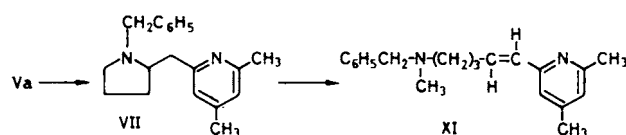


pyrrolidinylmethyl)-4,6-dimethylpyridine (VII) (8% yield) resulting from reduction of the pyrrole ring by diborane (16) was isolated as a by-product. This compound was also found in trace amounts in the crude VIa obtained by reduction in diglyme. Its nmr spectrum showed only two signals in the aromatic region at δ 6.84 (2H) and δ 7.33 (5H) due to the pyridine and benzene protons, respectively. The magnetically non-equivalent *N*-methylene protons (17) appeared as two doublets ($J = 14$ Hz, geminal coupling) at δ 3.27 and 4.06.

When reduction of ketone Va was carried out by the operatively easier Wolff-Kishner procedure, the pyrrolylmethylpyridine VIa was obtained in comparative yield to that of the diborane reduction. Methiodide VIIIa was obtained by quaternization of the pyridine VIa with methyl iodide. Its nmr spectrum showed a singlet at δ 4.11 due to the *N*-methyl group. Sodium borohydride reduction in methanolic solution of methiodide VIIIa afforded a mixture of four isomeric 2-(2-pyrrolylmethyl)tetrahydropyridines (*cis*- and *trans*-IXa and *cis*- and *trans*-Xa) in approximately equimolecular ratio (glc), from which isomers

trans-IXa and *cis*-Xa were separated by column chromatography. Structural and stereochemical elucidation for these tetrahydropyridines was carried out by proton magnetic resonance and spin-decoupling experiments. Signals assignment was achieved on the basis of two criteria: the downfield shift of the groups in a *cis* relationship with the tetrahydropyridine nitrogen lone pair (18) and the vinyl proton shielding in Δ^3 -2-arylmethyltetrahydropyridines with respect to its Δ^4 -isomers (19).



Scheme II

From one reduction attempt of VIIIa, besides the above tetrahydropyridines, a small amount of *E*-2-[5-(benzylmethylamino)-1-penten-1-yl]-4,6-dimethylpyridine (XI) was isolated. This compound arises from the pyrrolidine VII which accompanied pyrrolylmethyl pyridine VIa prepared

Table I

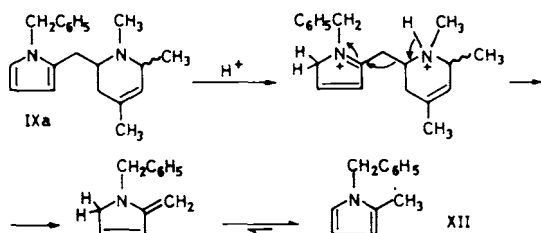
Analyses

| Compound No. | M.p. (°C) (solvent) (a) | Formula | Carbon % | | Hydrogen % | | Nitrogen % | | Halogen % | |
|-----------------------|-------------------------|---|----------|-------|------------|-------|------------|-------|-----------|-------|
| | | | Calcd. | Found | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| Ib (picrate) | 173-175 (E) | C ₁₉ H ₂₃ N ₅ O ₇ | 52.65 | 52.74 | 5.35 | 5.28 | 16.16 | 15.94 | | |
| Va (hydrochloride) | 119-121 (A) | C ₁₉ H ₁₉ ClN ₂ O | 66.18 | 66.24 | 6.14 | 6.03 | 8.12 | 8.12 | 10.30 | 10.56 |
| Vb (picrate) | 153-155 (E) | C ₁₈ H ₁₅ N ₅ O ₈ | 50.36 | 50.52 | 3.52 | 3.54 | 16.31 | 16.32 | | |
| VIa (hydrochloride) | 163-165 (A) | C ₁₉ H ₂₁ ClN ₂ | 72.94 | 73.07 | 6.77 | 6.94 | 8.96 | 8.99 | 11.33 | 11.33 |
| VIb (picrate) | 128-130 (E) | C ₁₈ H ₁₇ N ₅ O ₇ | 52.05 | 52.05 | 4.13 | 4.16 | 16.86 | 16.89 | | |
| VII (dipicrate) | 205-206 (E-A) | C ₃₁ H ₃₀ N ₈ O ₁₄ | 50.41 | 50.15 | 4.09 | 4.12 | 15.17 | 14.90 | | |
| VIIIa | 171-172 (A) | C ₂₀ H ₂₃ IN ₂ | 57.42 | 57.30 | 5.54 | 5.45 | 6.70 | 6.65 | 30.34 | 30.33 |
| VIIIb | 212-214 (A) | C ₁₃ H ₁₇ IN ₂ | 47.58 | 47.31 | 5.22 | 4.97 | 8.54 | 8.66 | 38.67 | 38.43 |
| IXb (picrate) | 119-120 (E) | C ₁₉ H ₂₃ N ₅ O ₇ | 52.65 | 52.68 | 5.35 | 5.24 | 16.16 | 16.19 | | |
| <i>cis</i> -Xa (b) | - (c) | C ₂₀ H ₂₆ N ₂ | 81.58 | 81.85 | 8.90 | 8.81 | 9.52 | 9.59 | | |
| XI (dipicrate) | 181-183 (E) | C ₃₂ H ₃₂ N ₈ O ₁₄ | 51.07 | 51.10 | 4.29 | 4.22 | 14.89 | 14.76 | | |
| XII | - (d) | C ₁₂ H ₁₃ N | 84.17 | 84.30 | 7.65 | 7.62 | 8.18 | 7.99 | | |
| XV | 108-109 (F) | C ₁₇ H ₁₆ N ₂ O | 77.24 | 77.03 | 6.10 | 6.14 | 10.60 | 10.30 | | |
| XVI | 84-85 (F) | C ₁₇ H ₁₈ N ₂ | 81.56 | 81.20 | 7.24 | 7.11 | 11.18 | 11.03 | | |
| XVII | 147-149 (F) | C ₁₇ H ₁₈ N ₂ O | 76.66 | 76.80 | 6.81 | 6.93 | 10.51 | 10.47 | | |
| XVIII (picrate) | 145-147 (E) | C ₂₃ H ₂₃ N ₅ O ₇ | 57.37 | 57.28 | 4.81 | 5.04 | 14.54 | 14.27 | | |
| XIX | 216-217 (A-E) | C ₁₈ H ₂₁ N ₂ | 55.11 | 55.22 | 5.39 | 5.42 | 7.14 | 7.11 | 32.35 | 32.24 |
| XX (oxalate) | 154-156 (E) | C ₂₀ H ₂₆ N ₂ O ₄ | 67.06 | 66.86 | 7.25 | 7.15 | 7.81 | 7.91 | | |
| XXII | 199-200 (A) | C ₁₈ H ₁₉ IN ₂ O | 53.20 | 52.90 | 4.71 | 4.71 | 6.99 | 6.66 | 31.25 | 31.07 |
| XXIII (oxalate) | 149-151 (E) | C ₂₀ H ₂₄ N ₂ O ₅ | 64.51 | 64.49 | 6.45 | 6.55 | 7.52 | 7.47 | | |
| XXIVa (hydrochloride) | 218-220 (E) | C ₁₈ H ₂₅ ClN ₂ O ₂ | 64.18 | 63.88 | 7.40 | 7.38 | 8.31 | 8.10 | 10.52 | 10.41 |
| XXIVb (hydrochloride) | 236-238 (A) | C ₁₇ H ₂₃ ClN ₂ O ₂ | 63.45 | 63.61 | 6.88 | 7.16 | 8.70 | 8.77 | 11.01 | 11.01 |
| XXVI | 187-188 (A-F) (e) | C ₁₈ H ₁₆ N ₂ | 82.73 | 82.75 | 6.16 | 6.16 | 10.17 | 10.18 | | |
| XXVII | 175-176 (A-F) (f) | C ₂₇ H ₂₇ N ₃ | 82.41 | 82.30 | 6.91 | 7.02 | 10.67 | 10.71 | | |
| XXVIII | 160-162 (A) | C ₂₆ H ₂₅ N ₃ | 82.28 | 82.04 | 6.39 | 6.66 | 11.07 | 11.04 | | |
| XXIX | 168-170 (A) | C ₁₆ H ₁₈ N ₄ O | 68.06 | 68.35 | 6.42 | 6.45 | 19.84 | 19.78 | | |

(a) Solvents: A = acetone, E = ethanol, F = ether. (b) Analysis from the mixture of isomers *cis*-IXa, *trans*-IXa, *cis*-Xa and *trans*-Xa: Calcd., C, 81.58, H, 8.90, N, 9.52. Found: C, 81.49, H, 8.92, N, 9.61. (c) B.p. 150-160° (0.3 mm). (d) B.p. 120° (0.1 mm). (e) Lit. (38) 186-188°. (f) Lit. 178° (39a), 173-174° (39b).

by diborane reduction. Quaternization of the pyrrolidine nitrogen atom of VII and further Hofmann elimination in the basic medium of the sodium borohydride reduction led to the *trans*-alkene XI (scheme II). Its ir spectrum showed an absorption at 1670 cm^{-1} , due to the alkene double bond, while its nmr spectrum showed, as characteristic signals, a singlet at $\delta\ 3.43$ due to the benzylic methylene protons and a multiplet (AB part of an ABX_2 system) at $\delta\ 6.35$ and 6.70 for two olefinic protons, whose coupling constant ($J_{AB} = 15\text{ Hz}$) indicates a *trans* substituted double bond.

Treatment of the tetrahydropyridine mixture, *cis*-IXa, *trans*-IXa, *cis*-Xa and *trans*-Xa, with proton or Lewis acids (20) did not afford in any case the pyrrolomorphan Ia. Strong proton acids, such as hydrobromic acid and phosphoric acid, or Lewis acids such as aluminum trichloride or stannic tetrachloride, common reagents in this kind of cyclizations, caused pyrrole decomposition. Acetic acid and its mixture with trifluoroacetic acid, as well as boron trifluoride etherate, promoted fragmentation of the starting tetrahydropyridines to 1-benzyl-2-methylpyrrole (XII) (Scheme III). The nmr spectrum of XII showed two singlets at $\delta\ 2.09$ and 4.96 due to the methyl and methylene groups, respectively, and signals for eight aromatic protons. The formation of pyrrole XII can be interpreted on the basis of the initial protonation of the pyrrole nucleus, more basic than the tetrahydropyridine double bond, and the further fragmentation promoted by the tetrahydropyridine nitrogen atom.

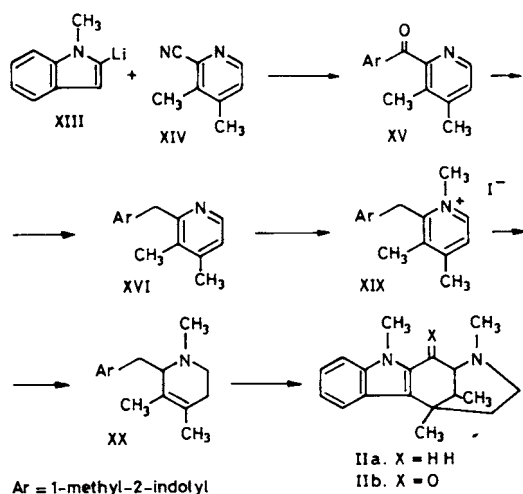


Scheme III

Attempts of cyclization with polyphosphoric acid afforded a complex mixture from which any product could have been separated. The nmr spectra of the crude reaction mixture and those of the fractions obtained by column chromatography showed the absence of benzylic *N*-methylene signals and the presence of singlets in the $\delta\ 3.8$ region, thus suggesting a benzyl group migration from the pyrrole nitrogen atom to other ring positions (21). On the other hand, doublets at $\delta\ 0.3$ - 0.4 , characteristic of methyl groups in cyclization products from related 6-methyl-2-arylmethyltetrahydropyridines (1,22) were also observed. This results encouraged us to investigate tetrahydropyridine cyclizations upon *N*-methyl substituted pyrrole systems, expecting that the lower migratory aptitude of the methyl group could avoid the above rearrangement.

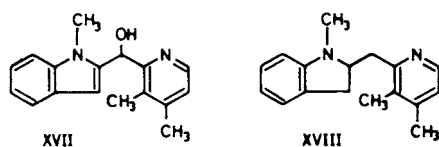
The elaboration of the required 2-(1-methyl-2-pyrrolyl-methyl)tetrahydropyridines was carried out by a similar route to the preceding one (Scheme I). Thus, condensation between *N*-methylpyrrole (IVb) and 2-cyano-4-methylpyridine (IIIb) (11) in boron trifluoride etherate and dichloromethane solution (23) in presence of dry hydrochloric acid led to the pyridyl pyrrolyl ketone Vb (ir: 1625 cm^{-1}) in good yield. The Wolff-Kishner reduction of Vb afforded the pyrrolylmethylpyridine VIb, whose methylene group was observed in the nmr spectrum at $\delta\ 4.00$. The quaternization of VIb with methyl iodide led to the pyridinium salt VIIb, whose sodium borohydride reduction afforded a mixture of two isomeric tetrahydropyridines IXb and Xb, in which the Δ^4 -isomer predominated (6.6:1, glc) as expected in borohydride reductions of 1,2,4-trisubstituted pyridinium salts (24). The major isomer IXb was isolated by fractional crystallization of its picrate salt. Its nmr spectrum showed as characteristic signals three singlets at $\delta\ 1.66$, 2.34 and 3.56 due to the methyl groups on 4 and 1 positions of the tetrahydropyridine ring and on the pyrrole nitrogen atom, respectively, and one broad singlet at $\delta\ 5.35$ due to the vinylic proton (25). Treatment of the IXb and Xb tetrahydropyridine mixture with polyphosphoric acid promoted the cyclization upon the 3 position of the pyrrole nucleus leading to a single pyrrolomorphan Ib (systematic name: 1,4,7-trimethyl-4,5,6,7,8,9-hexahydro-4,8-methanopyrrolo[2,3-*d*]azocine). Its nmr spectrum showed two doublets ($J = 3.3\text{ Hz}$) in the aromatic region due to the α and β pyrrole hydrogens, thus indicating a cyclization product, and three singlets at $\delta\ 1.20$, 2.29 and 3.46 due to the methyl groups on 4-, 7- and 1-positions, respectively. Therefore, cyclization of 2-(2-pyrrolylmethyl)tetrahydropyridines is a suitable method for the preparation of pyrrolo[3,2-*f*]morphans.

In order to apply this method to the synthesis of indolo[3,2-*f*]morphans II, 2-(2-indolylmethyl)tetrahydropyridine XX was prepared in a similar way. (Scheme IV). Thus, condensation between 2-lithio-1-methylindole (XIII) (26) and 2-cyano-3,4-dimethylpyridine (XIV) (5c) followed by acid hydrolysis led to the indolyl pyridyl ketone XV (ir: 1640 cm^{-1}) in good yields. Its reduction under Wolff-Kishner conditions afforded the 2-(pyridylmethyl)indole XVI, whose nmr spectrum showed as more characteristic signal a singlet at $\delta\ 4.22$ for the interannular methylene group. The best yield (74%) was obtained when the hydrazone of ketone XV was previously formed, water from the reaction medium was removed and potassium hydroxide was added. This procedure avoids the formation of the indolyl pyridyl methanol XVII which is found in a great extent (40%) (27) when the reaction is carried out under usual Huang-Minlon conditions (28). Alcohol XVII shows an ir absorption at 3380 cm^{-1} , as well as a singlet at $\delta\ 5.70$ in its nmr spectrum, due to the methine group.



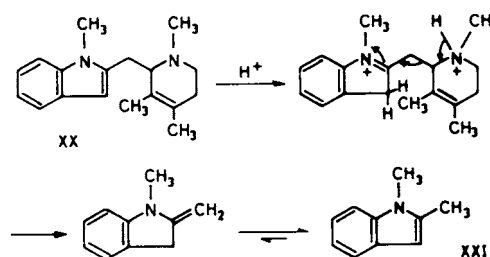
Scheme IV

Alternatively, reduction of 2-indolylketone XV with diborane generated internally in diglyme (14), followed by acetone hydrolysis of the boron complexes (29), led to the 2-pyridylmethylindole XVI in 30% yield, lower than the obtained by the Wolff-Kishner procedure. When the borane reductions were carried out on mild reaction conditions (time and temperature) the indolyl pyridyl methanol XVII was also isolated. On the other hand, when hydrolysis of the boron complexes was effected with hydrochloric acid the pyridylmethylindoline XVIII was also isolated. Its formation is interpreted on the basis of the indole protonation and further reduction by intramolecular hydride transfer from the pyridine-borane adduct (30). In the nmr spectrum of indoline XVIII the absence of the indole β proton and an upfield shift of its N-methyl group were observed.



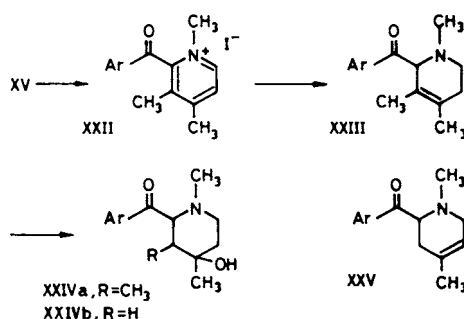
Scheme V

Quaternization of pyridylmethylindole XVI with methyl iodide, followed by borohydride reduction of the resulting methiodide XIX, afforded the desired 2-(2-indolylmethyl)-tetrahydropyridine XX in 77% overall yield. Its nmr spectrum showed characteristic singlets at δ 3.62 and 2.32 for the *N*-methyl groups on the indole and the tetrahydropyridine rings, respectively, and at δ 1.62 and 1.55 for the methyl groups on the double bond. Cyclization attempts in acid media (31) were unsuccessful since 1,2-dimethylindole (XXI) resulting from fragmentation of the starting tetrahydropyridine XX (Scheme VI) was always obtained in high yields.



Scheme VI

This behavior, different from the observed in the cyclization of 2-(3-indolylmethyl)tetrahydropyridines to indolo[2,3-*f*]morphans (8) is interpreted as a consequence of the higher basic character of 1,2-disubstituted indoles in relation to 1,3-disubstituted ones (32). The former present the 3-position widely protonated, what prevents their cyclization and promotes the observed fragmentation. These results suggested us the assay of tetrahydropyridine cyclizations upon the 3-position of 2-acylindoles, whose carbonyl group was expected to avoid indole protonation and subsequent fragmentation reaction. Related cyclizations of iminium salts upon the 3-position of 2-acylindoles have been described (33). On this purpose, the 2-indolyl 2-tetrahydropyridyl ketone XXIII was prepared from the ketone XV by quaternization of the pyridine nitrogen atom followed by borohydride reduction (Scheme VII). Ketone XXIII showed an ir absorption at 1650 cm^{-1} and singlets in its nmr spectrum at δ 1.51, 1.68, 2.30 and 3.98, due to the methyl groups on the double bond, and to tetrahydropyridine and indole *N*-methyl groups, respectively.



Scheme VII

Polyphosphoric acid treatment of the tetrahydropyridyl ketone XXIII did not lead to the indolo[3,2-*f*]morphans IIb but to the 4-piperidinol XXIVa resulting from the double bond hydration. Compound XXIVa showed ir absorptions at 3380 and 1635 cm^{-1} due to the hydroxyl and carbonyl groups, respectively. Its nmr spectrum showed a singlet at δ 1.15 due to the C-4 methyl group, a doublet at δ 0.9 due to the C-3 methyl group and five hydrogens in the aromatic region, indicating therefore the absence of a

cyclization product (34). The formation of the alcohol XXIVa confirms the double bond protonation of the tetrahydropyridine. However, the cyclization does not occur because of the protonation of the conjugated carbonyl group. Similarly, polyphosphoric acid treatment of indolyl tetrahydropyridyl ketone XXV described in a previous work (35), led to 4-piperidinol XXIVb. A similar result has been observed in the cyclization attempts of the 2-furyl 1,4-dimethyl-1,2,3,6-tetrahydro-2-pyridyl ketone (9b). Thus, cyclizations upon the aromatic ring in aryl tetrahydropyridyl ketones do not represent a valid alternative to those in 2-(arylmethyl)tetrahydropyridines.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer model R-24B (60 MHz, tetramethylsilane at δ 0.0 as internal standard) with deuteriochloroform as a solvent unless otherwise indicated. Chemical shifts are reported as δ values in parts per million (ppm). The infrared spectra were determined on a Perkin-Elmer model 577 spectrophotometer. The glc were run isothermally on a Perkin-Elmer F-11 chromatograph 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. Elemental analyses (Table I) were performed by Instituto de Química Orgánica Aplicada de Catalunya, Barcelona.

1-Benzyl-2-pyrrolyl 4,6-Dimethyl-2-pyridyl Ketone (Va).

To a stirred and ice-bath cooled solution of 9.0 g. (68 mmoles) of 2-cyano-4,6-dimethylpyridine (IIIa) (11) and 13.4 g. (85 mmoles) of 1-benzylpyrrole (IVa) (12) in 60 ml. of boron trifluoride etherate, 1.0 g. of powdered anhydrous zinc chloride was added and dry hydrogen chloride was bubbled through the mixture for 1 hour. The resulting dark-red solution was allowed to stand at room temperature for 24 hours, poured into ice-water, made alkaline with concentrated sodium hydroxide solution and extracted with chloroform. The organic layers were evaporated and the residue was taken up in 200 ml. of 4*N* hydrochloric acid. The solution was refluxed for 5 minutes, cooled, basified with aqueous sodium hydroxide and extracted with ether. The ethereal layers were dried and the solvent removed under reduced pressure giving 15.5 g. (75% yield) of the ketone Va; nmr: 2.34 (s, 3, C-4 CH₃), 2.57 (s, 3, C-6 CH₃), 5.74 (s, 2, CH₂), 6.30 (dd, 1, pyrrole-C4 H), 7.0;7.6 (m, 10, aromatic).

2(1-Benzyl-2-pyrrolylmethyl)-4,6-dimethylpyridine (VIa).

a) Diborane Reduction.

Sodium borohydride (9.5 g., 0.25 mole) was added portionwise to a stirred solution of 32 g. (0.11 mole) of Va in 200 ml. of dry diglyme. Then, a solution of 50 g. of boron trifluoride etherate in 150 ml. of diglyme was added dropwise (temperature between 5 and 10°). The resulting mixture was stirred at room temperature for 4 hours, the solvent was removed under reduced pressure and the residue was dissolved in 500 ml. of methanol. Hydrochloric acid (6*N*, 100 ml.) was added slowly and the mixture was refluxed for 25 minutes. Methanol was evaporated under vacuum and water (100 ml.) ice (50 g.) and excess of concentrated ammonia were added. The basic solution was extracted with ether and the dried ethereal layers were evaporated leaving an oily residue, which was purified by distillation (b.p. 110°, 0.3 mm) giving 17.9 g. (59% yield) of VIa, nmr 2.13 (s, 3, C-4 CH₃), 2.42 (s, 3, C-6 CH₃), 4.02 (s, 2, interannular CH₂), 5.07 (s, 2, N-CH₂), 6.0-6.3 (m, 2, pyrrole C-3 H and C-4 H), 6.68-7.35 (m, 8, aromatic).

When the reduction was carried out in tetrahydrofuran as a solvent, a mixture of VIa (35% yield) and pyrrolidine VII (10% yield) was obtained. Compound VII was isolated by silica gel column chromatography

(chloroform-acetone 8:2 as eluent) and purified by vacuum distillation (b.p. 210°, 0.3 mm); nmr: 1.6-1.8 (m, 4, pyrrolidine C-3 H₂ and C-4 H₂), 2.22 (s, 3, C-4 CH₃), 2.48 (s, 3, C-6 CH₃), 2.0-3.3 (m, 5, pyrrolidine C-2 H and C-5 H₂ and interannular CH₂), 3.27 (d, J = 14 Hz, 1, N-CH₂), 4.06 (d, J = 14 Hz, 1, N-CH₂), 6.84 (broad singlet, 2, pyridine), 7.33 (broad singlet, 5, benzene).

b) Wolff-Kishner Reduction.

Ketone Va (70 g., 0.24 mole) and 80% hydrazine hydrate (45 g., 0.72 mole) were added to a solution of 47 g. (0.84 mole) of potassium hydroxide in 330 ml. of ethylene glycol. The resulting mixture was heated under reflux for 2 hours and then the whole water and the exceeding hydrazine hydrate were distilled to raise the temperature to 190°, and the remaining solution was refluxed for 4 hours. The reaction mixture was poured over 1.5 liters of ice-water and extracted several times with ether. The ethereal extracts were washed with water, dried and the solvent removed. The distillation of the oily residue gave 37.8 g. (57% yield) of VIa.

2(1-Benzyl-2-pyrrolylmethyl)-1,4,6-trimethylpyridinium Iodide (VIIIa).

A solution of 46.8 g. (0.17 mole) of VIa and 125 g. (0.88 mole) of methyl iodide in 250 ml. of anhydrous acetone and 40 ml. of dry benzene was gently refluxed for 5 hours. The reaction mixture was allowed to stand at 5° for 24 hours and the methiodide VIIIa (58.2 g., 82% yield) was collected by filtration; nmr: 2.27 (s, 3, C-4 CH₃), 2.76 (s, 3, C-6 CH₃), 4.11 (s, 3, N-CH₃), 4.43 (s, 2, interannular CH₂), 5.20 (s, 2, N-CH₂), 5.9-6.2 (m, 2, pyrrole C-3 H and C-4 H), 6.8-7.0 (m, 2, pyrrole C-5 H and pyridine C-3 H), 7.15 (s, 5, benzene), 7.50 (s, 1, pyridine C-5 H).

2(1-Benzyl-2-pyrrolylmethyl)-1,4,6-trimethyltetrahydropyridines (IXa and Xa).

To an ice bath cooled solution of 6.3 g. (15 mmoles) of VIIIa in 70 ml. of methanol, 1.10 g. (30 mmoles) of sodium borohydride were added portionwise. The resulting solution was refluxed for 3 hours, the solvent was removed at reduced pressure, 150 ml. of water were added and the aqueous basic solution was extracted with ether. The evaporation of the dried ethereal layers afforded 2.85 g. (65% yield) of an oil which on glc showed four peaks of approximately equal areas. Tetrahydropyridines *trans*-IXa and *cis*-Xa were isolated by silica gel column chromatography, on elution with chloroform-methanol (99:1) and (97:3), respectively; nmr: (*trans*-IXa) 0.98 (d, J = 6.8 Hz, 3, C-6 CH₃), 1.60 (s, 3, C-4 CH₃), 1.65-2.00 (m, 2, C-3 H₂), 2.23 (s, 3, N-CH₃), 2.3-3.2 (m, 4, C-6 H + C-2 H + interannular CH₂), 5.09 (s, 2, N-CH₂), 5.32 (broad singlet, 1, =CH), 5.95-6.25 (m, 2, pyrrole C-3 H and C-4 H); 6.65 (t, J = 2 Hz, 1, pyrrole C-5 H), 6.9-7.4 (m, 5, benzene); nmr: (*cis*-Xa) 1.11 (d, J = 6.2 Hz, 3, C-6 CH₃), 1.65-2.00 (m, 2, C-5 H₂), 2.30 (s, 3, N-CH₃), 2.1-2.5 (m, 1, C-6 H), 2.6-3.25 (m, 3, C-2 H + interannular CH₂), 5.29 (broad singlet, 1, =CH), C-4 CH₃, N-CH₂ and aromatic signals as in *trans*-IXa.

Tetrahydropyridines *cis*-IXa and *trans*-Xa could not be completely separated by column chromatography. The nmr spectra of the enriched mixtures allowed the following partial assignments; nmr: (*cis*-IXa) 1.20 (d, J = 5.0 Hz, 3, C-6 CH₃), 2.23 (s, 3, N-CH₃), 5.32 (broad singlet, 1, =CH), aromatic signals as in *trans*-IXa; (*trans*-Xa) 1.03 (d, J = 6.6 Hz, 3, C-6 CH₃), 2.21 (s, 3, N-CH₃), 5.29 (broad singlet, 1, =CH), aromatic signals as in *trans*-IXa.

When the reaction was carried out with a non-recrystallized sample of methiodide VIIIa, together with the above tetrahydropyridines, a small amount (4% yield) of pyridine XI was isolated; nmr: 1.5-2.0 (m, 2, CH₂-CH₂-CH₂), 2.14 (s, 3, C-4 CH₃), 2.22 (s, 3, C-6 CH₃), 2.05-2.60 (m, 4, CH₂-CH₂-CH₂), 3.42 (s, 2, N-CH₂-Ar), 6.40 (d, J = 15 Hz, 1, =CH), 6.45-6.9 (m, 3, =CH and pyridine C-3 H and C-5 H), 7.23 (s, 5, benzene).

Attempts of Cyclization of Tetrahydropyridines IXa and Xa: 1-Benzyl-2-methylpyrrole (XII).

A solution of 0.96 g. (3.2 mmoles) of the mixture of tetrahydropyridines *cis*-IXa, *trans*-IXa, *cis*-Xa and *trans*-Xa in 25 ml. of boron trifluoride etherate was refluxed for 3 hours. The reaction mixture was poured over ice-water, rendered basic with 50% sodium hydroxide solution and extracted with ether. The evaporation of the dried extracts gave

an oil which was filtered through a silica gel column. On elution with *n*-hexane-benzene (8:2), 0.25 g. (40% yield) of the pyrrole XII were obtained; nmr: 2.09 (s, 3, CH₃), 4.96 (s, 2, CH₂), 5.91 (m, 1, C-4 H), 6.10 (m, 1, C-3 H), 6.60 (m, 1, C-5 H), 6.9-7.4 (m, 5, benzene).

4-Methyl-2-pyridyl 1-Methyl-2-pyrrolyl Ketone (Vb).

A stream of dry hydrogen chloride was bubbled for 1 hour through a solution of 1 g. (8.4 mmoles) of 2-cyano-4-methylpyridine (IIIb) (11) and 1.2 g. (14.8 mmoles) of *N*-methylpyrrole (IVb) in 20 ml. of boron trifluoride etherate and 20 ml. of anhydrous dichloromethane (temperature between 0-5°). The resulting mixture was allowed to stand at room temperature for 24 hours, poured over ice, rendered basic with 50% sodium hydroxide solution and extracted with ether. The organic layers were evaporated and the residue dissolved in 50 ml. of 2*N* hydrochloric acid. This solution was refluxed for 3 minutes, cooled and basified with 2*N* sodium hydroxide solution. The extraction with ether gave 1.54 g. (75% yield) of Vb; nmr (carbon tetrachloride): 2.36 (s, 3, C-4 CH₃), 4.00 (s, 3, N-CH₃), 6.10 (dd, 1, pyrrole-C-4 H), 6.88 (dd, 1, pyrrole-C-3 H), 7.20 (d, J = 5 Hz, 1, pyridine-C-5 H), 7.62 (dd, 1, pyrrole-C-5 H), 7.84 (s, 1, pyridine-C-3 H), 8.56 (d, J = 5 Hz, 1, pyridine-C-6 H).

4-Methyl-2-(1-methyl-2-pyrrolylmethyl)pyridine (VIb).

To a solution of 1.5 g. (26 mmoles) of potassium hydroxide in 15 ml. of ethylene glycol, 1.5 g. (7.5 mmoles) of Vb and 1.5 g. (24 mmoles) of 80% hydrazine hydrate were added. The resulting mixture was refluxed for 1 hour, distilled to raise the temperature to 190° and then refluxed again for 3 hours. The reaction mixture was poured over ice-water and extracted with ether. The ethereal layer was washed with water, dried and the solvent removed, affording 0.93 g. (67% yield) of VIb, nmr (carbon tetrachloride): 2.22 (s, 3, C-4 CH₃), 3.44 (s, 3, N-CH₃), 4.00 (s, 2, CH₂), 5.92 (m, 2, pyrrole-C-3 H and C-4 H), 6.46 (m, 1, pyrrole-C-5 H), 6.84 (s, 1, pyridine-C-3 H), 6.90 (d, J = 5.5 Hz, 1, pyridine-C-5 H), 8.36 (d, J = 5.5 Hz, 1, pyridine-C-6 H).

1,4-Dimethyl-2-(1-methyl-2-pyrrolylmethyl)pyridinium Iodide (VIIIb).

To a solution of 5.7 g. (30 mmoles) of VIb in 45 ml. of anhydrous acetone and 9 ml. of dry benzene, 22.7 g. (160 mmoles) of methyl iodide were added. The resulting mixture was refluxed for 3 hours and allowed to stand at room temperature for 24 hours. The methiodide VIIIb (9.0 g., 90% yield) was obtained by filtration; nmr (hexadeuteriodimethylsulfoxide): 2.53 (s, 3, C-4 CH₃), 3.56 (s, 3, pyrrole-N-CH₃), 4.32 (s, 3, N-CH₃), 4.56 (s, 2, CH₂), 5.86 (m, 1, pyrrole-H β), 6.02 (m, 1, pyrrole-H β), 6.86 (m, 1, pyrrole-H α), 7.38 (broad singlet, 1, pyridine-C-3 H), 7.93 (broad doublet, 1, pyridine-C-5 H), 9.00 (d, J = 6.2 Hz, 1, pyridine-C-6 H).

1,4-Dimethyl-2-(1-methyl-2-pyrrolylmethyl)tetrahydropyridines (IXb and Xb).

To an ice-bath cooled solution of 2.5 g. (7.6 mmoles) of VIIIb in 50 ml. of methanol, 1.0 g. (26.4 mmoles) of sodium borohydride was added portionwise. The resulting solution was refluxed for 3 hours, the solvent was removed at reduced pressure, 100 ml. of water were added and the aqueous basic solution was extracted with ether. The evaporation of the dried ethereal layers afforded 1.12 g. (78% yield) of an oil which on glc showed two peaks of relative areas 6.6:1. The major isomer, IXb, was obtained and purified by fractional crystallization of its picrate, nmr (carbon tetrachloride): 1.66 (s, 3, C-4 CH₃), 1.88 (broad signal, 2, C-3 H₂), 2.34 (s, 3, N-CH₃), 2.54-3.30 (m, 5, C-6 H₂ + C-2 H + interannular CH₂), 3.56 (s, 3, pyrrole-N-CH₃), 5.35 (broad singlet, 1, =CH), 5.72-6.00 (m, 2, pyrrole-H β), 6.44 (m, 1, pyrrole-H α).

1,4,7-Trimethyl-4,5,6,7,8,9-hexahydro-4,8-methanopyrrolo[2,3-*d*]azocine (Ib).

Polyphosphoric acid (50 g.) and 1.12 g. (5.5 mmoles) of the mixture of tetrahydropyridines IXb and Xb were stirred at 130-140° for 6 hours. The cooled solution was poured into an excess of concentrated ammonium hydroxide-ice and extracted with ether. The solvent was removed from the dried extracts leaving an oily residue which was filtered through a silica gel column. On elution with chloroform-methanol (98:2),

0.32 g. (28.5% yield) of Ib were obtained; nmr (carbon tetrachloride): 1.20 (s, 3, C-4 CH₃); 1.1-3.4 (m, 9, alicyclic protons), 2.29 (s, 3, N-7 CH₃), 3.46 (s, 3, N-1 CH₃), 5.67 (d, J = 3.3 Hz, 1, pyrrole-H β), 6.25 (d, J = 3.3 Hz, 1, pyrrole-H α).

3,4-Dimethyl-2-pyridyl 1-Methyl-2-indolyl Ketone (XV).

A solution of 35 g. (0.27 mole) of *N*-methylindole in 130 ml. of ether was added dropwise to a stirred solution of butyllithium in ether (1.46*N*, 180 ml.). The resulting mixture was refluxed for 9 hours, ice cooled, and a solution of 32.5 g. (0.25 mole) of 2-cyano-3,4-dimethylpyridine (XIV) (5c) in 150 ml. of benzene was slowly added. The solution was stirred at room temperature for 13 hours and then extracted twice with 350 ml. portions of 10% hydrochloric acid. The aqueous layers were refluxed for 30 minutes, cooled and a stream of ammonia was bubbled through the solution until a slightly basic pH. On standing, the ketone XV precipitated and it was purified by recrystallization in anhydrous ether, affording 44.8 g. (70.7% yield); nmr: 2.25 (s, 3, CH₃), 2.31 (s, 3, CH₃), 4.18 (s, 3, N-CH₃), 6.81 (s, 1, indole-C-3 H), 7.0-7.8 (m, 5, pyridine-C-5 H and indole), 8.36 (d, J = 6 Hz, 1, pyridine-C-6 H).

When the condensation was carried out in shorter times and without removing the unreacted indole before the final acid hydrolysis, ketone XV was isolated in 41% yield (silica gel chromatography) together with four other compounds. On elution with benzene, 1,1'-dimethyl-3,3'-biindole (XXVI) was isolated; nmr (carbon tetrachloride): 3.75 (s, 6, CH₃), 7.0-8.0 (m, 8, aromatic), 7.10 (s, 2, indole-C-2 H). In hexadeuteriodimethylsulfoxide solution the last signal appeared at δ 7.63, indicating therefore an indole α -hydrogen (36).

On elution with benzene-chloroform (9:1), *o*-[2,2-bis(1-methyl-3-indolyl)ethyl]-*N*-methylaniline (XXVII, *N*-methylindole trimer) was isolated; nmr: 2.35 (s, 3, NH-CH₃), 2.8-3.1 (broad signal, 1, NH), 3.32 (d, J = 7 Hz, 2, CH₂), 3.62 (s, 6, N-CH₃), 4.80 (t, J = 7 Hz, 1, CH), 6.4-7.6 (m, 14, aromatic), 6.83 (s, 2, indole-C-2 H).

On elution with chloroform-benzene (8:2), (3,4-dimethyl-2-pyridyl)bis(1-methyl-3-indolyl)methane (XXVIII) was isolated; nmr: 2.28 (s, 3, pyridine-CH₃), 2.33 (s, 3, pyridine-CH₃), 3.61 (s, 6, N-CH₃), 6.17 (s, 1, CH), 6.58 (s, 2, indole-C-2 H), 6.8-7.4 (m, 9, aromatic), 8.18 (d, J = 6 Hz, 1, pyridine-C-6 H). The signal at δ 6.58 is shifted at δ 6.84 in hexadeuteriodimethylsulfoxide, indicating therefore an indole α -hydrogen (36).

On elution with chloroform-methanol (1:1), 4-[2-amino-2-(3,4-dimethyl-2-pyridyl)vinyl]-3-methylpyridine-2-carboxamide (XXIX) was isolated, ir: ν NH 3200, 3405, 3300 cm⁻¹, ν C=O 1625 cm⁻¹; nmr: 2.30 (s, 3, CH₃), 2.32 (s, 3, CH₃), 2.63 (s, 3, CH₃), 3.00 (broad singlet, 2, NH₂), 6.00-6.40 (broad signal, 2, CONH₂), 7.18 (d, 1, pyridine-H β), 7.24 (s, 1, =CH), 7.28 (d, 1, pyridine), 8.31 (d, 1, pyridine), 8.60 (d, 1, pyridine). Compound XXIX slowly decomposes giving 3,4-dimethylpyridine-2-carboxamide.

2-(3,4-Dimethyl-2-pyridylmethyl)-1-methylindole (XVI).

a) Wolf-Kishner Reduction.

To a solution of 20 g. (75.7 mmoles) of XV in 200 ml. of diethylene glycol, 7.70 ml. of 80% hydrazine hydrate were added. The resulting solution was refluxed for 1.5 hours, distilled to raise the temperature to 220° and a solution of 10.8 g. (191 mmoles) of potassium hydroxide in 140 ml. of diethylene glycol was added. The resulting mixture was refluxed for 4 hours 30 minutes, cooled, poured over ice-water and extracted with ether. The ethereal layer was washed with water, dried and the solvent was removed giving 14 g. (74% yield) of XVI; nmr: 2.20 (s, 6, C-CH₃), 3.68 (s, 3, N-CH₃), 4.22 (s, 2, CH₂), 6.00 (s, 1, indole-C-3 H), 6.8-7.5 (m, 5, pyridine-C-5 H and indole), 8.2 (d, 1, pyridine-C-6 H).

When the reduction was carried out under usual Huang-Minlon conditions (28), a mixture of pyridine XVI (40.8% yield) and alcohol XVII (40% yield) was obtained; nmr: (XVII) 1.97 (s, 3, C-CH₃), 2.24 (s, 3, C-CH₃), 3.83 (s, 3, N-CH₃), 5.48 (broad signal, 1, OH), 5.70 (s, 1, CH), 6.30 (s, 1, indole-C-3 H), 6.9-7.55 (m, 5, pyridine-C-5 H and indole), 8.35 (d, 1, pyridine-C-6 H).

b) Diborane Reduction.

To an ice-bath cooled solution of 10 g. (37.8 mmoles) of XV and 3.2 g.

(84.7 mmoles) of sodium borohydride in 100 ml. of diglyme, 14 ml. of boron trifluoride etherate dissolved in 60 ml. of diglyme were added dropwise. The resulting mixture was heated at 55° for 8 hours and then poured into 800 ml. of anhydrous acetone. The solution was refluxed for 2 hours, the solvent was removed at reduced pressure and the oily residue was filtered through a silica gel column. On elution with benzene-chloroform (6:4), 3 g. (31% yield) of XVI were obtained. When the above crude reaction mixture was poured into 2N hydrochloric acid and refluxed for 45 minutes, a mixture of compound XVI and indoline XVIII was obtained. Their separation was achieved by column chromatography on elution with benzene-chloroform (6:4) and (2:8), respectively; nmr: (XVIII) 2.23 (s, 6, C-CH₃), 2.72 (s, 3, N-CH₃), 2.75-4.00 (m, 5, indole-C-2 H and C-3 H₂ + interannular CH₂), 6.4-7.2 (m, 5, pyridine-C-5 H and indole), 8.24 (d, 1, pyridine-C-6 H).

1,3,4-Trimethyl-2-(1-methyl-2-indolylmethyl)pyridinium Iodide (XIX).

A solution of 4 ml. (9.12 g., 64.2 mmoles) of methyl iodide in 8 ml. of dry benzene was added portionwise to a stirred solution of 3.98 g. (15.9 mmoles) of XVI in 24 ml. of anhydrous acetone. The mixture was stirred at room temperature for 1 hour, refluxed for 2 hours and then allowed to stand at 5° for 12 hours. The methiodide XIX (5.6 g., 90.5% yield) was obtained by filtration; nmr: 2.40 (s, 3, CH₃), 2.55 (s, 3, CH₃), 3.92 (s, 3, indole-N-CH₃), 4.48 (s, 3, N-CH₃), 4.82 (s, 2, CH₂), 5.51 (s, 1, indole-C-3 H), 6.7-7.6 (m, 4, indole), 7.75 (d, 1, pyridine-C-5 H), 9.15 (d, 1, pyridine-C-6 H).

1-Methyl-2-(1,3,4-trimethyl-1,2,5,6-tetrahydro-2-pyridylmethyl)indole (XX).

To an ice-bath cooled solution of 4.7 g. (10 mmoles) of XIX in 225 ml. of methanol and 25 ml. of water, 0.68 g. (20 mmoles) of sodium hydroxide pellets and 0.83 g. (20 mmoles) of sodium borohydride were slowly added. The resulting solution was refluxed for 6 hours 30 minutes, the methanol was removed at reduced pressure, 100 ml. of water were added and the basic solution was extracted with chloroform. The evaporation of the dried extracts gives an oil which was purified by distillation (b.p. 160°, 0.1 mm) affording 2.37 g. (83% yield) of XX; nmr: 1.55 (s, 3, C-CH₃), 1.62 (s, 3, C-CH₃), 1.8-2.3 (m, 2, C-5 H₂), 2.32 (s, 3, N-CH₃), 2.5-3.3 (m, 5, C-6 H₂ + C-2 H + interannular CH₂), 3.62 (s, 3, indole-N-CH₃), 6.30 (s, 1, indole-C-3 H), 6.9-7.7 (m, 4, indole).

Attempts of Cyclization of Tetrahydropyridine XX: 1,2-Dimethylindole (XXI).

A solution of 3 g. (11.2 mmoles) of XX in 37.5 ml. of 48% hydrobromic acid was heated at 135° for 3 hours. The reaction mixture was poured over ice-water, basified with concentrated ammonia and extracted with ether. The organic layers were dried and evaporated giving 1.53 g. (94% yield) of the indole XXI, m.p. 56-57° (ether) [lit. (37) 56°]; nmr: 2.20 (s, 3, C-CH₃), 3.30 (s, 3, N-CH₃), 6.05 (s, 1, indole-C-3 H), 6.5-7.6 (m, 4, indole).

1,3,4-Trimethyl-2-(1-methyl-2-indolylcarbonyl)pyridinium Iodide (XXII).

A solution of 11.6 ml. (26.4 g., 186 mmoles) of methyl iodide in 16 ml. of dry benzene was added dropwise to a stirred solution of 16.2 g. (61.3 mmoles) of XV in 81 ml. of anhydrous acetone. The mixture was stirred at room temperature for 1 hour, refluxed for 3 hours and then allowed to stand at 5° for 12 hours. The methiodide XXII (23 g., 92% yield) was collected by filtration; nmr: 2.30 (s, 3, C-CH₃), 2.62 (s, 3, C-CH₃), 4.20 (s, 3, N-CH₃), 4.32 (s, 3, N-CH₃), 7.10-7.83 (m, 5, indole), 8.01 (d, 1, pyridine-C-5 H), 9.41 (d, 1, pyridine-C-6 H).

1-Methyl-2-indolyl 1,3,4-Trimethyl-1,2,5,6-tetrahydro-2-pyridyl Ketone (XXIII).

Sodium borohydride (5.1 g., 135 mmoles) was added portionwise to a stirred and ice-cooled solution of 18.3 g. (45 mmoles) of the iodide XXII in 120 ml. of methanol. The resulting solution was refluxed for 5 hours, the solvent was removed at reduced pressure, 200 ml. of water were added and aqueous solution was extracted with ether. After drying and evaporation of the solvent, 10 g. of crude XXIII was obtained. The filtration through a silica gel column gave, on elution with benzene-

chloroform (7:3), 8.0 g. (63% yield) of XXIII; nmr: 1.51 (s, 3, C-CH₃), 1.68 (s, 3, C-CH₃), 2.0-3.8 (m, 4, C-5 H₂ + C-6 H₂), 2.30 (s, 3, N-CH₃), 3.88 (s, 1, C-2 H), 3.98 (s, 3, indole-N-CH₃), 6.9-7.6 (m, 5, indole).

Attempts of Cyclization of Tetrahydropyridine XXIII: 4-Hydroxy-1,3,4-trimethyl-2-piperidyl 1-Methyl-2-indolyl Ketone (XXIVa).

Polyphosphoric acid (10 g.) and 1.0 g. (3.5 mmoles) of XXIII were stirred under nitrogen at 100° for 2 hours. The mixture was poured over an excess of concentrated ammonium hydroxide-ice and extracted with ether. The evaporation of dried ethereal extracts gave an oil which was filtered through a silica gel column. On elution with benzene-chloroform (7:3) and with chloroform-methanol (99:1), 50 mg. of unreacted XXIII and 200 mg. (19.8% yield) of XXIVa, respectively, were obtained; nmr: (XXIVa) 0.9 (d, J = 7 Hz, 3, C-3 CH₃), 1.15 (s, 3, C-4 CH₃), 1.4-2.2 (m, 3, C-3 H + C-5 H₂), 2.30 (s, 3, N-CH₃), 2.4-3.9 (m, 2, C-6 H₂), 3.98 (s, 3, indole-N-CH₃), 4.35 (d, J = 8 Hz, 1, C-2 H), 4.5 (broad signal, 1, OH), 6.8-7.7 (m, 5, indole).

4-Hydroxy-1,4-dimethyl-2-piperidyl 1-Methyl-2-indolyl Ketone (XXIVb).

Operating in the same manner, from 0.7 g. (2.6 mmoles) of XXV, 0.2 g. (26% yield) of XXIVb were obtained; nmr: 1.28 (s, 3, C-CH₃), 2.28 (s, 3, N-CH₃), 2.75 (m, 2, C-6 H₂), 3.04 (dd, 1, C-2 H), 4.04 (s, 3, indole-CH₃), 7.79-8.89 (m, 5, indole).

Acknowledgement.

We acknowledge Drs. Mercedes Alvarez and Francisco López for helpful collaboration and experimental assistance at the initial stages of this work.

REFERENCES AND NOTES

- (1) Paper XIII: J. Bosch, D. Mauleón and R. Granados, *J. Heterocyclic Chem.*, **17**, 1061 (1980).
- (2) D. C. Palmer and M. J. Strauss, *Chem. Rev.*, **77**, 1 (1977).
- (3) Compounds coming from isosteric substitution by an heterocyclic ring of the benzene ring in 6,7-benzomorphans.
- (4) R. L. Perry and N. F. Albertson, *J. Med. Chem.*, **10**, 1184 (1967).
- (5a) T. A. Montzka and J. D. Matiskella, *J. Heterocyclic Chem.*, **11**, 853 (1974); (b) M. Alvarez, J. Bosch and J. Canals, *An. Quim.*, **71**, 807 (1975); (c) J. Bosch, R. Granados and F. López, *J. Heterocyclic Chem.*, **12**, 651 (1975); (d) M. Alvarez, J. Bosch, R. Granados and F. López, *ibid.*, **15**, 193 (1978).
- (6) M. Alvarez, J. Bosch and M. Feliz, *ibid.*, **15**, 1089 (1978).
- (7) D. Kishore, P. K. Khandelval and B. C. Joshi, *Arch. Sci.*, **27**, 39 (1974).
- (8a) G. C. Morrison, R. O. Waite, A. N. Caro and J. Shavel Jr., *J. Org. Chem.*, **32**, 3691 (1967); (b) J. Bosch and F. Boncompagni, *An. Quim.*, **75**, 357 (1979).
- (9a) J. Bosch, R. Granados and R. Llobera, *ibid.*, **75**, 360 (1979); (b) J. Bosch, R. Granados, R. Llobera and D. Mauleón, *ibid.*, **75**, 939 (1979).
- (10) R. Crewe, *Angew. Chem.*, **59**, 194 (1947).
- (11) W. E. Feely and E. M. Beavers, *J. Am. Chem. Soc.*, **81**, 4004 (1959).
- (12) C. F. Hobbs, C. K. McMillin, E. P. Papadopoulos and C. A. VanderWerf, *ibid.*, **84**, 43 (1962).
- (13) N. W. Gabel, *J. Heterocyclic Chem.*, **4**, 627 (1967).
- (14) K. M. Biswas and A. H. Jackson, *Tetrahedron*, **24**, 1145 (1968).
- (15) Boron complexes were detected by their strong ir absorption at 2000-2500 cm⁻¹ (B-H stretching). Hydrolysis attempts with acetone, methanol or sodium hydroxide (14) were unsuccessful.
- (16) To our knowledge examples of reductions of the pyrrole ring to pyrrolidine by diborane treatment do not exist.
- (17) R. K. Hill and Tak-Hang Chan, *Tetrahedron*, **21**, 2015 (1965).
- (18) A. F. Casy, "PMR spectroscopy in Medicinal and Biological Chemistry" Academic Press, London, 1971, Chapters 4 and 6.
- (19) M. Takeda, A. E. Jacobson and E. L. May, *J. Org. Chem.*, **34**, 4158 and 4161 (1969).
- (20) The cyclization agents employed were 50% hydrobromic acid

(135°, 1 hour), 80% phosphoric acid (160°, 3 hours), aluminum trichloride (carbon disulfide, room temperature for 2 hours, or reflux for 4-24 hours), stannic tetrachloride (carbon disulfide, reflux, 2 hours), acetic acid (reflux, 1-42 hours), acetic and trifluoroacetic acid mixtures (50:1 and 7:1, reflux, 0.5-2 hours), boron trifluoride etherate (reflux, 3 hours) and polyphosphoric acid (135°, 4-16 hours).

(21) The thermal rearrangement of 1-substituted pyrroles is well established. R. Alan Jones and G. P. Bean, "The Chemistry of Pyrroles", Academic Press, London, New York, San Francisco, 1977, Chapter 6, p. 249.

(22) R. T. Parfitt and S. M. Walters, *J. Med. Chem.*, **14**, 565 (1971).

(23) In the absence of dichloromethane, the reaction takes place on heterogeneous phase and the ketone Vb was obtained in lower than 10% yield, being the 4-methylpyridine-2-carboxamide the major product.

(24) R. E. Lyle and P. S. Anderson, *Adv. Heterocyclic Chem.*, **6**, 45 (1966).

(25) In the Δ^3 -tetrahydropyridine Xb this signal appears at higher fields (δ 5.18) than in the Δ^4 -isomer (19).

(26) D. A. Shirley and P. A. Roussel, *J. Am. Chem. Soc.*, **75**, 375 (1953).

(27) The formation of alcohols is a known secondary process in the Wolff-Kishner reductions: D. Todd, in "Organic Reactions", Vol. 6, R. Adams, Ed., John Wiley and Sons, Inc., New York, N.Y. 1948, p. 378.

(28) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(29) S. A. Monti and R. R. Schmidt III, *Tetrahedron*, **27**, 3331 (1971).

(30) J. G. Berger and S. R. Teller, *Tetrahedron Letters*, 1807 (1975).

(31) The cyclization agents employed were 50% hydrobromic acid (135°, 3 hours), glacial acetic acid (130°, 45 minutes), aluminum trichloride (carbon disulfide, reflux, 20 hours), polyphosphoric acid (90°, 1.5 hours and 145°, 3 hours) and boron trifluoride-etherate (reflux, 1 hour).

(32a) R. L. Hinman and J. Lang, *Tetrahedron Letters*, 12 (1960); (b) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

(33) A. Jackson, N. D. V. Wilson, A. J. Gaskell and J. A. Joule, *J. Chem. Soc. C*, 2738 (1969).

(34) Another cyclization agents led to unidentified mixtures: polyphosphoric acid (100°, 2 hours), aluminum tribromide (carbon disulfide, reflux, 8 hours), aluminum trichloride (carbon disulfide, reflux, 7 hours), 80% phosphoric acid (165°, 3 hours), 50% hydrobromic acid (135°, 3 hours) and acetic acid (110°, 2 hours).

(35) J. Bosch, M. Alvarez, R. Llobera and M. Feliz, *An. Quim.*, **75**, 712 (1979).

(36) S. P. Hiremath and R. S. Hosmane, *Adv. Heterocyclic Chem.*, **15**, 277 (1973).

(37) L. Marion and C. W. Oldfield, *Can. J. Res.*, **25B**, 1 (1947).

(38) T. Hino, K. Yamada and S. Akaboshi, *Chem. Ind. (London)*, 275 (1967).

(39a) O. Schmitz-DuMont and K. H. Geller, *Ber.*, **66**, 766 (1933); (b) W. E. Noland, C. G. Richards, H. S. Desai and M. R. Venkiteswaran, *J. Org. Chem.*, **26**, 4254 (1961).