Tetrahedron Vol. 42, No. 2, pp. 637 to 647, 1986
Printed in Great Britain.

0040-4020/86 $3.00 + .00

SYNTHETIC APPLICATIONS OF 2-CYANOPIPERIDINES. II.[1,2]

MODEL STUDIES IN THE SYNTHESIS OF THE INDOLE ALKALOID VINOXINE

M.-LLUISA BENNASAR and JOAN BOSCH*

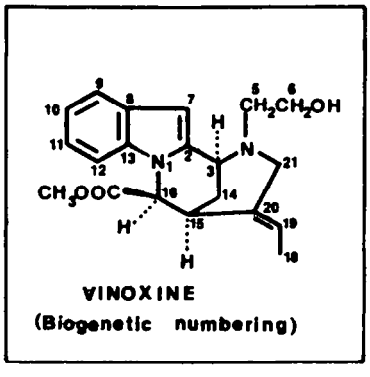
Department of Organic Chemistry, Faculty of Pharmacy,
University of Barcelona, 08028-Barcelona, Spain.

(*Received in UK* 28 *October* 1985)

Abstract - A synthetic way for the construction of the tetracyclic ring system of vinoxine that allows the introduction of the ethylidene substituent present in the alkaloid is reported. The synthesis implies the acid cyclization of 4-(1-indolylmethyl)-2-cyano-5-piperidinols **10** followed by oxidation of the resulting alcohols **11** and, finally, a Wittig reaction from ketone **12**. The required 2-cyanopiperidinols **10** were prepared by reductive cyanation of 3-hydroxypyridinium iodide **5c**.

2-Cyanopiperidines and 2-cyanotetrahydropyridines are useful synthons in alkaloid synthesis, especially in that of indole alkaloids, because they can be considered as latent forms of iminium salts which are able to react with activated aromatic rings such as indole.[3] This property has been successfully applied to the synthesis of the indole alkaloids dihydrogambirtannine,[4] ellipticine,[5] deplancheine,[6] and 20-epiuleine,[3,7] as well as to the elaboration of the tetracyclic ring skeleton or to the synthesis of simplified analogues of the indole alkaloids ervitsine,[3,8,9] dasycarpidone,[9,10] and vinoxine.[1]

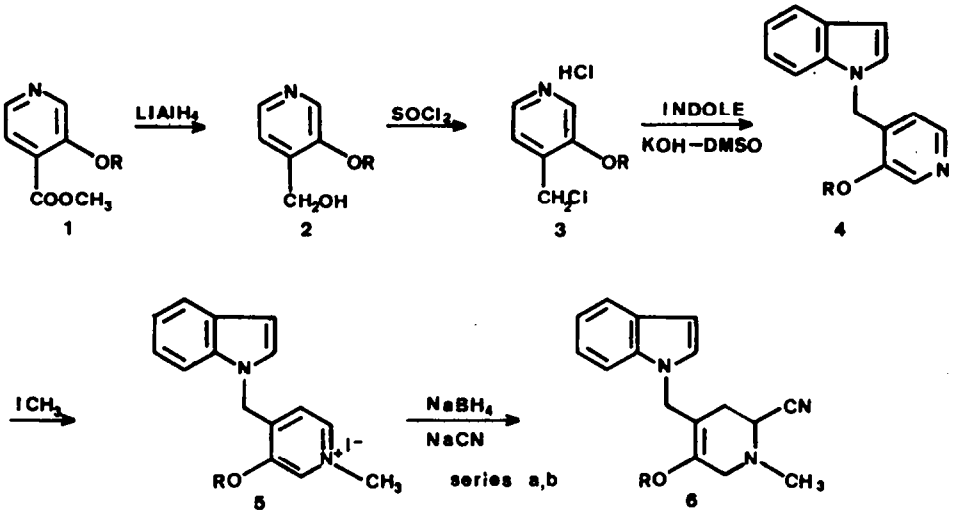
In the context of our studies[1,11] directed to the synthesis[12] of vinoxine,[13] in a previous paper[1] we reported that acid cyclization of 2-cyano-4-(1-indolylmethyl)piperidines was an efficient method for the construction of the hexahydro-2,6-methano[1,4]diazocino[1,2-*a*]indole system that embodies the fundamental tetracyclic framework of the alkaloid.



SCHEME I

This result prompted us to study the extension of similar cyclizations to the preparation of more complex vinoxine analogues functionalized at the 3-position (corresponding to the 20-position in the biogenetic numbering[14]) so that later synthetic steps allow the elaboration of the exocyclic ethylidene substituent of the alkaloid.[15] For this purpose we selected as starting materials 2-cyanotetrahydropyridines 6a and 6b, which bear an alkoxy substituent at the 5-position of the pyridine ring. Hydrolysis of the enol ether moiety under the acidic conditions required for cyclization would generate a keto function (3-piperidone 12) from which the ethylidene substituent could be introduced by a Wittig reaction.[16,17] A similar synthetic strategy constitutes the basis of a synthesis of deplancheine,[6] though in this synthesis cyclization of 2-cyanotetrahydropyridine upon indole took place before the hydrolysis of the enol ether function since, unlike our case, the double bond of the latter, once cyclization was effected, is not located in a bridgehead position.

The required 5-alkoxy-2-cyanotetrahydropyridines 6a and 6b were prepared in the usual way, by reductive cyanation[18] of the corresponding pyridinium salts, which in turn were obtained in four steps through the reaction sequence depicted in the Scheme II.



a: R=CH$_3$; b: R = CH$_2$C$_6$H$_5$; c: R = H

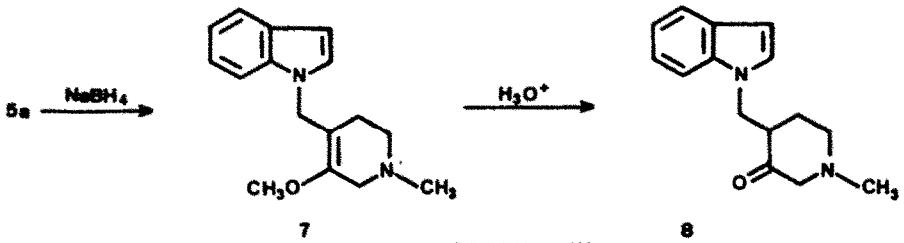
SCHEME II

Lithium aluminium hydride reduction of esters 1a and 1b followed by reaction of the resulting alcohols 2a and 2b with thionyl chloride gave 4-(chloromethyl)-pyridine hydrochlorides 3a and 3b, respectively, which were condensed with indole using dimethyl sulfoxide as the solvent[19] and potassium hydroxide as the base, according to the general procedure for the *N*-alkylation of indoles.[20] 1-(Pyridylmethyl)indoles 4a and 4b were identified by the ^{1}H-NMR singlet at $\delta \sim 5.1$, due to the interannular methylene protons, and were easily converted to the corresponding pyridinium salts, 5a and 5b, by reaction with methyl iodide. As expected, treatment of 5a and 5b with sodium borohydride and a large excess of sodium cyanide in an ether-water two phase system afforded 2-cyanotetrahydropyridines 6a and 6b, respectively, which were extracted from the non-aminated fraction of the reaction mixture owing to the weak basicity of the amino group as a consequence of the electron-withdrawing effect exerted by the cyano group.

The IR spectrum of both nitriles showed characteristic absorptions at 2220 (weak) and 1690 cm^{-1} (strong) due to the cyano group and the tetrasubstituted

enol ether double bond, respectively, whereas the most significant features in the the ^{1}H-NMR spectra were two singlets due to the *N*- and *O*-methyl (or *O*-methylene) protons and the diastereotopic character of the interannular methylene protons, which appear as two broad (homoallylic coupling with protons at C-6) doublets with J_{gem}=15 Hz.

In order to establish the experimental conditions required for the hydrolysis of the tetrasubstituted enol ether moiety in a 3-alkoxy-4-(1-indolylmethyl)-1,2,-5,6-tetrahydropyridine system, the model tetrahydropyridine 7 was prepared by sodium borohydride reduction of pyridinium salt 5a and then converted to the 3-piperidone 8. The best set of conditions was heating at 50°C in the presence of 6N hydrochloric acid in tetrahydrofuran for 3 h 30 min. However, even under these conditions polymerization was produced to some extent as a consequence of the lability in acidic media of indoles unsubstituted at the 2- and 3-positions. Although 3-piperidone 8 was found to be unstable and decomposed in contact with air,[21] it was characterized by its spectroscopic data, in particular from the IR absorption at 1720 cm^{-1} and from the absence of a singlet attributable to the methoxy group in the ^{1}H-NMR spectrum.



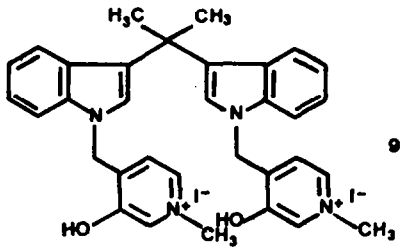
7 8

SCHEME III

Despite this satisfactory result, all attempts to hydrolyze enol ethers 6a and 6b under acidic conditions with simultaneous cyclization to the tetracyclic ketone 12 were unsuccessful,[22] and only unidentifiable polymeric mixtures were obtained. This result can be accounted for by considering that formation of the iminium salt from the α-amino nitrile moiety takes place faster than hydrolysis of the enol ether function, so that intramolecular attack of the iminium salt upon indole is highly disfavoured since it would lead to a bridged system having a double bond in a bridgehead position. Consequently, an intermolecular attack occurs, causing extensive polymerization.

The suppression of the carbon-carbon double bond was a necessary requisite to effect the key cyclization upon the indole ring. For this reason, and in the light of recent work on the reduction of *N*-substituted-3-oxidopyridiniums,[23] we turned our attention to the pyridinol 4c. We expected that after quaternization and reductive cyanation it would lead to 2-cyanopiperidinols 10, lacking the undesirable tetrahydropyridine double bond. These compounds can be considered as synthetic precursors of tetracyclic alcohols 11, from which piperidone 12 could be easily attainable by oxidation.

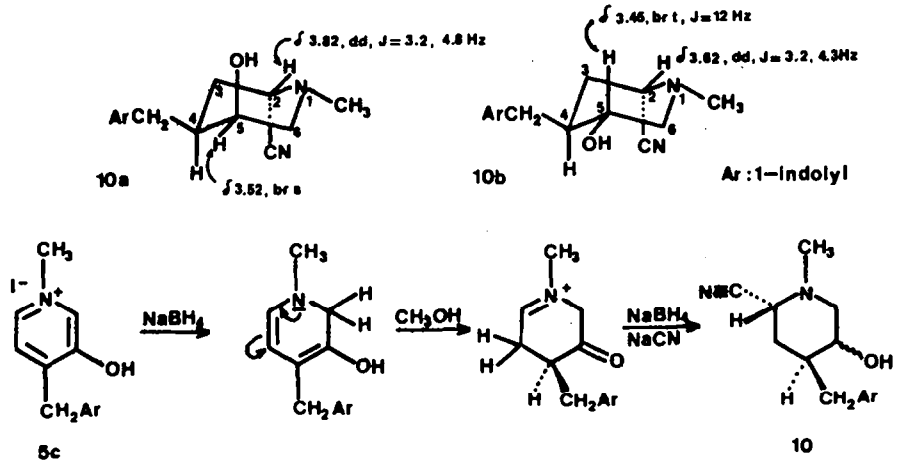
The required pyridinol 4c was prepared in nearly quantitative yield by hydrogenolysis of the benzyloxy derivative 4b. In contrast, condensation between chloromethylpyridine 3c, obtained in the usual way by treatment of the corresponding alcohol 2c with thionyl chloride, and indole took place in yields lower than 5%.[24] Although pyridinium iodide 5c was obtained in 94% yield by quaternization of pyridinol 4c with methyl iodide in methanol, the reaction offered some difficulties because it required a week for completion. Two reasons can explain this fact: i) it is known[26] that, in solution, 3-hydroxypyridines are in equilibrium with the



9

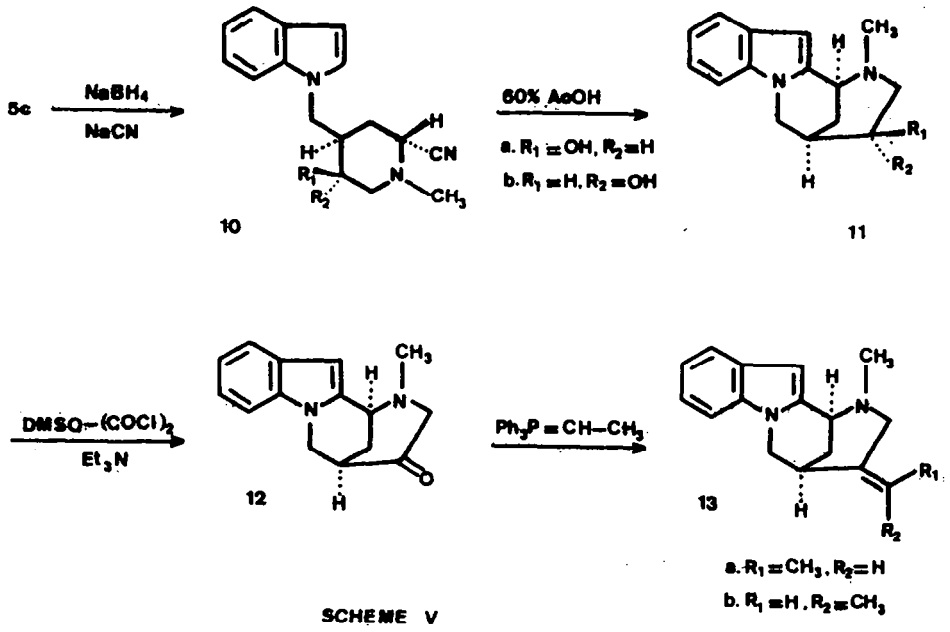
corresponding betaines, in which the pyridine nitrogen is protonated, and ii) due to its acidic character, 3-hydroxypyridinium iodide 5c, once formed, can protonate the starting 3-hydroxypyridinol 4c to give the corresponding 3-oxidopyridinium and 4c hydroiodide. On the other hand, the acidic character of pyridinium salt 5c was also evidenced when quaternization was effected in acetone solution; the dimeric pyridinium salt 9 was obtained as the only product.[27]

Prolonged exposure of 5c to a mixture of sodium cyanide and sodium borohydride in methanol-ether-water gave a stereoisomeric mixture of 2-cyanopiperidinols. After column chromatography, two stereoisomers were isolated as the major components and assigned from their ^{1}H-NMR data as the C-5 epimeric 2-cyano-5-piperidinols 10a and 10b. It is worth mentioning that the alternative, undesired regioisomers 2-cyano-3-piperidinols were not detected. As it can be observed in the following Scheme, the most significant ^{1}H-NMR (200 MHz) signal in both isomers was the doublet of doublets, with J=3.2 and ~4.5 Hz, due to the C-2 methine proton. This multiplicity and coupling constants ruled out the presence of the hydroxy substituent at C-3 and clearly established the axial orientation of the cyano group. On the other hand, the presence of a broad singlet in the ^{1}H-NMR spectrum of 10a and a broad triplet with J=12 Hz in that of 10b, attributable to the C-5 methine protons, allowed the assignment of the relative configuration at this center as depicted in the Figure.



SCHEME IV

Formation of cyanoalcohols 10 implies the initial attack of an hydride ion at the 2-position of the pyridine ring. After protonation, as usual, at the central, unsubstituted position of the resulting dienamine,[28] the corresponding keto tautomer would undergo reduction of the carbonyl group and attack of a cyanide ion upon the carbon-nitrogen double bond to give 10 (Scheme IV). The relative configuration at carbon 2 in both isomers, having an axial cyano group, can be rationalized in two ways: i) by considering the easy epimerization at this center and the axial



SCHEME V

preference of cyano group in 2-cyanopiperidines,[29] probably due to an anomeric-type effect,[30] and ii) taking into account that cyanide ion addition to 4-substituted 3,4,5,6-tetrahydropyridinium salts has been reported to occur stereospecifically to give the corresponding 2,4-*trans*-diastereomers, in which the cyano group is positioned axially.[8,31]

As was anticipated, cyclization of 2-cyanopiperidinols 10a and 10b upon the indole 2-position took place, through the corresponding iminium salts, by heating in aqueous acetic acid solution. The corresponding tetracyclic alcohols 11a and 11b were obtained in excellent yields. The structures of 11a and 11b were inferred from their ^{1}H-NMR data (200 MHz). Thus, a singlet for the indole 3-proton clearly indicated that cyclization had occurred. The expected relative configuration at C-3, with an equatorial hydroxy group in 11a and an axial one in 11b, was corroborated from the multiplicity of signals due to the 3-methine and axial C-4 protons, which were observed as an apparent quintet (J=4.8, 5.4, and 12 Hz) and a triplet (J=12 Hz), respectively, in 11a and as a broad singlet and a doublet of doublets (J=13.2 and 4 Hz) in 11b.

Tetracyclic alcohols 11 have the appropriate functionality to allow the introduction of the ethylidene substituent present in vinoxine. Thus, oxidation of 11a or 11b by means of dimethyl sulfoxide-oxalyl chloride-triethylamine[32] afforded the ketone 12 (a 3-piperidone), which appeared to be highly unstable so that it was only characterized by its IR absorption at 1720 cm^{-1} and was used without further purification in the next step. A Wittig reaction of ketone 12 with ethyltriphenylphosphonium bromide-sodium amide led (37.5% overall yield from 11a) to a nearly equimolecular mixture of *E*- and *Z*-ethylidene derivatives 13, which were separated by column chromatography.

The most significant signals in the ^{1}H-NMR spectra of 13 were a doublet of doublets and a quartet of doublets due to the methyl and methine protons of the ethylidene substituent. The comparison of the ^{13}C-NMR spectra of 13a and 13b allowed the assignment of the ethylidene chain configuration.[33] Thus, in the unnatural *Z*-isomer 13a a 1,4-gauche interaction is observed between the methyl group of the side chain and C_4-H, which results in an upfield shift (7.57 ppm) of C-4 with respect to the *E*-isomer 13b. A similar interaction between the methyl group and

C_2-H appears in the E-isomer 13b, causing an upfield shift (8.89 ppm) of C-2 as compared with 13a.[34]

Furthermore, both isomers could be differentiated by ^{1}H-NMR by considering the deshielding effect exerted by the methyl group of the ethylidene substituent upon the equatorial C-4 proton in the Z-isomer 13a (δ3.42; compare with δ2.96 in 13b)[35] and upon the C-2 methine proton in the E-isomer 13b (δ3.40; compare with δ2.90 in 13a).[36]

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Perkin-Elmer R-24B (60 MHz) instrument or, when indicated, on a Varian XL-200 (200 MHz) spectrometer. ^{13}C-NMR spectra were determined on a Varian XL-200 spectrometer. Unless otherwise noted, NMR spectra were measured in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) downfield from internal TMS. IR spectra were taken with a Perkin-Elmer 577 spectrophotometer, and only noteworthy absorptions (reciprocal centimeters) are listed. Column chromatography was done with Merck silica gel 60 (catalog No. 7734). Thin layer chromatography was carried out on Merck silica gel 60 F_{254}, aluminium pre-coated sheets, and the spots were located with UV light or iodoplatinate reagent. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate powder. Microanalyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

4-Chloromethyl-3-methoxypyridine Hydrochloride (3a). The alcohol 2a hydrochloride[37] (8 g, 45.5 mmol) was dissolved at 0°C in thionyl chloride (26.5 ml), and the resulting solution was refluxed for 1 h 30 min. The mixture was cooled and then anhydrous benzene (77 ml) was added. The precipitate was filtered, washed several times with anhydrous benzene, and dried to give the hydrochloride 3a (3.6 g, 40%). A sample recrystallized from ether-ethanol melted at 217-218°C; NMR (DMSO-d_6) 4.1 (s, 3H, OCH_3), 4.85 (s, 2H, CH_2), 8.05 (d, J=5 Hz, 1H, H-5), 8.55 (d, J=5 Hz, 1H, H-6), 8.65 (s, 1H, H-2). (Found: C, 43.32; H, 4.80; N, 7.34; Cl, 36.51. Calcd. for $C_7H_9Cl_2NO$: C, 43.32; H, 4.67; N, 7.21; Cl, 36.54).

Methyl 3-Benzyloxy-4-pyridinecarboxylate (1b). A solution of 3-benzyloxy-4-pyridinecarbonitrile[41] (20 g, 95 mmol) in methanol saturated with dry hydrogen chloride (250 ml) was refluxed over a 7 h period. The reaction mixture was cooled, filtered, and evaporated to give a semisolid residue which was dissolved in water and washed with ether. The aqueous layer was basified with ammonium hydroxide and extracted several times with ether. Drying and evaporation of the ethereal extracts gave ester 1b (17 g, 74%); NMR 3.8 (s, 3H, OCH_3), 5.1 (s, 2H, CH_2), 7.25 (m, 5H, benzene), 7.45 (d, J=5 Hz, 1H, H-5), 8.15 (d, J=5 Hz, 1H, H-6), 8.35 (s, 1H, H-2); IR (NaCl) 1735 (CO). The hydrochloride melted at 140-141°C (ether-ethanol). (Found: C, 59.83; H, 4.99; N, 5.02; Cl, 12.67. Calcd. for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; N, 5.00; Cl, 12.67).

3-Benzyloxy-4-pyridinemethanol (2b). A solution of ester 1b (20 g, 0.08 mol) in anhydrous ether (200 ml) was slowly added under nitrogen to a suspension of lithium aluminium hydride (7.6 g, 0.2 mol) in anhydrous ether (200 ml). The mixture was stirred for 30 min and then ethyl acetate (30 g, 0.34 mol) and water (20 g, 1.1 mol) were added dropwise at 0°C. The ethereal suspension was filtered, and the solid was digested with boiling ether (2 × 100 ml). The combined organic extracts were dried and evaporated to give an oil (15 g) which was dissolved in absolute ethanol-anhydrous ether and precipitated with ethereal hydrogen chloride as 2b hydrochloride (10 g, 49%). A sample recrystallized from ethanol-ether melted at 164-165°C; NMR (DMSO-d_6) 4.6 (s, 2H, CH_2OH), 5.25 (s, 2H, $CH_2C_6H_5$), 7.25 (m, 5H, benzene), 7.85 (d, J=5 Hz, 1H, H-5), 8.4 (d, J=5 Hz, 1H, H-6), 8.55 (s, 1H, H-2); IR (KBr) 2500-3400 (OH, NH). (Found: C, 61.69; H, 5.65; N, 5.69; Cl, 14.22. Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.60; N, 5.56; Cl, 14.08).

3-Benzyloxy-4-chloromethylpyridine Hydrochloride (3b). The alcohol 2b hydrochloride (15 g, 59 mmol) was dissolved at 0°C in thionyl chloride (30 ml), and the resulting solution was stirred at room temperature for 4 h. The mixture was cooled to 0°C and then anhydrous ether (50 ml) was added. The precipitate was filtered, washed several times with anhydrous ether, and dried to give the hydrochloride 3b (15 g, 94%). A sample recrystallized from ethanol melted at 190-191°C; NMR (DMSO-d_6) 4.85 (s, 2H, CH_2Cl), 5.4 (s, 2H, $CH_2C_6H_5$), 7.35 (m, 5H, benzene), 7.95 (d, J=5 Hz, 1H, H-5), 8.5 (d, J=5 Hz, 1H, H-6), 8.7 (s, 1H, H-2). (Found: C, 57.84; H, 4.88; N, 4.90; Cl, 26.33. Calcd. for $C_{13}H_{13}Cl_2NO$: C, 57.79; H, 4.85; N, 5.18; Cl, 26.24).

1-(3-Methoxy-4-pyridylmethyl)indole (4a). Indole (5.48 g, 46 mmol) was added under nitrogen to a suspension of ground potassium hydroxide (9.3 g, 0.166 mol) in dimethyl sulfoxide (55 ml). The resulting mixture was stirred at room temperature for 90 min, and then 4-chloromethylpyridine hydrochloride 3a (3.3 g, 17 mmol) was added portionwise. The suspension was stirred at room temperature for 4 h, poured into ice-water, and extracted with ether. The ethereal layers were washed with water and extracted with 10% hydrochloric acid. The acidic aqueous phase was basified with concentrated ammonium hydroxide and extracted with ether. The organic extracts were dried and evaporated to give pyridylmethylindole 4a (4 g, 98%); NMR 3.8 (s, 3H, OCH_3), 5.1 (s, 2H, CH_2), 6.3 (d, J=5 Hz, 1H, pyridine H-5), 6.45 (d, J=4 Hz, 1H, indole H-3), 6.9-7.2 (m, 4H, indole), 7.4-7.7 (m, 1H, indole H-4), 7.9 (d, J=5 Hz, 1H, pyridine H-6), 8.15 (s, 1H, pyridine H-2). The picrate melted at 180-181°C (ethanol). (Found: C, 53.70; H, 3.56; N, 14.69. Calcd. for $C_{21}H_{17}N_5O_8$: C, 53.97; H, 3.66; N, 14.98).

1-(3-Benzyloxy-4-pyridylmethyl)indole (4b). Chloromethylpyridine hydrochloride 3b (15 g, 55 mmol) was allowed to react as above with indole (16.2 g, 0.138 mol) and potassium hydroxide (31.1 g, 0.55 mmol) in dimethyl sulfoxide (300 ml). The reaction mixture was poured into ice-water and extracted with ether and benzene. The organic layers were washed with water, dried, and evaporated to give an oil (29.7 g) which was chromatographed. On elution with 4:6 benzene-chloroform, pyridylmethylindole 4b (11.8 g, 68%) was obtained. A sample recrystallized from ether-chloroform melted at 94-95°C; NMR 5.1 (s, 2H, $IndCH_2$), 5.2 (s, 2H, $CH_2C_6H_5$), 6.35 (d, J=5 Hz, 1H, pyridine H-5), 6.45 (d, J=4 Hz, 1H, indole H-3), 6.9-7.2 (m, 4H, indole), 7.3 (s, 5H, benzene), 7.4-7.7 (m, 1H, indole H-4), 7.95 (d, J=5 Hz, 1H, pyridine H-6), 8.2 (s, 1H, pyridine H-2). (Found: C, 80.21; H, 5.77; N, 8.79. Calcd. for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91).

4-(1-Indolylmethyl)-3-methoxy-1-methylpyridinium Iodide (5a). A solution of methyl iodide (6.8 g, 48 mmol) in anhydrous benzene (4 ml) was added dropwise to a solution of pyridylmethylindole 4a (3.85 g, 16.2 mmol) in acetone (22 ml). The resulting mixture was stirred at room temperature for 10 h, and the precipitate of 5a (5.25 g, 86%) was collected by filtration. A sample recrystallized from ethanol melted at 170-174°C; NMR (DMSO-d_6) 4.1 (s, 3H, OCH_3), 4.25 (s, 3H, NCH_3), 6.45 (d, J=4 Hz, 1H, indole H-3), 6.65-7.65 (m, 6H, pyridine H-5, indole), 8.35 (d, J=5 Hz, 1H, pyridine H-6), 8.85 (s, 1H, Pyridine H-2). (Found: C, 50.55; H, 4.38; N, 7.32; I, 33.60. Calcd. for $C_{16}H_{17}IN_2O$: C, 50.54; H, 4.50; N, 7.36; I, 33.37).

3-Benzyloxy-4-(1-indolylmethyl)-1-methylpyridinium Iodide (5b). Operating as above, from pyridylmethylindole 4b (2.5 g, 7.9 mmol) and methyl iodide (3.4 g, 24 mmol), pyridinium iodide 5b (3 g, 83%) was obtained. A sample recrystallized from absolute ethanol melted at 159-160°C; NMR (DMSO-d_6) 4.2 (s, 3H, NCH_3), 5.3 (s, 2H, $CH_2C_6H_5$), 5.6 (s, 2H, $IndCH_2$), 6.7-7.7 (m, 11H, indole, benzene, and pyridine H-5), 8.35 (d, J=5 Hz, 1H, pyridine H-6), 8.9 (s, 1H, pyridine H-2). (Found: C, 58.05; H, 4.61; N, 6.15; I, 27.79. Calcd. for $C_{22}H_{21}IN_2O$: C, 57.90; H, 4.63; N, 6.13; I, 27.81).

4-(1-Indolylmethyl)-5-methoxy-1-methyl-1,2,3,6-tetrahydropyridine-2-carbonitrile (6a). Hydrochloric acid (6N, 2.5 ml) was added dropwise to a stirred solution of sodium cyanide (1.84, 37.5 mmol) in water (45 ml), layered with ether (85 ml), and kept below 15°C. To the resulting mixture were added the pyridinium iodide 5a (3.82 g, 10 mmol) and then sodium borohydride (0.46 g, 12.1 mmol) portionwise. The mixture was stirred at room temperature for 4 h, the ether was decanted, and the aqueous layer was extracted with ether. The combined ethereal solutions were washed with aqueous 5% hydrochloric acid, dried, and evaporated to give 2-cyanotetrahydropyridine 6a (1.36 g, 48%). An analytical sample was obtained by column chromatography (chloroform as eluent); NMR 2.3 (s, 3H, NCH_3), 3.4 (dd, 1H, NCH), 3.6 (s, 3H, OCH_3), 4.55 and 4.85 (2d, 1H each, J=15 Hz, $IndCH_2$), 6.35 (d, J=4 Hz, 1H, indole H-3), 6.8-7.35 (m, 4H, indole), 7.4-7.7 (m, 1H, indole H-4); IR (NaCl) 2200 (Cyano), 1690 (C=C). (Found: C, 72.76; H, 6.87; N, 14.58. Calcd. for $C_{17}H_{19}N_3O$: C, 72.57; H, 6.80; N, 14.93).

5-Benzyloxy-4-(1-indolylmethyl)-1-methyl-1,2,3,6-tetrahydropyridine-2-carbonitrile (6b). Operating as above, from pyridinium iodide 5b (2.56 g, 5.6 mmol), sodium cyanide (1 g, 0.02 mol), and sodium borohydride (0.25 g, 6.5 mmol), 2-cyanotetrahydropyridine 6b (1.3 g, 65%) was obtained. A sample recrystallized from ethanol-ether melted at 79-80°C; NMR 2.3 (s, 3H, NCH_3), 2.8-3.4 (m, 3H, NCH and NCH_2), 4.3 and 4.65 (2d, 1H each, J=15 Hz, $IndCH_2$), 4.6 (s, 2H, $CH_2C_6H_5$), 6.3 (d, J=4 Hz, 1H, indole H-3), 6.7 (d, J=4 Hz, 1H, indole H-2), 6.8-7.2 (m, 3H, indole), 7.3 (s, 5H, benzene), 7.4-7.6 (m, 1H, indole H-4); IR (KBr) 2200 (cyano), 1690 (C=C). (Found: C, 77.23; H, 6.62; N, 11.58. Calcd. for $C_{23}H_{23}N_3O$: C, 77.26; H, 6.49; N, 11.76).

1-(3-Methoxy-1-methyl-1,2,5,6-tetrahydro-4-pyridylmethyl)indole (7). Sodium borohydride (0.69 g, 18.6 mmol) was added to a solution of pyridinium iodide 5a (3 g, 7.89 mmol) in methanol (60 ml) and 0.1N aqueous sodium hydroxide (21 ml).

The mixture was stirred at room temperature for 4 h, the solvent was removed, and the resulting residue was dissolved in water and extracted with ether. Drying and evaporation of the ethereal extracts gave tetrahydropyridine 7 (1.52 g, 75%) as an oil; NMR 2.2 (s, 3H, NCH_3), 3.5 (s, 3H, OCH_3), 4.65 (s, 2H, $IndCH_2$), 6.35 (d, J=4 Hz, 1H, indole H-3), 6.95 (d, J=4 Hz, 1H, indole H-2), 7.0-7.7 (m, 4H, indole); IR ($CHCl_3$) 1690 (C=C). The oxalate melted at 162-163°C (ethanol-ether). (Found: C, 62.21; H, 6.49; N, 8.04. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.42; H, 6.40; N, 8.08).

4-[1-Indolylmethyl]-1-methyl-3-piperidone (8). Hydrochloric acid (6N, 19.5 ml) was added to a stirred solution of tetrahydropyridine 7 (1.56 g, 6.09 mmol) in tetrahydrofuran (39 ml). The resulting mixture was heated at 50°C for 3 h 30 min. After evaporation of tetrahydrofuran, the aqueous solution was basified with sodium carbonate solution and extracted with ether. The extract was dried and evaporated to give an oil (1.3 g) which was chromatographed. On elution with chloroform, piperidone 8 (0.6 g, 40%) was obtained as an unstable oil that quickly darkened in contact with air; NMR 2.1 (s, 3H, NCH_3), 3.95 (dd, J=7.5 and 15 Hz, 1H, $IndCH_2$), 4.55 (dd, J=5.5 and 15 Hz, 1H, $IndCH_2$), 6.35 (d, J=4 Hz, 1H, indole H-3), 6.8-7.3 (m, 4H, indole), 7.35-7.65 (m, 1H, indole H-4); IR ($CHCl_3$) 1720 (CO).

4-Choromethyl-3-hydroxypyridine Hydrochloride (3c). Operating as in the above methoxy series, from 2c hydrochloride[44] (3.3 g, 20.4 mmol) and thionyl chloride (25 ml), the hydrochloride 3c (3.4 g, 93%) was obtained. A sample recrystallized from ethanol-ether melted at 170-171°C; NMR (DMSO-d_6) 4.8 (s, 2H, CH_2), 8.0 (d, J=5 Hz, 1H, H-5), 8.45 (d, J=5 Hz, 1H, H-6), 8.55 (s, 1H, H-2). (Found: C, 40.42; H, 3.98; N, 7.97; Cl, 39.34. Calcd. for $C_6H_7Cl_2NO$: C, 40.02; H, 3.91; N, 7.78; Cl, 39.38).

1-[3-Hydroxy-4-pyridylmethyl]indole (4c). A solution of pyridylmethylindole 4b (11.8 g, 37.5 mmol) in methanol (200 ml) was hydrogenated at room temperature and atmospheric pressure over 1.77 g of 10% palladium on charcoal. When the absorption ceased, the catalyst was filtered off, and the filtrate was evaporated to give pyridinol 4c (8.2 g, 97%). A sample recrystallized from ether-methanol melted at 210-212°C; NMR ($CDCl_3$-CD_3OD) 5.25 (s, 2H, CH_2), 6.3 (d, J=5 Hz, 1H, pyridine H-5), 6.45 (d, J=4 Hz, 1H, indole H-3), 6.8-7.3 (m, 4H, indole), 7.4-7.8 (m, 2H, indole H-4 and pyridine H-6), 8.0 (s, 1H, pyridine H-2). (Found: C, 69.54; H, 5.52; N, 11.24. Calcd. for $C_{14}H_{12}N_2O.H_2O$: C, 69.41; H, 5.82; N, 11.56).

3-Hydroxy-4-[1-indolylmethyl]-1-methylpyridinium Iodide (5c). Methyl iodide (35 ml, 0.56 mol), was added to a solution of pyridylmethylindole 4c (12 g, 53.5 mmol) in methanol (350 ml) and the resulting mixture was stirred at room temperature for a week. The solvent was removed to give pyridinium iodide 5c (18.5 g, 94%); NMR (DMSO-d_6) 4.1 (s, 3H, NCH_3), 5.5 (s, 2H, CH_2), 6.4 (d, J=4 Hz, 1H, indole H-3), 6.6-7.6 (m, 7H, indole, pyridine H-5, and OH), 8.15 (d, J=5 Hz, 1H, pyridine H-6), 8.2 (s, 1H, pyridine H-2). The picrate, obtained by addition of an aqueous sodium picrate solution, melted at 203-205°C (ethanol). (Found: C, 54.11; H, 3.67; N, 14.66. Calcd. for $C_{21}H_{17}N_5O_8$: C, 53.97; H, 3.66; N, 14.98).

When the reaction was carried out using acetone as the solvent, the dimeric pyridinium salt 9 was obtained. The dipicrate melted at 215-216°C (ethanol); NMR (DMSO-d_6) 1.8 (s, 6H, CH_3), 4.1 (s, 6H, NCH_3), 5.5 (s, 4H, CH_2), 6.5-8.1 (m, 16H, indole and pyridine), 8.4 (s, 4H, benzene). (Found: C, 54.81; H, 4.14; N, 13.99. Calcd. for $C_{45}H_{38}N_{10}O_{16}$: C, 54.45; H, 3.92; N, 14.37).

(2RS, 4RS, 5SR)- and (2RS, 4RS, 5RS)-5-Hydroxy-4-[1-indolylmethyl]-1-methyl-2-piperidinecarbonitrile (10). Hydrochloric acid (6N, 6.4 ml) was added dropwise to a stirred solution of sodium cyanide (4.6 g, 93.8 mmol) in water (50 ml), methanol (100 ml), and ether (50 ml), keeping the temperature below 15°C. To the resulting solution were added the pyridinium iodide 5c (5 g, 13.6 mmol) and then sodium borohydride (1 g, 26.3 mmol). After the mixture was stirred at room temperature for seven days, the solvent was evaporated to one fourth of its volume, and the resulting solution was extracted several times with ether. The ethereal extracts were dried and evaporated to give an oil (1.2 g). The material coming from two reductive cyanations as above was chromatographed. On elution with 6:4 benzene-chloroform, cyanopiperidine 10a (560 mg, 7.6%) was obtained as an oil; NMR (200 MHz) 1.68 (dt, J=3.2, 4.1, and 13.5 Hz, 1H, H-3eq), 1.96 (td, J=4.8, 13, and 13.5 Hz, 1H, H-3ax), 2.10-2.30 (m, 1H, H-4ax), 2.36 (s, 3H, NCH_3), 2.48 (s, 1H, OH), 2.50 (dd, J=1.6 and 13 Hz, 1H, H-6ax), 2.74 (dd, J=4 and 13 Hz, 1H, H-6eq), 3.52 (broad s, 1H, H-5eq), 3.82 (dd, J=3.2 and 4.8 Hz, 1H, H-2eq), 4.06 (dd, J=6.4 and 14.4 Hz, 1H, $IndCH_2$), 4.24 (dd, J=8.8 and 14.4 Hz, 1H, $IndCH_2$), 6.50 (d, J=3.1 Hz, 1H, indole H-3), 7.10-7.42 (m, 4H, indole), 7.63 (d, J=7 Hz, 1H, indole H-4); IR ($CHCl_3$) 2220 (cyano), 3300-3600 (OH). Elution with 3:7 benzene-chloroform gave cyanopiperidine 10b (870 mg, 12%). A sample recrystallized from ether melted at 106-107°C; NMR (200 MHz) 1.54 (td, J=4.3, 13, and 13.6 Hz, 1H, H-3ax), 1.78 (dt, J=3.2, 3.2, and 13.6 Hz, 1H, H-3eq), 1.90-2.18 (m, 1H, H-4ax), 2.26 (t, J=12 Hz, 1H, H-6ax), 2.29 (s, 3H, NCH_3), 2.40 (s, 1H, OH), 2.84 (dd, J=4.8 and 12 Hz, 1H, H-6eq), 3.45 (broad t, J=12 Hz, 1H, H-5ax), 3.62 (dd, J=3.2 and 4.3 Hz, 1H, H-2eq), 4.16 (dd, J=7.2 and 16 Hz, 1H, $IndCH_2$), 4.40 (dd, J=4 and 16 Hz, 1H, $IndCH_2$), 6.50 (d, J=3.1 Hz, 1H, indole H-3), 7.00-7.42 (m, 4H, indole), 7.62 (d, J=7 Hz, 1H,

indole H-4); IR (KBr) 2220 (cyano), 3300-3600 (OH). (Found: C, 71.30; H, 7.13; N, 15.45. Calcd. for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.11; N, 15.60).

(2RS, 3SR, 6SR)-3-*Hydroxy*-5-*methyl*-1,2,3,4,5,6-*hexahydro*-2,6-*methano*[1,4]-*diazocino*[1,2-a]*indole* (11a). A stirred solution of cyanopiperidine 10a (1 g, 3.7 mmol) in 60% acetic acid (50 ml) was heated under nitrogen at 70-80°C for 12 h. The resulting solution was cooled, basified with sodium carbonate solution, and extracted with ether. Drying and evaporation of the ethereal extracts gave an oil (1 g) which was purified by column chromatography. On elution with 95:5 chloroform-methanol, 11a (0.71 g, 81%) was obtained. A sample recrystallized from acetone-ether melted at 128-129°C; NMR (200 MHz) 1.82 (t, J=12 Hz, 1H, H-4ax), 2.16 (dt, J=3.6, 3.6, and 13.2 Hz, 1H, H-12β), 2.30 (masked, 1H, H-12α), 2.33 (s, 3H, NCH_3), 2.57 (broad s, 1H, H-2), 2.72 (dd, J=5.4 and 12 Hz, 1H, H-4eq), 3.34 (broad, 1H, OH), 3.92 (t, J=3.6 Hz, 1H, H-6), 3.92 (dd, J=6 and 12 Hz, 1H, H-1), 4.20 (apparent quintet, J=4.8, 5.4, and 12 Hz, H-3ax), 4.58 (d, J=12 Hz, 1H, H-1), 6.26 (s, 1H, H-7), 7.06-7.40 (m, 3H, indole), 7.60 (d, J=7 Hz, 1H, H-8); IR (KBr) 3000-3500 (OH). Found: C, 70.77; H, 7.61; N, 10.01. Calcd. for $C_{15}H_{18}N_2O.1/4H_2O.1/4C_3H_6O$: C, 70.69; H, 7.91; N, 9.99).

(2RS, 3RS, 6SR)-3-*Hydroxy*-5-*methyl*-1,2,3,4,5,6-*hexahydro*-2,6-*methano*[1,4]-*diazocino*[1,2-a]*indole* (11b). Operating as above, from cyanopiperidine 10b (1.5 g, 5.57 mmol) and 60% acetic acid (75 ml), an oil (1.5 g) was obtained. Column chromatography using 98:2 chloroform-methanol as eluent afforded 11b (0.72 g, 52%). A sample recrystallized from acetone-ether melted at 164-165°C; NMR (200 MHz) 1.86 (broad d, J= 12 Hz, 1H, H-12β), 2.04 (dd, J=4 and 13.2 Hz, 1H, H-4ax), 2.25 (s, 3H, NCH_3), 2.30 (m, 1H, H-2), 2.50 (broad d, J=13.2 Hz, 1H, H-4eq), 2.58 (dt, J=4, 4, and 12 Hz, 1H, H-12α), 3.38 (broad s, 1H, OH), 3.80 (broad s, 2H, H-6 and H-3eq), 4.00 (d, J=12 Hz, 1H, H-1), 4.10 (dd, J=6 and 12 Hz, 1H, H-1), 6.24 (s, 1H, H-7), 7.10-7.30 (m, 3H, indole), 7.60 (d, J=7 Hz, 1H, H-8); IR (KBr) 3000-3500 (OH). (Found: C, 74.33; H, 7.58; N, 11.56. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.48; N, 11.56).

(Z)- *and* (E)-3-*Ethylidene*-5-*methyl*-1,2,3,4,5,6-*hexahydro*-2,6-*methano*[1,4]-*diazocino*[1,2-a]*indole* (13). A solution of dimethyl sulfoxide (0.69 g, 8.8 mmol) in methylene chloride (2 ml) was added dropwise under nitrogen to a stirred solution of oxalyl chloride (0.51 g, 0.35 ml, 4.07 mmol) in methylene chloride (10 ml) cooled at -60°C. After 20 min, a solution of alcohol 11a (0.9 g, 3.7 mmol) in methylene chloride (7 ml) was added to the resulting solution, and the mixture was stirred under nitrogen at -60°C for 30 min. Then,triethylamine (1.86 g, 2.57 ml, 18.5 mmol) was added over a 10 min period. The cooling bath was removed, water (15 ml) was added at room temperature, and stirring was continued for 10 min. The organic layer was separated, washed with water, dried, and evaporated to afford 0.7 g of the unstable ketone 12; IR ($CHCl_3$) 1720 (CO). The same ketone 12 was obtained when starting from alcohol 11b and from a diastereomeric mixture of alcohols 11a and 11b.

Ethyltriphenylphosphonium bromide-sodium amide (Instant Ylide,[46] 2.4 mmol/g, 1.8 g, 4.35 mmol) was stirred under nitrogen in tetrahydrofuran (15 ml) at room temperature for 15 min. To the resulting red-orange solution was added the ketone 12 (0.7 g, 2.9 mmol) in tetrahydrofuran (15 ml), and the resulting mixture was stirred at 40-50°C for 20 h. The solvent was removed and the oily residue was dissolved in water and extracted with chloroform. The organic layer was dried and evaporated to give an oil (1.5 g) which was chromatographed. On elution with chloroform, a nearly equimolecular mixture of ethylidene derivatives 13 (0.32 g, 37.5% from 10a) was obtained. Both isomers were separated by further column chromatography using chloroform as eluent. Z-Isomer 13a: ^{1}H-NMR (200 MHz) 1.60 (dd, J=1.5 and 6.8 Hz, 3H, $CHCH_3$), 2.10 (dt, J=2.8 and 13.5 Hz, 1H, H-12), 2.20-2.40 (m, 2H, H-12, H-4ax), 2.35 (s, 3H, NCH_3), 2.90 (broad, 1H, H-2), 3.42 (d, J= 13.4 Hz, 1H, H-4eq), 4.03 (apparent t, J=3 Hz, 1H, H-6), 4.04-4.20 (m, 2H, H-1), 5.49 (qd, J=2 and 6.8 Hz, 1H, $CHCH_3$), 6.30 (s, 1H, H-7), 7.08-7.30 (m, 3H, indole), 7.64 (d, J=7 Hz, 1H, H-8); ^{13}C-NMR 12.7 ($CHCH_3$), 31.43 (C-12), 36.19 (C-2), 43.19 (NCH_3), 49.25 (C-1), 49.55 (C-4), 53.71 (C-6), 100.99 (C-7), 108.90 (C-11), 119.69 (C-10), 119.83 (C-8), 120.41 (C-9), 121.11 ($CHCH_3$), 127.61 (C-7a), 132.02 (C-6a), 136.27 (C-3), 137.05 (C-11a). The picrate melted at 187-188°C (ethanol). (Found: C, 57.47; H, 4.79; N, 14.22. Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.38; H, 4.81; N, 14.54). E-Isomer 13b: ^{1}H-NMR (200 MHz) 1.71 (dd, J=1.9 and 6.8 Hz, 3H, $CHCH_3$), 2.11 (dt, J=2 and 12.8 Hz, 1H, H-12), 2.30 (masked, 1H, H-12), 2.32 (s, 3H, NCH_3), 2.56 (broad d, J=13.2 Hz, 1H, H-4ax), 2.96 (d, J=13.2 Hz, 1H, H-4eq), 3.40 (broad, 1H, H-2), 4.04 (broad, 1H, H-6), 4.05 (d, J=12 Hz, 1H, H-1), 4.16 (dd, J=5.6 and 12 Hz, 1H, H-1), 5.40 (qd, J=1.2 and 6.8 Hz, 1H, $CHCH_3$), 6.31 (s, 1H, H-7), 7.08-7.34 (m, 3H, indole), 7.60 (d, J=7 Hz, 1H, H-8); ^{13}C-NMR 12.47 ($CHCH_3$), 27.30 (C-2), 30.95 (C-12), 42.84 (NCH_3), 47.80 (C-1), 53.74 (C-6), 57.12 (C-4), 101.05 (C-7), 108.86 (C-11), 119.23 (C-10), 119.84 (C-8), 120.39 (C-9), 121.13 ($CHCH_3$), 127.56 (C-7a), 131.91 (C-6a), 136.31 (C-3), 136.79 (C-11a). The picrate melted at 151-152°C (ethanol). (Found: C, 56.91; H, 4.84; N, 14.33. Calcd. for $C_{23}H_{23}N_5O_7$: C, 57.38; H, 4.81; N, 14.54).

Acknowledgement. This investigation was supported by the Comisión Asesora de Investigación Científica y Técnica, Spain (project number 1842/82) and, in part, by an Ajut a la Investigació de la Universitat de Barcelona. We are grateful to Ms. Lluisa Juan and Mr. Ramon Vila for experimental contributions.

REFERENCES AND NOTES

1. Part I: J. Bosch, M. Feliz, and M.-L. Bennasar, *Tetrahedron*, 1984, *40*, 1419.
2. This work was presented in a preliminary form as oral communication at the Third European Symposium on Organic Chemistry, Canterbury, England, 1983.
3. D. S. Grierson, M. Harris, and H.-P. Husson, *Tetrahedron*, 1983, *39*, 3683.
4. J. A. Beisler, *Tetrahedron*, 1970, *26*, 1961.
5. R. Besselièvre, C. Thal, H.-P. Husson, and P. Potier, *J. Chem. Soc., Chem. Commun.*, 1975, 90.
6. W. R. Ashcroft and J. A. Joule, *Tetrahedron Lett.*, 1980, *21*, 2341.
7. M. Harris, R. Besselièvre, D. S. Grierson, and H.-P. Husson, *Tetrahedron Lett.*, 1981, *22*, 331.
8. M. Harris, D. S. Grierson, C. Riche, and H.-P. Husson, *Tetrahedron Lett.*, 1980, *21*, 1957.
9. J. Bosch, M. Rubiralta, A. Domingo, J. Bolós, A. Linares, C. Minguillón, M. Amat, and J. Bonjoch, *J. Org. Chem.*, 1985, *50*, 1516.
10. M. Feliz, J. Bosch, D. Mauleón, M. Amat, and A. Domingo, *J. Org. Chem.*, 1982, *47*, 2435.
11. (a) J. Bosch, D. Mauleón, M. Feliz, and R. Granados, *J. Org. Chem.*, 1983, *48*, 4836; (b) J. Bosch, M. Feliz, and M.-L. Bennasar, *Heterocycles*, 1982, *19*, 853; (c) J. Bosch, M.-L. Bennasar, and E. Zulaica, *J. Org. Chem.*, submitted.
12. Only one synthetic route to vinoxine has been reported to date: J. Bosch, M.-L. Bennasar, E. Zulaica, and M. Feliz, *Tetrahedron Lett.*, 1984, *25*, 3119.
13. (a) Z. Votický, E. Grossmann, J. Tomko, G. Massiot, A. Ahond, and P. Potier, *Tetrahedron Lett.*, 1974, 3923; (b) Z. Votický, E. Grossmann, and P. Potier, *Coll. Czech. Chem. Commun.*, 1977, *42*, 548.
14. J. Le Men and W. I. Taylor, *Experientia*, 1965, *21*, 508.
15. For a review on the elaboration of the ethylidene substituent in the synthesis of indole alkaloids, see: J. Bosch and M.-L. Bennasar, *Heterocycles*, 1983, *20*, 2471.
16. A. Maercker, *Org. React. (N. Y.)*, 1965, *14*, 270.
17. For examples about the application of this reaction to the elaboration of an ethylidene substituent, see: (a) M. E. Kuehne and C. Bayha, *Tetrahedron Lett.*, 1966, 1311; (b) G. Van Binst and J. C. Nouls, *J. Chem. Soc. (C)*, 1970, 150; (c) See also reference 6.
18. (a) E. M. Fry, *J. Org. Chem*, 1963, *28*, 1869; (b) E. M. Fry, *J. Org. Chem.*, 1964, *29*, 1647.
19. H. Heaney and S. V. Ley, *J. Chem. Soc., Perkin Trans.*, 1973, 499.
20. (a) B. Cardillo, G. Casnati, A. Pochini, and A. Ricca, *Tetrahedron*, 1967, *23*, 3771; (b) R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970, pp 19-31.
21. This behaviour is usual in 3-piperidones: (a) P. Yates and F. N. Maclachlan, *J. Indian Chem. Soc.*, 1978, *55*, 1116; (b) P. J. Schirmann, R. S. Matthews, and D. C. Dittmer, *J. Org. Chem.*, 1983, *48*, 4426.
22. Aqueous hydrochloric, sulfuric, and acetic acids at different concentrations, temperatures, and reaction times were used.
23. W. R. Ashcroft and J. A. Joule, *Heterocycles*, 1981, *16*, 1883.
24. The reaction failed under the usual conditions (dimethyl sulfoxide and potassium hydroxide)[19], and when we used sodium methylsulfinylmethanide[25] as the base in dimethyl sulfoxide. Pyridinol *4c* was obtained in <5% yield when condensation was effected using sodium hydride as the base and tetrahydrofuran as the solvent.[20a]
25. (a) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1962, *84*, 866; (b) E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, *87*, 1345.
26. S. L. Shapiro, K. Weinberg, and L. Freedman, *J. Am. Chem. Soc.*, 1959, *81*, 5140.
27. The reaction of ketones with the indole ring under acidic conditions to give bis(3-indolyl)methanes is a well known process: W. J. Houlihan, ed., "Heterocyclic Compounds. Indoles, Part I", John Wiley and Sons, New York, 1972, p.105.
28. R. E. Lyle and P. S. Anderson, *Advan. Heterocyclic Chem.*, 1966, *6*, 45.
29. (a) M. Bonin, J. R. Romero, D. S. Grierson, and H.-P. Husson, *Tetrahedron Lett.* 1982, *23*, 3369; (b) M. Bonin, R. Besselièvre, D. S. Grierson, and H.-P. Husson, *Tetrahedron Lett.*, 1983, *24*, 1493.
30. M. Bonin, J. R. Romero, D. S. Grierson, and H.-P. Husson, *J. Org. Chem.*, 1984, *49*, 2392.
31. (a) D. S. Grierson, M. Vuilhorgne, and H.-P. Husson, *J. Org. Chem.*, 1982, *47*, 4439; (b) M. Y. Essawi and P. S. Portoghese, *J. Org. Chem.*, 1983, *48*, 2138; (c) L. Guerrier, J. Royer, D. S. Grierson, and H.-P. Husson, *J. Am. Chem. Soc.*, 1983, *105*, 7754.
32. (a) K. Omura and D. Swern, *Tetrahedron*, 1978, *34*, 165; (b) B. Danielli, G. Lesma, and G. Palmisano, *Gazz. Chim. Ital.*, 1981, *111*, 257.
33. G. Van Binst and D. Tourme, *Org. Magn. Resonance*, 1972, *4*, 625.
34. Similar effects were observed in the isomeric methyl 3*E*- and 3*Z*-ethylidene-

1-methoxycarbonyl-4-piperidineacetates: M. R. Uskoković, R. L. Lewis, J. J. Partridge, C. W. Despreaux, and D. L. Pruess, *J. Am. Chem. Soc.*, 1979, *101*, 6742.
35. A similar deshielding of an equatorial piperidine α-proton has been observed in 20-isodeplancheine, as compared with deplancheine: see reference 6.
36. A similar deshielding of an equatorial piperidine γ-proton in 3E-ethylidene-1-azabicyclo[2.2.2]octane, as compared with the Z-isomer, has been observed: J. C. Nouls, G. Van Binst, and R. H. Martin, *Tetrahedron Lett.*, 1967, 4065.
37. 3-Methoxy-4-pyridinemethanol (2a) was prepared in a five-step sequence, according to previously published procedures: 4-picoline was brominated[38,39] and then oxidized[38] with potassium permanganate to give 3-bromo-4-pyridinecarboxylic acid. Esterification[38] followed by nucleophilic substitution of bromine by methoxide[38] and, finally, lithium aluminium hydride reduction[40] of the resulting ester 1a afforded alcohol 2a, which was isolated as the hydrochloride.
38. J. V. Dejardin and C.-L. Lapière, *Bull. Soc. Chim. France*, 1976, 530.
39. (a) D. E. Pearson, W. W. Hargrove, C. K. Chow, and B. R. Suthers, *J. Org. Chem.*, 1961, *26*, 789; (b) L. Van der Goes and H. J. Den Hertog, *Rec. Trav. Chim. Pays Bas*, 1965, *84*, 951; (c) K. Palat, L. Novacek, and M. Celadnik, *Coll. Czech. Chem. Commun.*, 1967, *32*, 1191.
40. D. Heinert and A. E. Martell, *Tetrahedron*, 1958, *3*, 49.
41. 3-Benzyloxy-4-pyridinecarbonitrile was prepared accorded to previously reported procedures from 4-cyanopyridine N-oxide by reaction with phosphorus oxychloride and phosphorus pentachloride[42] to give 3-chloro-4-pyridinecarbonitrile followed by nucleophilic substitution of chlorine by benzyloxy.[43]
42. J. Rokach and I. Girard, *J. Heterocyclic Chem.*, 1978, *15*, 683.
43. J. LaMattina and R. L. Taylor, *J. Org. Chem.*, 1981, *46*, 4179.
44. 3-Hydroxy-4-pyridinemethanol (2c) was prepared by previously reported procedures: 3-bromo-4-pyridinecarboxylic acid[38] was converted to the corresponding 3-pyridinol,[38] esterified,[45] and then reduced with lithium aluminium hydride[40] to give 2c, which was isolated as the hydrochloride.
45. J. D. Crum and C. H. Fuchsman, *J. Heterocyclic Chem.*, 1966, *3*, 252.
46. Fluka, Catalog No.69500.