Tetrahedron Vol. 48, No. 31, pp. 6445-6454, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00

Studies on the Nucleophilic Addition to 3,5-Disubstituted Pyridinium Salts

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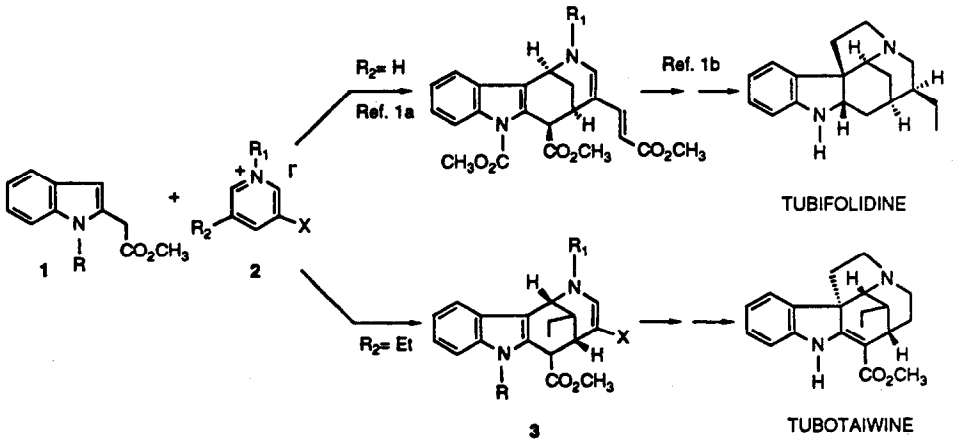
(*Received in UK* 22 *May* 1992)

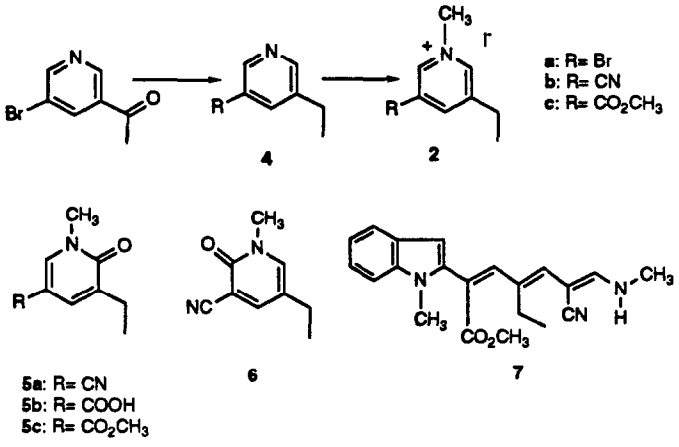
Abstract: The reactivity of pyridinium salts **2** towards nucleophiles has been studied. The interaction with enolates derived from esters **1** gave only trace amounts of the expected compounds **3**. Irreversible-type additions, however, allowed the preparation of indolyldihydropyridines **8** and **9** with high yields. Reaction of organometallic **10** with salt **2c**, followed by acidic cyclization, afforded tetracycle **12**.

The nucleophilic addition of enolates derived from indole-2-acetic esters **1** to pyridinium salts **2** bearing an electron-withdrawing substituent at the β position, followed by cyclization of the resulting 1,4-dihydropyridine, has proved to be useful[1] for the synthesis of pentacyclic *Strychnos* indole alkaloids[2] having the Strychnan skeleton (C_3- C_7 bond)[3], for instance tubifolidine. The extension of this methodology[4] to the synthesis of *Strychnos* alkaloids having the Aspidospermatan-type (C_7 - C_{21} bond), exemplified by tubotaiwine,[5,6] would imply the use of a pyridinium salt bearing an easily removable electron-withdrawing substituent, such as methoxycarbonyl, and an ethyl group at the β and β' positions, respectively (Scheme 1). To our knowledge, no examples of intermolecular additions upon such pyridinium salts have been reported.[4b]



SCHEME 1

N-Methylpyridinium salts **2b** and **2c** were used as starting materials for model studies (Scheme 2). These salts were prepared by alkylation of the corresponding pyridines **4b,c** with methyl iodide. Wolff-Kishner reduction of 3-acetyl-5-bromopyridine,[7] followed by reaction of the resulting 3-ethylpyridine **4a**[8] with copper cyanide in DMF,[9] gave nitrile **4b**. Acid-catalyzed methanolysis of **4b** produced ester **4c**.[10]



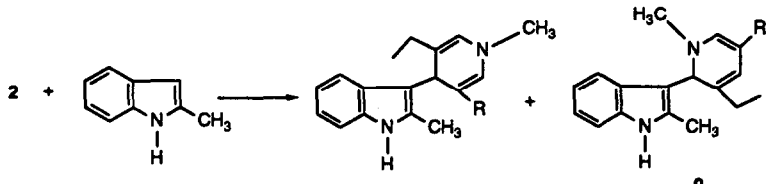
SCHEME 2

However, interaction of esters **1** (R = H[11] or CH_3[1a]) with pyridinium salts **2b** and **2c** under the usual reaction conditions (1. LDA, THF, -20°C, 2. HCl-C_6H_6) only allowed the recovery of unchanged starting material. Higher temperatures or longer reaction times did not lead to satisfactory results either. No traces of tetracyclic compounds **3** were found in these experiments, the only remarkable results being the detection of methyl α-hydroxy-1-methyl-2-indoleacetate, methyl 2-(methoxycarbonylmethyl)-1-methyl-α-(1-methyl-2-indolyl)-3-indoleacetate,[12] and pyridones **5a** and **5c**. The formation of the two former compounds has been previously reported in similar low-yielding addition-cyclization reactions,[12] and probably involves a radical mechanism[13]. Pyridones have been isolated previously in this type of chemistry.[14] Their structure was determined by independent syntheses. In order to have, if possible, the two α-pyridone isomers, potassium ferricyanide oxidation of pyridinium salts[15] was preferred to the more regioselective van der Plas method.[16] This was the result, in fact, since from salt **2b**, pyridones **5a** (16%) and **6** (48%) were obtained. A similar oxidation of pyridinium salt **2c** afforded acid **5b**, which was esterified to produce pyridone **5c** (55% overall yield).[17] The ^{13}C-NMR the chemical shifts of the quaternary carbons were of diagnostic value for the structure determination of the pyridones.[18] The regioselectivity of the above oxidations nicely agrees with that observed in the oxidation of several 3-substituted 1-methylpyridinium iodides.[19] Also unsuccessful was the attempt to trap oxidatively *in situ* the presumed 1,4-dihydropyridine intermediate with DDQ; only an enhanced production of pyridone **5a** was observed.

The desired tetracyclic compound **3** (R = R_1 = CH_3; X = CN) could only be detected, but in very low yield, when DMSO was used as cosolvent in the addition step.[20] Under these conditions, compound **7** was also detected, its formation being the result of an irreversible ring opening of the corresponding 1,2-dihydropyridine.[1a, 13a]

The above results constitute a serious limitation on the application of this methodology to the

synthesis of *Strychnos* alkaloids with the Aspidospermatan skeleton. Taking into account that the ethyl group present in **2b,c** could reduce the electrophilicity of the salt or sterically hamper the addition at the γ position, we decided to test the rectivity of pyridinium salts **2** toward nucleophiles in an irreversible process. The addition of indoles to activated pyridinium salts constitutes a method of general interest for the preparation of 3-indolyl-dihydropyridines[21] and was selected as a probe. On the basis of the solvent effect recently described,[22] DMSO was used to promote the formation of 1,4.dihydropyridines whereas methanol was the solvent of choice for the synthesis of 1,2-dihydropyridines.



8 **9**

a: R= CN

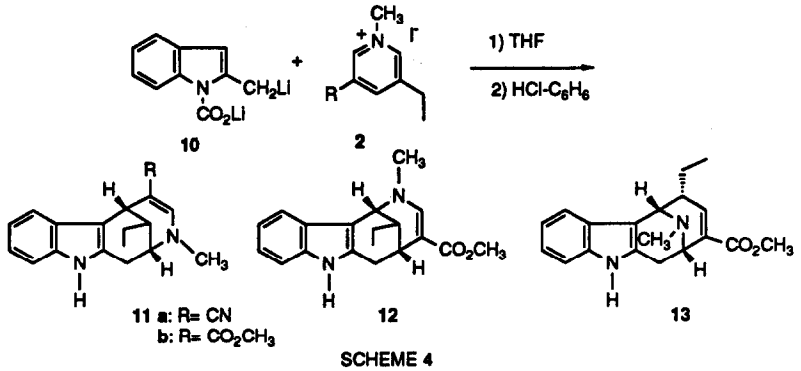
b: R= CO_2CH_3

SCHEME 3

Thus, addition of 2-methylindole to pyridinium salt **2b** in DMSO/NaH afforded regiospecifically 1,4-dihydropyridine **8a** in 98% yield (Scheme 3). The reaction upon salt **2c** gave **8b** (33%) together with 1,2-dihydropyridine **9b** (9%). Performing the reactions in MeOH/NaOMe, 1,2-dihydropyridines **9b** (95%) and **9a** (36%) were isolated, although in the latter case the corresponding 1,4-dihydropyridine **8a** was formed as the major product (51% yield). These results show the greater ability of the cyano group (as compared with methoxycarbonyl) to allow addition at the γ position of the pyridine ring and expand the scope of the aforementioned solvent-mediated regioselective dihydropyridine synthesis. Pyridinium salt **2a** was unreactive towards 2-methylindole under the above reaction conditions.

The structure of compounds **9** posed a question regarding the feasibility of the addition of the indole anion at either α or α' position. The univocal assignment was achieved with the aid of N.O.e/N.O.e difference and HETCOR experiments, which revealed that the indole ring is located aside the ethyl group in **9b**.

From the above results, the use of more powerful nucleophiles in an irreversible process was considered advantageous, and lithium 2-lithiomethyl-1-indolecarboxylate (**10**), which was prepared following the Katritzky's method[11b], was added *in* THF solution to pyridinium salts **2b** or **2c**, and then the corresponding mixtures were treated with acid (Scheme 4).



SCHEME 4

Reaction of **10** with salt **2b** gave tetracycle **11a** (7%), arising from addition of the nucleophile to the α position of the pyridine ring and further cyclization of the resulting 1,2-dihydropyridine upon its 4 position. This result was not unexpected, taking into account the hard character of organolithium nucleophiles. 1,4-Dihydropyridine **8a** was detected from the complex reaction mixture formed.

A similar reaction from salt **2c** afforded a complex mixture, from which tetracycles **11b** (6%), **12** (6%), and **13** (<1%) were separated after column chromatography. In this case, the attack of the nucleophile takes place at all three positions available in the pyridinium salt, giving three isomeric dihydropyridines, which undergo further cyclization upon the indole β-position.

When the lithium derivative **10** was treated with copper (I) bromide-dimethylsulfide complex prior to the addition-cyclization sequence (from **2b** and **2c**), the formation of very complex reaction mixtures was observed, with no improvement in the yield and regioselectivity for the cyclized products. Pyridones **5a** and **5c** were isolated in these reactions, as well as dihydropyridines **8a,b** and **9a,b**. Interestingly two additional compounds, 2-indolylmethanol[23] and 1,2-bis-(2-indolyl)ethane[24], were obtained in these reactions.

In conclusion, the scope and limitations of different nucleophilic additions to 5-ethylpyridinium salts with an electron-withdrawing substituent at the 3-position have been studied, and a straigthforward synthesis of the Aspidospermatan-type system **12** has been accomplished. The procedure deserves interest as it implies seven chemical transformations in a one-pot operation from easily available materials.

EXPERIMENTAL PART

General. All solvents were dried by standart methods. All reagents were of commercial quality from freshly opened containers. Prior to concentration, under reduced pressure, all organic extracts were dried with anhydrous sodium sulphate. Column chromatograpphy was carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm) or on Al_2O_3 (aluminium oxide, 90, neutral, activity I, Merck 0.063-0.200mm). TLC was carried out on SiO_2 (silica gel 60, Merck 0.063-0.200 mm) and the spots were located with UV light or iodine vapors. Melting points were taken using a Büchi apparatus and are uncorrected. Microanalyses were performed on a Carlo-Erba 1106 analyzer by Centro de Investigación y Desarrollo (CSIC), Barcelona. ^1H and ^{13}C-NMR spectra were obtained using a Varian XL-200 instrument in $CDCl_3$ with TMS as an internal reference unless otherwise specified. Heterocorrelation was obtained using a Varian 500 spectrometer. IR spectra were recorded on a Perkin Elmer 1600 series FTIR and on a Perkin Elmer 1430 spectrophotometer. UV spectra were obtained using an Hitachi U-2000 apparatus in MeOH. Mass spectra were determined on a

Hewlett-Packard 5930A spectrometer.

3-Bromo-5-ethylpyridine (4a). A solution of 3-acetyl-5-bromopyridine (31.5 g, 157 mmol), 80% hydrazine hydrate (63 ml), and potassium hydroxide (63 g, 1.6 mol) in diethylene glycol (110 ml) was stirred under nitrogen at 140°C for 6 h. After cooling to r.t., the solution was extracted with ether. The extract was washed with water, dried, and evaporated to give the product **4a** as an oil (21.5 g, 73%); ^{1}H NMR : 1.28 (t, J=7.7 Hz, 3H, CH_3), 2.64 (q, J=7.7 Hz, 2H, CH_2), 7.67 (s, 1H, H-4 pyridine), 8.38 (s, 1H, H-2 pyridine), 8.50 (s, 1H, H-6 pyridine). ^{13}C NMR : 13.3 (CH_3), 24.0 (CH_2), 119.2 (C-3 pyridine), 136.4 (C-4 pyridine), 139.6 (C-5 pyridine), 146.4 (C-6 pyridine), 146.8 (C-2 pyridine). IR (NaCl) : 1474 (C=C). UV, λ_{max} nm (logϵ) : 202 (3.96), 209 (3.86), 267 (3.52), 272 (3.57), 277 (3.47).

5-Ethylpyridine-3-carbonitrile (4b). Copper (I) cyanide (15.5 g, 244 mmol) was added to a solution of pyridine **4a** (21.5 g, 115 mmol) in dimethylformamide (90 ml). The mixture was stirred under nitrogen at 160°C for 24 h. The solvent was removed under reduced pressure, the residue was poured into saturated aqueous sodium cyanide and extracted with ethyl acetate. The organic extract was washed with water and saturated aqueous sodium cyanide, dried, and evaporated to give the nitrile **4b** as an oil (12 g, 79%); ^{1}H NMR : 1.30 (t, J=7.6 Hz, 3H, CH_3), 2.75 (q, J=7.6 Hz, 2H, CH_2), 7.81 (bs, 1H, H-4 pyridine), 8.68 (d, J=2 Hz, 1H, H-6 pyridine), 8.73 (d, J=2 Hz, 1H, H-2 pyridine). ^{13}C NMR : 14.4 (CH_3), 25.3 (CH_2), 109.5 (C-3 pyridine), 116.7 (C≡N), 138.2 (C-4 pyridine), 139.7 (C-5 pyridine), 149.8 (C-2 pyridine), 153.0 (C-6 pyridine). IR (NaCl) : 2220 (C≡N), 1550-1420 (C=C). UV, λ_{max} nm (logϵ) : 203 (3.97), 217 (3.94), 271 (3.50), 371 (1.62). MS (m/z, %) : 132 (M^+, 82), 131 (56), 117 (100), 90 (21).

Methyl 5-Ethylpyridine-3-carboxylate (4c). Sulfuric acid (5 ml) was added to a solution of nitrile **4b** (620 mg, 4.7 mmol) in methanol (20 ml). The resulting solution was stirred at reflux temperature for 48 h. The solvent was removed under reduced pressure and the residue was basified with aqueous sodium carbonate solution and extracted with ethyl acetate. The organic extract was dried and evaporated to yield pure ester **4c** (600 mg, 77%); ^{1}H NMR : 1.30 (t, J=7.6 Hz, 3H, CH_3), 2.72 (q, J=7.6 Hz, 2H, CH_2), 3.96 (s, 3H, OCH_3), 8.14 (s, 1H, H-4 pyridine), 8.64 (s, 1H, H-6 pyridine), 9.06 (s, 1H, H-2 pyridine). ^{13}C NMR : 14.6 (CH_3), 25.3 (CH_2), 51.9 (OCH_3), 125.5 (C-3 pyridine), 136.0 (C-4 pyridine), 138.9 (C-5 pyridine), 148.2 (C-6 pyridine), 153.2 (C-2 pyridine), 165.9 (C=O). IR (NaCl) : 1700 (C=O). UV, λ_{max} nm (log ϵ) : 203 (4.14), 219 (4.05), 270 (3.67).

General Procedure for the Preparation of Pyridinium Salts 2. A solution of methyl iodide (7 eq.) in anhydrous benzene (10 ml) was added dropwise to a solution of the pyridine **4** (1 eq.) in anhydrous acetone (5 ml), and the mixture was stirred at room temperature for 5 days. The resulting precipitate was filtered, washed with anhydrous ether, and dried in a dessicator under reduced pressure.

3-Bromo-5-ethyl-1-methylpyridinium Iodide (2a). Operating as above, from **4a** (2 g, 10.7 mmol) and methyl iodide (5 ml, 77.4 mmol), pyridinium salt **2a** (3.2 g, 88%) was obtained; ^{1}H NMR (DMSO-d_6) : 1.42 (t, J=7.7 Hz, 3H, CH_3), 2.98 (q, J=7.7 Hz, 2H, CH_2), 4.72 (s, 3H, NCH_3), 8.32 (s, 1H, H-4 pyridine), 9.14 (s, 1H, H-6 pyridine), 9.39 (s, 1H, H-2 pyridine). ^{13}C NMR (DMSO-d_6) : 14.3 (CH_3), 25.1 (CH_2), 48.1 (NCH_3), 121.4 (C-3 pyridine), 144.5 (C-4 pyridine), 145.2 (C-5 pyridine), 147.1 (C-2 and C-6 pyridine). IR (KBr) : 1475 (C=C). UV, λ_{max} nm (log ϵ) : 203 (4.68), 282 (3.92). Mp 183-185°C. Anal. Calcd for $C_8H_{11}BrIN$: C, 29.30; H, 3.35; N, 4.26. Found: C, 29.52; H, 3.29, N,4.07.

3-Cyano-5-ethyl-1-methylpyridinium Iodide (2b). Operating as above, from **4b** (4.33 g, 33 mmol) and methyl iodide (15.4 ml, 239 mmol), pyridinium salt **2b** (7.0 g, 78%) was obtained; ^{1}H NMR (DMSO-d_6) : 1.26 (t, J=7.6 Hz, 3H, CH_3), 2.83 (q, J=7.6 Hz, 2H, CH_2), 4.33 (s, 3H, NCH_3), 9.01 (s, 1H, H-4 pyridine),

9.23 (s, 1H, H-6 pyridine), 9.56 (s, 1H, H-2 pyridine). ^{13}C NMR (DMSO-d_6) : 13.3 (CH_3), 24.4 (CH_2), 48.0 (NCH_3), 111.2 (C-3 pyridine), 113.7 (C≡N), 143.8 (C-5 pyridine), 146.7 (C-2 pyridine), 147.1 (C-4 pyridine), 148.2 (C-6 pyridine). IR (KBr) : 2248 (C≡N), 1633 (C=C). UV, λ_{max} nm (log ϵ) : 202 (4.54), 217 (4.42), 276 (3.74), 409 (2.50). Mp 207-209°C (MeOH). Anal. Calcd for $C_9H_{11}IN_2$: C, 39.41; H, 4.01; N, 10.22. Found: C, 39.29; H, 4.09; N, 9.82.

3-Ethyl-1-methyl-5-methoxycarbonylpyridinium Iodide (2c). Operating as above, from **4c** (2.45g, 15 mmol) and methyl iodide (7 ml, 108 mmol), pyridinium salt **2c** (3.7 g, 81%) was obtained; ^1H NMR (DMSO-d_6) : 1.25 (t, J=7.5 Hz, 3H, CH_3), 2.87 (q, J=7.5 Hz, 2H, CH_2), 3.36 (s, 3H, OCH_3); 4.38 (s, 3H, NCH_3), 8.86 (s, 1H, H-4 pyridine), 9.16 (s, 1H, H-6 pyridine), 9.40 (s, 1H, H-2 pyridine). ^{13}C NMR (DMSO-d_6) : 14.4 (CH_3), 25.1 (CH_2), 48.4 (NCH_3), 53.1 (OCH_3), 128.7 (C-3 pyridine), 129.2 (C-5 pyridine), 144.5 (C-4 and C-6 pyridine), 148.6 (C-2 pyridine), 168.2 (C=O). IR (KBr) : 1734 (C=O), 1636 and 1602 (C=C). UV, λ_{max} nm (logϵ) : 201 (4.48), 219 (4.29), 272 (3.65), 419 (2.50). Mp 147-150°C (MeOH). Anal. Calcd for $C_{10}H_{14}INO_2$: C, 39.09; H, 4.56; N, 4.56. Found: C, 39.34; H, 4.58; N, 4.65.

Oxidation of Pyridinium Salt 2b. To a solution of pyridinium salt **2b** (500 mg, 1.82 mmol) in water (5 ml) kept at 0°C, were added simultaneously and dropwise a solution of potassium ferricyanide (1.5 g, 4.5 mmol) in water (5 ml) and a solution of sodium hydroxide (300 mg, 7.5 mmol) in water (2.5 ml). The rate of the additions was controlled to keep the temperature below 10°C. After the additions were complete, the resulting solution was stirred at room temperatue for 24 h. The solution was extracted with dichloromethane. Evaporation of the dried organic extracts gave a residue, which was chromatographed over silica-gel. Elution with hexanes-ethyl acetate (1:1) afforded **3-ethyl-1-methyl-2-oxo-1,2-dihydropyridine-5-carbonitrile (5a)** (48 mg, 16%) as a white solid. ^1H NMR : 1.19 (t, J=7.5 Hz, 3H, CH_3), 2.56 (q, J=7.5 Hz, 2H, CH_2), 3.59 (s, 3H, NCH_3), 7.25 (m, 1H, H-4), 7.74 (d, J=2.2 Hz, 1H, H-6). ^{13}C NMR : 11.6 (CH_3), 23.2 (CH_2), 38.0 (NCH_3), 90.6 (C-5), 116.7 (C≡N), 133.8 (C-4), 136.2 (C-3), 143.0 (C-6), 161.8 (C=O). IR ($CHCl_3$) : 2220 (C≡N), 1660 (C=O). UV, λ_{max} nm (logϵ) : 209 (4.53), 257 (4.48), 299 (4.07). MS (m/z %) : 162 (M^+, 68), 161 (50), 147 (100), 119 (27), 42 (27). Mp 110-112°C. Anal. Calcd for $C_9H_{10}N_2O$: C, 66.66; H, 6.17; N, 17.28. Found: C, 66.59; H, 6.29; N, 17.04. Further elution with hexanes-ethyl acetate (1:2) gave **5-ethyl-1-methyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (6)** (142 mg, 48%) as a white solid. ^1H NMR : 1.19 (t, J=7.6 Hz, 3H, CH_3), 2.46 (q, J=7.6 Hz, 2H, CH_2), 3.60 (s, 3H, NCH_3), 7.42 (d, J=2.5 Hz, 1H, H-4), 7.73 (d, J=2.5 Hz, 1H, H-6). ^{13}C NMR : 14.1 (CH_3), 23.7 (CH_2), 37.7 (NCH_3), 103.8 (C-3), 115.7 (C≡N), 120.7 (C-5), 141.6 (C-4), 147.9 (C-6), 159.5 (C=O). IR ($CHCl_3$) : 2220 (C≡N), 1655 (C=O). UV, λ_{max} nm (logϵ) : 213 (3.96), 235 (3.68), 342 (3.73). MS (m/z, %) : 162 (M^+, 39), 147 (100), 119 (11), 42 (32). Mp 151-152°C. Anal. Calcd for $C_9H_{10}N_2O$: C, 66.66; H, 6.17; N, 17.28. Found: C, 66.76; H, 6.26; N, 17.20.

Oxidation of Pyridinium Salt 2c. To a solution of pyridinium salt **2c** (800 mg, 2.6 mmol) in water (5 ml) kept at 0°C, were added simultaneously and dropwise a solution of potassium ferricyanide (1.1 g, 3.3 mmol) in water (4.5 ml) and a solution of sodium hydroxide (260 mg, 6.5 mmol) in water (2 ml). The rate of the addition was controlled to keep the temparature below 0°C. After the additions were complete, the resulting solution was stirred at room temperature for 5 h. Hydrochloric acid (2N) was added until pH 2, and the aqueous solution was extracted with ethyl acetate. Evaporation of the dried organic extracts gave **3-ethyl-1-methyl-2oxo-1,2-dihydropyridine-5-carboxylic acid (5b)** (265 mg, 56%). ^1H NMR ($CDCl_3$-CD_3OD) : 1.21 (t, J=7.6 Hz, 3H, CH_3), 2.57 (q, J=7.6 Hz, 2H, CH_2), 3.63 (s, 3H, NCH_3), 7.81 (m, 1H, H-4), 8.18 (bd, J=2.4 Hz, 1H, H-6). The acid **5b** (265 mg, 1.46 mmol) was dissolved in a 2.5 M methanol solution of dry hydrogen chloride (50 ml) and stirred at room temperature for 3 days. The solvent was

removed, the residue was basified with aqueous sodium carbonate and extracted with dichloromethane. The dried organic extracts were evaporated to afford **methyl 3-ethyl-1-methyl-2-oxo-1,2-dihydropyridine-5-carboxylate (5c)** (280 mg, 98%).^{1}H NMR : 1.20 (t, J=7.5 Hz, 3H, CH_3), 2.56 (q, J=7.56 Hz, 2H, CH_2), 3.62 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 7.71 (m, 1H, H-4), 8.10(bd, J=2.5 Hz, 1H, H-6). ^{13}C NMR : 12.1 (CH_3), 23.4 (CH_2),38.1 (NCH_3), 51.8 (OCH_3), 109.1 (C-5), 133.8 (C-4), 134.1(C-3), 140.5 (C-6), 163.2 (C-2), 165.3 (C=O). IR ($CHCl_3$) : 1720 (C=O ester), 1660 (C=O). UV, λ_{max} nm (logϵ) : 204 (4.43), 268 (4.28). MS (m/z, %) : 195 (M^+, 42), 180 (75), 152 (11), 136 (11), 65 (36), 42 (100). Mp 95-96°C. Anal. Calcd for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.66; N, 7.18. Found: C, 61.91; H, 6.96, N, 7.08.

General Procedure for the Preparation of 1,4-Dihydropyridines 8. A suspension of sodium hydride (60% in oil w/w, 2.5 mmol) in dimethyl sulfoxide (20 ml) was stirred at 80°C under nitrogen atmosphere for 30 min. The flask was cooled to room temperature, and 2-methylindole (1 mmol) was added all at once. The solution was stirred at room temperature for 10 min, and the pyridinium salt **2** (1.2 mmol) was added in one portion. Stirring was continued for 24 h, and the solvent was removed under reduced pressure. The residue was taken up in water and extracted with ethyl acetate. The organic extracts were washed with water and dried. The solvent was evaporated and the residue was chromatographed over aluminium oxide (hexanes/ethyl acetate) to give pure product **8**.

5-Ethyl-1-methyl-4-(2-methyl-3-indolyl)-1,4-dihydropyridine-3-carbonitrile (8a). Operating as above, essentially pure product **8a** (98%) was obtained. ^{1}H NMR : 0.90 (t, J=7.0 Hz, 3H, CH_3), 1.75 (q, J=7.0 Hz, 2H, CH_2), 2.38 (s, 3H, CH_3 indole), 3.13 (s, 3H, NCH_3), 4.59 (s, 1H, H-4), 5.67 (s, 1H, H-6), 6.57 (s, 1H, H-2), 7.00-7.14 (m, 2H, indole), 7.25 (dd, J=7.3 and 1.5 Hz, 1H, H-7 indole), 7.51 (d, J= 7.2 Hz, 1H, H-4 indole), 7.97 (bs, 1H, NH). ^{13}C NMR : 10.9 (CH_3), 11.1 (CH_3 indole), 24.9 (CH_2), 33.0 (C-4), 40.9 (NCH_3), 80.5 (C-3), 110.3 (C-3 indole), 110.5 (C-7 indole), 113.3 (C≡N), 118.3 (C-4 indole), 119.1 (C-5 indole), 120.7 (C-6 indole), 121.4 (C-3a indole), 122.3 (C-5), 122.6 (C-6), 127.7 (C- 3a indole)), 131.9 (C-2 indole), 135.6 (C-7a indole), 141.4 (C-2). IR (KBr) : 3463 (N-H), 2192 (C≡N), 1684, 1607, 1459 (C=C). UV, λ_{max} nm (logϵ) : 203 (4.65), 221 (4.69), 282 (4.07), 339 (3.8). MS (m/z, %) : 277 (M^+, 45), 262 (20), 248 (100), 233 (8), 147 (55).

Methyl 5-Ethyl-1-methyl-4-(2-methyl-3-indolyl)-1,4-dihydropyridine-3-carboxylate (8b). Operating as above, product **8b** (33%) was obtained after chromatography (elution with hexanes/ethyl acetate 1:1). ^{1}H NMR : 0.92 (t, J=7.5 Hz, 3H, CH_3), 1.75 (q, J=7.5 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3 indole), 3.18 (s, 3H, NCH_3), 3.51 (s, 3H, OCH_3), 4.73 (s, 1H, H-4), 5.67 (s, 1H, H-6), 6.95-7.20 (m, 3H, indole), 7.21 (s, 1H, H-2), 7.45 (d, J= 7.2 Hz, 1H, H-4 indole), 8.00 (bs, 1H, NH). ^{13}C NMR : 11.2 (CH_3), 11.2 (CH_3 indole), 24.9 (CH_2), 31.5 (C-4), 40.9 (NCH_3), 50.3 (OCH_3), 98.8 (C-3), 110.3 (C-7 indole), 115.4 (C-3 indole), 118.4 (C-4 indole), 118.6 (C-5 indole), 120.0 (C-6 indole), 121.5 (C-5), 122.3 (C-6), 127.9 (C-3a indole), 131.7 (C-2 indole), 135.3 (C-7a indole), 140.5 (C-2), 169.1 (C=O). IR (KBr) : 3430 (N-H), 1680 (C=O), 1649, 1579 (C=C). UV, λ_{max} nm (logϵ) : 233 (4.53), 274 (4.27), 3.49 (3.82). Mp 180-182°C (methanol-ether). Anal. Calcd for $C_{19}H_{22}N_2O_2.1/3H_2O$: C, 72.15; H, 7.15; N, 8.86. Found : C, 72.29; H, 7.21; N, 8.75. Further elution with hexanes-ethyl acetate (1:3) afforded product **9b** (9%).

General Procedure for the Preparation of 1,2-Dihydropyridines 9. To a solution of sodium methoxide (2.5 mmol) in methanol (20 ml), kept under nitrogen atmosphere, was added a solution of 2-methylindole (1 mmol) in methanol (5 ml). Stirring was continued at room temperature for 30 min and a solution of the pyridinium salt **2** (1 mmol) in methanol (10 ml) was added. The solution was stirred at room temperature for 24 h. The solvent was evaporated and the residue was taken up in water and extracted with

ethyl acetate. The organic extracts were washed with brine and dried. The solvent was removed under reduced pressure and the residue was chromatographed over aluminium oxide (hexanes/ethyl acetate) to afford products **9**.

3-Ethyl-1-methyl-2-(2-methyl-3-indolyl)-1,2-dihydropyridine-5-carbonitrile (9a). Operating as above, product **9a** (36%) was obtained after chromathograpy (elution with hexanes/ethyl acetate 1:1). ^{1}H NMR : 0.91 (t, J=7.1 Hz, 3H, CH_3), 1.69 (m, 2H, CH_2), 2.44 (s, 3H, CH_3 indole), 2.65 (s, 3H, NCH_3), 5.38 (s, 1H, H-2), 5.74 (bs, 1H, H-4), 6.77 (bs, 1H, H-6), 7.05-7.35 (m, 3H, indole), 7.62 (dd, J=7.2 and 1.5 Hz, 1H, H-4 indole), 8.20 (bs, 1H. NH). ^{13}C NMR : 10.6 (CH_3), 11.4 (CH_3 indole), 25.7 (CH_2), 40.7 (NCH_3), 58.5 (C-2), 73.3 (C-5), 110.6 (C-7 indole), 113.2 (C-4), 118.6 (C≡N), 118.9 (C-4 indole), 119.8 (C-6 indole), 121.5 (C-5 indole), 123.7 (C-3), 127.0 (C-3 indole), 127.6 (C-3a indole), 133.2 (C-2 indole), 135.4 (C-7a indole), 146.2 (C-6). IR ($CHCl_3$) : 3464 (N-H), 2240 (C≡N). UV, λ_{max} nm (logϵ) : 215 (4.51), 272 (3.94), 279 (3.93), 345 (3.60). MS (m/z, %) : 277 (M^+, 9), 276 (12), 248 (22), 130 (100). On elution with hexanes/ethyl acetate (1:3), product **8a** (51%) was obtained.

Methyl 3-Ethyl-1-methyl-2-(2-methyl-3-indolyl)-1,2-dihydropyridine-5-carboxylate (9b). Operating as above, essentially pure product **9b** (95%) was obtained. ^{1}H NMR : 0.92 (t, J=7.3 Hz, 3H, CH_3), 1.69 (m, 2H, CH_2), 2.39 (s, 3H, CH_3 indole), 2.65 (s, 3H, NCH_3), 3.76 (s, 3H, OCH_3), 5.39 (s, 1H, H-2), 6.26 (s, 1H, H-4), 7.00-7.21 (m, 2H, indole), 7.11(d, J=7.1 Hz, 1H, H-7 indole), 7.35 (s, 1H, H-6), 7.58 (d, J=7.2 Hz, 1H, H-4 indole), 8.45 (bs, 1H, NH). ^{13}C NMR : 11.6 (CH_3), 12.0 (CH_3 indole), 26.6 (CH_2), 41.6 (NCH_3), 51.3 (OCH_3), 59.8 (C-2), 94.8 (C-5), 111.4 (C-3 indole), 111.5 (C-7 indole), 114.8 (C-4), 119.7 (C-4 indole), 120.3 (C-5 indole), 121.9 (C-6 indole), 126.9 (C-3), 127.9 (C-3a indole), 134.2 (C-2 indole), 136.4 (C-7a indole), 146.9 (C-6),169.0 (C=O). IR (KBr) : 3392 (N-H), 1650 (C=O), 1592, 1459, 1440 (C=C). UV, λ_{max} nm (logϵ) : 203 (5.45), 218 (5.47), 271 (5.08), 353 (4.19), 371 (4.11). MS (m/z, %) : 310 (M^+, 40), 295 (6), 282 (100), 251 (30), 180 (73). An analytical sample was obtained by column chromatography (elution with hexanes/ethyl acetate 1:2). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.55; H, 7.10; N, 9.03. Found: C, 73.19; H, 6.77; N, 8.83.

(2*RS*,6*RS*,12*RS*)-12-Ethyl-3-methyl-1,2,3,6-tetrahydro-2,6-methanoazocino[4,5-*b*]indole-5-carbonitrile (11a). To a solution of 2-methylindole (1g, 7.6 mmol) in anhydrous THF (40 ml) at -70°C was added n-BuLi (1.6M, 5ml, 8 mmol), and the resulting solution stirred at this temperature for 15 min. Carbon dioxide gas (dried with $CaCl_2$) was passed into the solution at -70°C for 10 min. The solvent was removed at ca. 0°C under reduced pressure. The flask was flushed with argon, and anhydrous THF (50 ml) was added. The solution was cooled at -70°C, flushed with argon for 5 min, and *tert*-BuLi (1.7M, 5 ml, 8.3 mmol) was added. The solution was stirred at -20°C for 45 min and cooled again at -70°C, and pyridinium salt **2b** (2g, 7.2 mmol) was added all at once. The resulting suspension was stirred for 1h at -70°C, and then allowed to warm at -20°C and stirred for 1h. Enough of a saturated benzene solution of dry HCl was added dropwise to bring the pH to 2.5-3, and the mixture was stirred for 1.5 h at -10°C. The reaction mixture was poured into saturated aqueous sodium carbonate and extracted with ethyl acetate. Evaporation of the dried organic extracts gave a residue wich was chromatographed over silica-gel. Elution with hexanes-ethyl acetate (1:5) gave **11a** (150 mg, 7%). ^{1}H NMR : 0.94 (t, J=7.5 Hz, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.95 (m, 1H, H-12), 2.80-3.00 (cs, 2H, H-1); 2.88 (s, 3H, N-CH_3), 3.50 (bs, 1H, H-6), 3.62 (d, J=10.6 Hz, 1H, H-2), 6.46 (s, 1H, H-4), 7.08-7.26 (m, 3H, indole), 7.65 (m, 1H, H-7), 8.01 (bs, 1H, NH). ^{13}C NMR : 12.0 (CH_3), 21.8 (CH_2), 24.6 (C-1), 29.4 (C-6), 38.9 (C-12), 41.1 (NCH_3), 55.7 (C-2), 78.9 (C-5), 110.6 (C-10), 113.7 (C≡N), 118.4 (C-7), 119.7 (C-8), 121.6 (C-9), 123.5 (C-6a), 126.6 (C-6b), 129.0 (C-11a), 136.5 (C-10a), 146.2 (C-4). IR

(KBr) : 3400 (N-H), 2190 (C≡N), 1610 (C=C), UV, λ_{max} nm (logϵ): 223 (4.4), 270 (4.1). MS (m/z, %) : 277 (M^+, 17), 248 (5), 193 (22), 119 (18), 70 (38), 42 (100).

Addition of Lithium 2-Lithiomethylindole-1-carboxylate (10) to Pyridinium Salt 2c. Operating as above, from 2-methylindole (600 mg, 4.6 mmol), n-BuLi (1.6 M, 4 ml, 6.4 mmol), carbon dioxide, tert-BuLi (1.7 M, 3.8 ml, 6.4 mmol), pyridinium salt **2c** (1.8 g, 6 mmol), and a saturated benzene solution of dry HCl, a crude was obtained which was chromatographed over silica-gel. On elution with hexanes-ethyl acetate (1:1), **methyl (1*RS*,5*RS*,12*SR*)-12-ethyl-2-methyl-1,2,5,6-tetrahydro-1,5-methanoazocino[4,3-*b*]indole-4-carboxylate (12)** (80 mg, 6%) was obtained. ^{1}H NMR : 0.96 (t, J=7.1 Hz, 3H, CH_3), 1.32 (m, J=7.1 and 3.5 Hz, 2H, CH_2), 1.97 (m, 1H, H-12), 2.80 (dd, J=16.4 and 1.5 Hz, 1H, H-6), 2.98 (dd, J=16.4 and 4.8 Hz, 1H, H-6), 3.09 (bs, 1H, H-5), 3.13 (s, 3H, NCH_3), 3.66 (s, 3H, OCH_3), 4.20 (bs, 1H, H-1), 7.00-7.35 (m, 3H, indole), 7.21 (s, 1H, H-3), 7.58 (m, 1H, H-8), 8.15 (bs, 1H, NH). ^{13}C NMR : 12.1 (CH_3), 22.0 (CH_2), 26.9 (C-6), 28.5 (C-5), 39.4 (C-12), 42.3 (NCH_3), 50.4 (OCH_3), 53.0 (C-1), 99.9 (C-4), 110.8 (C-8), 111.0 (C-11b), 117.3 (C-11), 119.6 (C-10), 121.0 (C-9), 121.2 (C-11a), 135.4 (C-6a), 136.2 (C-7a), 146.2 (C-3), 168.6 (C=O). IR ($CHCl_3$) : 3465 (N-H), 1665 (C=O), 1609 (C=C). UV, λ_{max} nm (logϵ) : 206 (4.3), 221 (4.4), 282 (4.1), 290 (4.0), 304 (3.9). MS (m/z, %) : 310 (M^+, 38), 249 (26), 196 (40), 180 (96), 168 (53), 128 (43), 42 (100). On elution with hexanes- ethyl acetate (4:6), **methyl (2*RS*,5*SR*,6*RS*)-5-ethyl-12-methyl-1,2,5,6-tetrahydro-2,6-iminocycloocta[*b*]indole-3-carboxylate (13)** (7 mg, 0.5%) was obtained. ^{1}H NMR : 1.20 (t, J=7.6 Hz, 3H, CH_3), 1.55 (m, 2H, CH_2), 2.28 (m, 1H, H-5), 2.48 (s, 3H, NCH_3), 2.55 (bd, J=15.1 Hz, 1H, H-1), 3.18 (dd, J=15.1 and 5.0 Hz, 1H, H-1), 3.72 (s, 3H, OCH_3), 3.96 (bs, 1H, H-6), 4.08 (dd, J=5.0 and 1.4 Hz, 1H, H-2), 6.93 (d, J=4.5 Hz, 1H, H-4), 7.00-7.31 (m, 3H, indole), 7.38 (m, 1H, H-10), 7.85 (bs, 1H, NH). ^{13}C NMR : 12.7 (CH_3), 21.0 (CH_2), 26.0 (C-1), 40.4 (NCH_3), 45.7 (C-5), 51.9 (OCH_3), 52.6 (C-2), 54.6 (C-6), 110.9 (C-10), 117.4 (C-7), 119.4 (C-8), 121.3 (C-9), 142.9 (C-4). IR ($CHCl_3$) : 3450 (N-H), 1707 (C=O). UV, λ_{max} nm (logϵ) : 221 (4.2), 267 (3.6), 299 (3.4). MS (m/z, %) : 310 (M^+, 17), 183 (100), 180 (32), 128 (21), 43 (70). On elution with hexanes-ethyl acetate (3:7), **methyl (2*RS*,6*RS*,12*RS*)-12-ethyl-3-methyl-1,2,3,6-tetrahydro-2,6-methanoazocino[4,3-*b*]indole-5-carboxylate (11b)** (90 mg, 6%) was obtained. ^{1}H NMR : 0.96 (t, J=7.3 Hz, 3H, CH_3), 1.39 (q, J=7.3 Hz, 2H, CH_2), 1.91 (bs, 1H, H-12), 2.80-3.00 (m, 2H, H-1), 3.03 (s, 3H, NCH_3), 3.51 (bs, 1H, H-6), 3.69 (s, 3H, OCH_3), 4.05 (bs, 1H, H-2), 7.00-7.12 (m, 2H, indole), 7.21 (s, 1H, H-4), 7.25 (m, 1H, H-10), 7.75 (bs, 1H, NH), 7.85 (m, 1H, H-7). ^{13}C NMR : 12.2 (CH_3), 22.2 (CH_2), 24.9 (C-1), 27.0 (C-6), 39.5 (C-12), 41.3 (NCH_3), 50.4 (OCH_3), 56.1 (C-2), 101.6 (C-5), 110.3 (C-10), 119.4 (C-8), 119.8 (C-7), 121.3 (C-9), 145.4 (C-4). IR ($CHCl_3$) : 3472 (N-H), 1665 (C=O), 1609 (C=C). UV, λ_{max} nm (logϵ) : 203 (3.9), 225 (4.0), 281 (3.7), 302 (3.5). MS (m/z, %) : 310 (M^+, 51), 194 (42), 180 (55), 167 (83), 152 (52), 85 (42), 70 (100).

Acknowledgements. Financial support from DGICYT (Spain) through project PB 88-0316 is gratefully acknowledged. One of us (T.G.) thanks the Fundació Pedro i Pons for a fellowship. Dr. M. Rubiralta is thanked for the gift of a starting material.

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