) N. J. Bach, E. C. Kornfeld, N. D. Jones, M. O. Chaney, D. E. Dorman, J. W. Paschal, J. A. Clemens, and E. B. Smalstig, *J. Med. Chem.* **1980**, *23*, 481; f) D. Berney, *Helv. Chim. Acta* **1982**, *65*, 1694; g) D. C. Horwell, D. E. Tupper, and W. H. Hunter, *J. Chem. Soc. Perkin Trans. 1*, **1983**, 1545.
5. For other types of indolomorphans, see: a) indolo[2,3-*f*]morphans: G. C. Morrison, R. O. Waite, A. N. Caro, and J. Shavell Jr., *J. Org. Chem.* **1967**, *32*, 3691; J. Bosch and F. Boncompte, *An. Quim.* **1979**, *75*, 357; J. Bosch, J. Bonjoch, and I. Serret, *Heterocycles* **1980**, *14*, 1983; b) indolo[3,2-*f*]morphans: J. Bonjoch, N. Casamitjana, and J. Bosch, *Tetrahedron* **1982**, *38*, 2883; c) indolo[2,3-*g*]morphans: J. Bosch, J. Bonjoch, A. Diez, A. Linares, M. Moral, and M. Rubiralta, *Tetrahedron*, **1985**, *41*, 1753 and references cited therein; d) indolo[3,2-*g*]morphans: L. J. Dolby and S. J. Nelson, *J. Org. Chem.* **1973**, *38*, 2882; J. Bosch, M. Feliz, and M.-L. Bennasar, *Tetrahedron*, **1984**, *40*, 1419; see also ref 30.
6. a) D. C. Horwell, *Tetrahedron* **1980**, *36*, 3123; b) J. Rebek Jr., D. F. Tai, and Y. K. Shue, *J. Am. Chem. Soc.* **1984**, *106*, 1813; c) and references cited therein.
7. a) For a review on the synthesis of 4-substituted indoles and their elaboration to the ergot alkaloids, see: A. P. Kozikowski, *Heterocycles* **1981**, *16*, 267; b) For a synthetic entry to these alkaloids involving the elaboration of the indole ring in the last step, see: W. E. Haefliger, *Helv. Chim. Acta* **1984**, *67*, 1942.
8. a) B. Robinson, *Chem. Rev.* **1969**, *69*, 785; b) S. A. Monti and R. R. Schmidt III, *Tetrahedron* **1971**, *27*, 3331; c) J. G. Berger, *Synthesis* **1974**, 508; d) G. W. Gribble, P. D. Lord, J. Skotnicki, S. E. Dietz, J. T. Eaton, and J. L. Johnson, *J. Am. Chem. Soc.* **1974**, *96*, 7812; e) Y. Kikugawa, *J. Chem. Res. (S)* **1977**, 212; f) G. W. Gribble and J. H. Hoffman, *Synthesis* **1977**, 859; g) Y. Kikugawa, *Chem. Pharm. Bull.* **1978**, *26*, 108.
9. a) See references 8c and 8d; b) J. G. Berger, S. R. teller, C. D. Adams, and L.J. Guggenberger, *Tetrahedron Lett.* **1975**, 1807; c) J. G. Berger, F. Davidson, and G. E. Jangford, *J. Med. Chem.* **1977**, *20*, 600; d) Y. Kikugawa, *J. Chem. Res (S)* **1978**, 184; e) B. E. Maryanoff and D. F. McComsey, *J. Org. Chem.* **1978**, *43*, 2733; f) B. E. Maryanoff, D. F. McComsey, and S. O. Nortey, *J. Org. Chem.* **1981**, *46*, 355; g) A. J. Elliott and H. Guzik, *Tetrahedron Lett.* **1982**, *23*, 1983; h) J. G. Berger, P. Tahbaz, A. T. McPhail, and K. D. Onan, *Tetrahedron Lett.* **1983**, *24*, 2469; i) O. Repic and D. J. Long, *Tetrahedron Lett.* **1983**, *24*, 1115.
10. J. Bosch, M. Alvarez, R. Llobera, and M. Feliz, *An. Quim.* **1979**, *75*, 712.
11. For a discussion about this double bond isomerization, see references 10, 12, and 13.
12. J. Bosch and M. Feliz, *An. Quim.* **1982**, *78C*, 240.
13. M. Feliz, J. Bosch, D. Mauleón, M. Amat, and A. Domingo, *J. Org. Chem.* **1982**, *47*, 2435.

14. Only the *erythro* isomer was formed under the last conditions (see Experimental). The relative stereochemistry was deduced when it was converted to the corresponding acetyl derivative *erythro*-**6** (see later).
15. No reaction was observed with pyridine-borane in aqueous ethanolic HCl,[8e] or with sodium borohydride in AcOH or TFA.[8d]
16. J. Bosch, D. Mauleón, F. Boncompte, and R. Granados, *J. Heterocycl. Chem.* **1981**, *18*, 263.
17. For the reduction of indoles bearing an amino group in the side chain using a preformed amine-borane complex, see references 9b,g,h.
18. K. M. Biswas and A. H. Jackson, *Tetrahedron* **1968**, *24*, 1145.
19. K. Nagarajan, M. D. Nair, and P. M. Pillai, *Tetrahedron* **1967**, *23*, 1683.
20. For a similar stereochemical analysys by ^{1}H-NMR of related *erythro* and *threo* isomers of the phtalideisoquinoline type, see: M. Shamma and V. St. Georgiev, *Tetrahedron Lett.* **1974**, 2339.
21. Compare this chemical shift with $\delta \sim 5.3$ for the Δ^4 isomers **5** and **6**, and $\delta \sim 5.4$ for the 3-(tetrahydropyridyl)indoles **3**[10] and **4**.
22. A. F. Casy, A. O. Ogundaini, and R. T. Parfitt, *Org. Magn. Reson.* **1982**, *20*, 254.
23. H. Fritz and T. Winkler, *Helv. Chim. Acta* **1976**, *59*, 903.
24. J. Bonjoch, N. Casamitjana, J. Quirante, M. Rodríguez, and J. Bosch, *J. Org. Chem.* **1987**, *52*, 000.
25. A similar conformational inversion has been observed in epimeric 8-substituted 2-azabiciclo[3.3.1]nonan-7-ones: J. Bonjoch, N. Casamitjana, A. Torrens, J. Quirante, A. Paniello, and J. Bosch, unpublished results.
26. A. B. A. Jansen, J. M. Johnson, and J. R. Surtees, *J. Chem. Soc.* **1964**, 5573.
27. For other methods of dehydrogenation of indolines to indoles, see: a) M. Kawase, Y. Miyake, and Y. Kikugawa, *J. Chem. Soc. Perkin Trans. 1*, **1984**, 1401; b) I. Ninomiya, C. Hashimoto, T. Kiguchi, D. H. R. Barton, X. Luschini, and P. Milliet, *Tetrahedron Lett.* **1985**, *26*, 4187.
28. See references 5b,c and references cited therein.
29. For similar cyclizations of related 4-(arylmethyl)piperidines, see reference 5c.
30. The formation of lactams under mercuric acetate cyclization conditions has been previously observed and discussed: J. Bosch, D. Mauleón, M. Feliz, and R. Granados, *J. Org. Chem.* **1983**, *48*, 4836 and references cited therein.
31. E. M. Fry, *J. Org. Chem.* **1964**, *29*, 1647.
32. K. Freter, *J. Org. Chem.* **1975**, *40*, 2525.
33. T. Kralt, W. J. Asma, H. H. Haeck, and H. D. Moed, *Recl. Trav. Chim. Pays-Bas* **1961**, *80*, 313.