SYNTHETIC APPLICATIONS OF 2-ARYL-4-PIPERIDONES. IX.[1] SYNTHESIS OF PYRIDO[1',2':1,2]IMIDAZO[4,5*a*]-QUINOLIZIDIN-2-ONE

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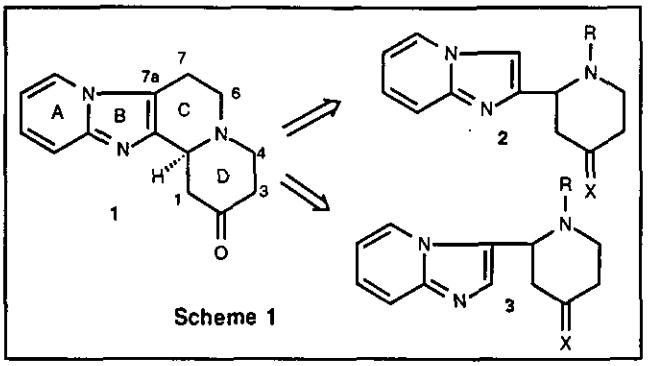
Abstract – The synthesis of the new heterocyclic compound pyrido[1',2':1,2]imidazo-[4,5-*a*]quinolizidin-2-one (**1**), an aza analog of indolo[2,3-*a*]quinolizidin-2-one, has been effected in four steps from an appropriate 2-aryl-4-piperidone (**2**), including closure of ring C as the key step.

INTRODUCTION

In continuing our interest in the study of both indolo[2,3-*a*]quinolizidines[2] and of nitrogen bridgehead azaindolizidines,[3] we report in the present paper the synthesis of pyrido[1',2':1,2]imidazo[4,5-*a*]quinolizidin-2-one (**1**), a new heterocyclic system (Scheme 1), taking into account that the addition of a nitrogen atom in a structure may increase and generate modifications of the pharmacological activities.

Indolo[2,3-*a*]quinolizidine alkaloids, such as the *Corynanthe* and *Yohimbe* families, are important compounds due to their sympathetic inhibitor activity. Moreover, indolo[2,3-*a*]quinolizidin-2-one itself has been shown to be a GABA uptake inhibitor with an activity superior to that of guvacine,[4] and, independently, pyrido[1',2':1,2]imidazo[5,4-*c*]isoquinoline has been investigated as a mutagenic compound.[5]



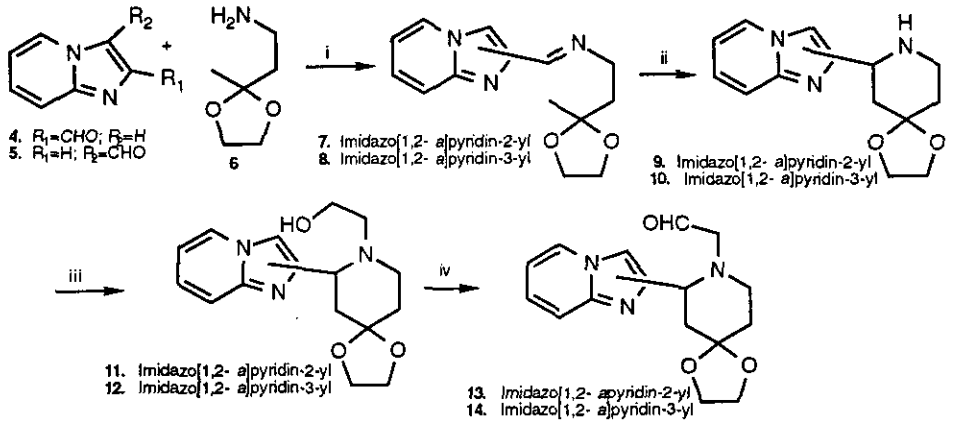
Scheme 1

In the light of our experience, the synthesis of **1** was planned either from 2-arylpiperidone (**2**)[6] in order to elaborate the C ring of the system by closure of 7-7a bond as the key step of the approach,[7] or from 2-arylpiperidine (**3**). Since position 2 in imidazo[1,2-*a*]pyridines is known to be little reactive, or even to react as an electrophile,[8] we were expecting several possibilities among which were: i) cyclization upon the aromatic C-2 position, and ii) substitution on the aromatic C-3 position leading to a spiro derivative salt, an analog of 3-spiroindolenine, which is known to rearrange toward an indolo[2,3-*a*]quinolizidine system.[9]

RESULTS AND DISCUSSION

The starting 2-(imidazo[1,2-*a*]pyridin-2-yl)piperidin-4-one ethylene acetal (**9**) has been prepared by our general method, through condensation of imidazo[1,2-*a*]pyridine-2-carbaldehyde (**4**)[10] with aminoacetal (**6**),[6] followed by *p*-TsOH cyclization of the resulting imine (**7**) (Scheme 2). It is worth mentioning that the *Z* isomer of imine (**7**), which is usually not observed when the aryl group is an indole or a phenyl group,[7b] was obtained together with *E*-**7**, but was not isolated due to its isomerization during the chromatographic purification. Thus, in the ^{1}H nmr spectrum of the mixture of *Z* and *E* imines the singlets corresponding to the aromatic C-3 methine proton and the imine proton were the most significant signals, more deshielded when close to the nitrogen electron lone pair ($\Delta\delta$ = 0.62 ppm). The formation of piperidine (**9**) was evidenced in the ^{1}H nmr spectrum by the disappearance of the imine proton and the presence of a doublet-of-doublets at δ 4.15 characteristic of a piperidine axial 2-H. All the data were comparable to those of the 2-(2-indolyl)piperidine analog for both the bases and the hydrochlorides. However, an additional protonation of the nitrogen atom of the imidazole ring in the case of **2**·HCl was demonstrated by the chemical shift of the aromatic C-5 proton ($\Delta\delta$~0.8 ppm).

Alkylation of piperidine (**2**) with 2-bromoethanol in the presence of Na_2CO_3 furnished the corresponding aminoethanol (**11**) in 77% yield, requiring long reaction times and at least two equivalents of the alkylating reagent to be satisfactorily achieved. Comparison of the ^1H nmr spectra of **9** and **11** showed a *ca.* 0.6 ppm shielding for the signals corresponding to 2-Ha and 6-Ha when the nitrogen atom is alkylated. The ^{13}C nmr spectra showed a typical deshielding effect on C-2 and C-6 due to the alkylation.[11]



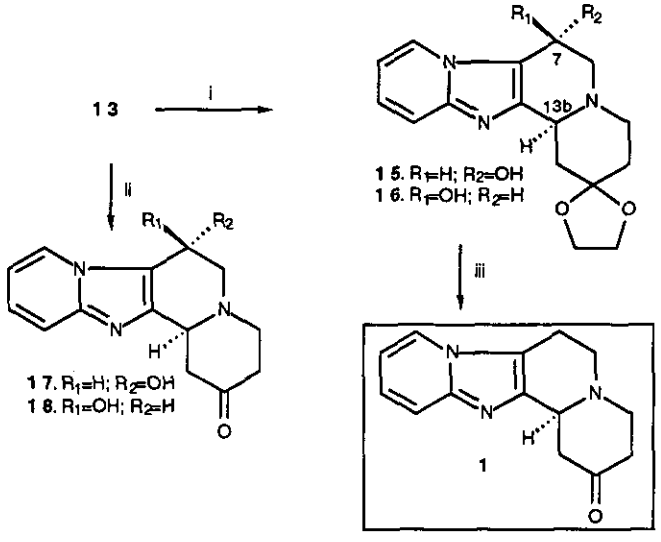
Reagents and conditions: i) C_6H_6, 0°C, 1 h; room temperature, 17 h; reflux, 3 h; Dean-Stark, 6 h ; ii) dry *p*-TsOH, C_6H_6, reflux, 1h ; iii) $BrCH_2CH_2OH$, Na_2CO_3, EtOH, reflux, 3 days; iv) 1. $(COCl)_2$-DMSO, CH_2Cl_2, -60°C. 2. Et_3N, -60°C.

Scheme 2

Alcohol (**11**) was then oxidized to the corresponding aldehyde (**13**) in 67% yield by treatment with $(COCl)_2$-DMSO and Et_3N. A small proportion (27%) of the cyclized alcohol (**15**), identified by comparison of the spectral data with those obtained later, was also isolated, showing the facility of the following step. Aldehyde (**13**) showed a singlet at δ 9.25 and an AB system at δ 2.92 and 3.12 in its ^1H nmr spectrum as well as signals at δ 64.2 and 201.1 in its ^{13}C nmr spectrum , characteristic of the acetaldehyde chain.

The following treatment of aldehyde (**13**) with cold 4*N* HCl (0°C) led to an equimolecular mixture of the C-7 epimeric 7-hydroxypyrido[1',2':1,2]imidazo[4,5-*a*]quinolizidin-2-one ethylene acetals (**15**) and (**16**) in 74% total yield (Scheme 3). From the nmr data, the C/D *trans* conformation of the quinolizidine framework in both epimers was very clear[12]. Thus, 13b-H appeared as a broad doublet (**15**) or a doublet-of-doublets (**16**) at δ 3.70 and 3.52, respectively, which indicates its axial disposition, *anti* regarding the nitrogen electron lone pair. Similarly, the ^{13}C nmr spectra showed signals at δ 59.5 and 62.5 (**15**), and δ 60.9 and 60.5 (**16**) for C-7 and C-13b, respectively. Another main feature was the signal multiplicity in the ^1H nmr of 7-H, which allowed the assignment of the hydroxy group stereochemistry in each case. Thus, compound

(**15**) showed a triplet at δ 5.29 for 7-H indicating its pseudoaxial disposition, *syn* regarding the nitrogen electron lone pair, which leaves the hydroxy group in a *cis* relationship with respect to 13b-H. In the case of compound (**16**), 7-H appears at δ 4.92, indicating an opposite configuration, in which the hydroxy group is *trans* with respect to 13b-H.



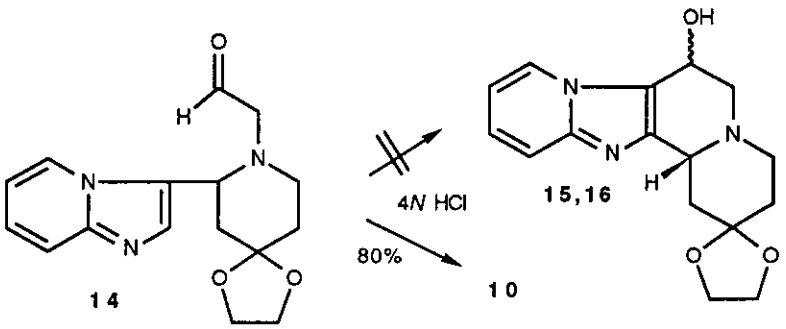
Reagents and conditions: i) 4*N* HCl, 0°C, 8 h; ii) 4*N* HCl, 60°C, 5.5 h; iii) Et_3SiH, CF_3COOH, reflux, 24 h.

Scheme 3

Parallelly, and in order to study the reactivity of the imidazopyridine moiety, our second approach was developed. A similar sequence of reactions was carried out from imidazo[1,2-*a*]pyridine-3-carbaldehyde (**5**) and aminoacetal (**6**) (Scheme 2), leading to the corresponding 2-arylpiperidine (**10**), which was alkylated with 2-bromoethanol to aminoethanol (**12**) and oxidized to obtain aldehyde (**14**) (all spectral data correlated with the already gathered). An interesting observation, nevertheless, was that when the alkylation step was effected in the presence of air instead of an inert atmosphere, alcohol (**12**) was accompanied by a slight amount of aldehyde (**14**), but not enough to enable the transformation to be done in one step.

At this point, when aldehyde (**14**) was treated with 4*N* HCl to achieve the cyclization at 0°C, the starting material was recovered unaltered. But when forcing the reaction conditions by stirring at room temperature for two days, only piperidine (**10**) was recovered in high yield (80%), resulting from the loss of the two carbon chain in the reaction medium (Scheme 4). This fact can be accounted for by considering that even if aldehyde (**14**) showed to be stable and could be purified and manipulated without any problem, in the hot acidic medium in the presence of air it could be oxidized to the

corresponding α-amino acid, which would decarbonylate as it is well known.[13] In order to avoid such a problem, we transformed alcohol (**10**) into the corresponding tosylate, which proved to be highly unstable and had to be used immediately without any purification. However, all assays to cyclize the tosylate of **12** were unsuccessful.



Scheme 4

Back to the 2-aryl series (Scheme 2), and in order to shorten the cyclization reaction time, we assayed the treatment of aldehyde (**13**) with 4*N* HCl at 60°C. In this case the ring closure occurred in the space of 5-6 h, but the acetal hydrolysis was also observed, leading to an equimolecular mixture of alcohols (**17**) and (**18**), which were separated by flash chromatography. In this case, the nmr data were in accordance with a *cis* C/D ring conformation. Thus, the ^{1}H nmr spectrum of quinolizidine (**17**) showed as most characteristic signals i) a singlet at δ 5.55 corresponding to 7-H, pseudoaxial and *syn* with respect to the nitrogen electron lone pair, and ii) a doublet-of-doublets at δ 4.40 (*J*=12 and 3 Hz) for 13b-H, indicating its axial disposition in the D ring and its *syn* relationship with respect to the nitrogen electron lone pair.[14]

The main features in the ^{1}H nmr spectrum of **18** were a broad signal at δ 4.50 assignable to 7-H , pseudoequatorial and *anti* with respect to the nitrogen electron lone pair and a broad doublet at δ 4.61 for 13b-H.

Finally, reduction of the hydroxy group on C-7 was effected on quinolizidine acetals (**15**) and (**16**) (Scheme 3). Thus, treatment of **15** and **16** with Et_3SiH and an excess of CF_3COOH directly furnished the target pyrido[1',2':1,2]imidazo[4,5-*a*]quinolizidin-2-one (**1**). As expected, since the carbonyl group had been deprotected, the C/D rings conformation of **1** was also *cis*, as shown in the nmr spectra. The ^{1}H nmr showed a doublet-of-doublets at δ 4.45 corresponding to 13b-H, in a *syn* relationship with the nitrogen lone pair, and by *ca.* 0.79 ppm more deshielded than its indolyl analog in a *trans* conformation. On the other hand, the reduction of the carbinol was evidenced by the shift, in the ^{13}C nmr spectrum, of the signal at δ~60 to δ 22.6, corresponding to C-7.

The different stability of the *cis* conformers in pyrido[1',2':1,2]imidazo[4,5-*a*]quinolizidin-2-ones compared to indolo[2,3-*a*]quinolizidin-2-ones can be explained by considering that in the *cis* conformation of **17**, **18** and **1** the steric strain between the aromatic substituent and 13b-H is decreased as a consequence of the loss of the indole nitrogen proton.

CONCLUSIONS

We have prepared in an efficient way a new heterocyclic compound, pyrido[1',2':1,2]imidazo[4,5-*a*]quinolizidin-2-one (**1**), which, in its conception, has a great potential pharmacological interest as an antihypertensive, tranquilizer, cardiotonic and antimitotic agent.

In addition, this new compound shows a structural interest, since the quinolizidine ring system keeps a *trans* conformation as long as an acetal ring is present on position 2 (compounds **15** and **16**), but when the acetal function is hydrolysed, the system adopts a *cis* conformation.

EXPERIMENTAL

Melting points were determined in a capillary tube on a CTP-MP 300 hot plate apparatus and are uncorrected. ^{1}H and ^{13}C nmr spectra were recorded on a Varian Gemini-200 instrument. Unless otherwise noted, nmr spectra were registered in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) relative to internal Me_4Si. Ir spectra were recorded on a Nicolet FT-IR spectrophotometer. Mass spectra were determined on a Hewlett-Packard 5988A mass spectrometer. Flash column chromatography was carried out on SiO_2 (silica gel 60, 40-63 μm, Macherey-Nagel) or, when indicated, Al_2O_3 (aluminumoxide 90, activity II-III, 63-200 μm, Merck). Tlc was performed on SiO_2 (silica gel 60 F254, Merck) or Al_2O_3 (aluminumoxide 60, F254, neutral Typ E, Merck) and developed with the solvent described in each case for flash chromatography. The spots were located by uv light and hexachloroplatinate reagent. Purification of reagents and solvents was effected according to standard methods. Prior to concentration under reduced pressure, all extracts were dried over anhydrous Na_2SO_4 powder. Microanalyses were performed on a Carlo Erba 1106 analyzer by the Departament de Química Orgànica i Biològica, CID, Barcelona.

2-(Pyrido[1,2-*a*]imidazo-2-yl)-4-piperidone Ethylene Acetal (9). A mixture of aminoacetal (**6**)[6] (2.64 g, 20 mmol), and pyrido[1,2-*a*]imidazo-2-carbaldehyde (**4**)[10] (2.82 g, 19 mmol) in dry benzene (200 ml) was stirred at 0° C for 30 min, at room temperature for 17 h, refluxed for 3 h, and with water removal with a Dean-Stark apparatus for 6 h. The

solvent was evaporated yielding a 7:1 mixture of *trans*-**7** and *cis*-**7** , which were separated by crystallisation in CH_2Cl_2. *trans*-**7** (Higher Rf, solid, 3.74g, 76%): mp 242°C (CH_2Cl_2); ir ($CHCl_3$) 1640 cm^{-1} (C=N); ^1H nmr 1.40 (s, 3H, CH_3), 2.11 (t, J = 7 Hz, 2H, CH_2CH_2N), 3.76 (t, J = 7 Hz, 2H, NCH_2), 3.98 (s, 4H, CH_2O), 6.81 (t, J = 6 Hz, 1H, Ar-6H), 7.20 (t, J = 6 Hz, 1H, Ar-7H), 7.61 (d, J = 6 Hz, 1H, Ar-8H), 7.97 (s, 1H, Ar-3H), 8.11 (d, J = 6 Hz, 1H, Ar-5H), 8.48 (s, 1H, CH=N); ^{13}C nmr 24.2 (CH_3), 39.8 (CH_2CH_2N), 57.3 (NCH_2), 64.5 (OCH_2), 109.3 (OCO), 112.2 (Ar-C3), 113.3 (Ar-C8), 118.4 (Ar-C6), 125.4 and 126.1 (Ar-C5 and ArC-7), 143.5 (Ar-C8a), 156.4 (C=N); ms (*m/z*, %) 259 (M^+, 80), 145 (15), 118 (39), 90 (32), 78 (100).

cis-**7** (Lower Rf, solid, 0.56 g, 11%): mp 257°C (CH_2Cl_2); ir ($CHCl_3$) 1640 cm^{-1} (C=N); ^1H nmr 1.35 (s, 3H, CH_3), 2.18 (t, J = 5 Hz, 2H, CH_2CH_2N), 3.15 (t, J = 5 Hz, 2H, NCH_2), 3.98-4.10 (br s, 4H, CH_2O), 6.81 (t, J = 6 Hz, 1H, Ar-6H), 7.20 (t, J = 6 Hz, 1H, Ar-7H), 7.35 (s, 1H, Ar-3H), 7.61 (d, J = 6 Hz, 1H, Ar-8H), 8.11 (d, J = 6 Hz, 1H, Ar-5H), 8.95 (s, 1H, CH=N); ^{13}C nmr 23.3 (CH_3), 35.6 (CH_2CH_2N), 52.0 (NCH_2), 64.5 (OCH_2), 109.0 (OCO), 113.6 (Ar-C3), 114.2 (Ar-C8), 118.1 (Ar-C6), 126.1 (Ar-C5 and ArC-7), 142.0 (Ar-C8a), 157.0 (C=N).

To a hot solution of anhydrous *p*-TsOH (2.21 g, 13 mmol) in dry benzene (100 ml), a solution of the mixture of iminoacetals (**7**) (1.67 g, 6.4 mmol) in dry benzene (100 ml) was slowly added. After refluxing for 1 h, the mixture was poured on ice-water and basified with Na_2CO_3. The organic phase was washed with saturated aqueous Na_2CO_3. The organic extracts were dried, evaporated, and flash chromatographed (92:8, CH_2Cl_2-MeOH) to furnish **9** (1.13 g, 68%), as a yellow solid: mp 93°C (CH_2Cl_2); ^1H nmr 1.70-1.95 (m, 3H, 3-H and 5-Ha), 2.18 (dt, J = 12, 2 Hz, 1H, 5-He), 2.94-3.26 (m, 2H, 6-H), 4.00 (s, 4H, CH_2O), 4.15 (dd, J = 12, 3 Hz, 1H, 2-Ha), 6.70 (t, J = 7 Hz, 1H, Ar-6H), 7.10 (t, J = 7 Hz, 1H, Ar-7H), 7.50 (d, J = 7 Hz, 1H, Ar-8H), 7.51 (s, 1H, Ar-3H), 8.02 (d, J = 7 Hz, 1H, Ar-5H); ^{13}C nmr 35.4 (C-5), 41.3 (C-3), 43.9 (C-6), 53.4 (C-2), 64.2 (OCH_2), 108.0 (C-4), 108.3 (Ar-C3), 112.1 (Ar-C8), 117.3 (Ar-C6), 124.5 (Ar-C5), 125.8 (Ar-C7), 145.0 (Ar-C8a); ms (*m/z*, %) 259 (M^+, 5), 214 (16), 172 (14), 145 (100), 132 (7), 118 (11).

9·2HCl: mp 253-254 °C (acetone); ^1H nmr 1.93 (br d, J = 13 Hz, 1H, 5-He), 2.24 (td, J = 13, 5 Hz, 1H, 5-Ha), 2.34 (br d, J = 13 Hz, 1H, 3-He), 2.53 (t, J = 13 Hz, 1H, 3-Ha), 3.38 (td, J = 12 , 2 Hz, 1H, 6-Ha), 3.42 (br d, J = 12 Hz, 1H, 6-He), 4.00 (s, 4H, OCH_2), 4.90 (dd, J = 12, 2 Hz, 1H, 2-Ha), 5.00 (br s, 2H, NH_2^+), 7.49 (t, J = 6 Hz, 1H, Ar-6H), 7.90-8.09 (m, 2H, Ar-8H and Ar-7H), 8.60 (s, 1H, Ar-3H), 8.85 (d, J = 6 Hz, 1H, Ar-5H); ^{13}C nmr (CD_3OD) 30.2 (C-5), 35.8 (C-3), 42.4 (C-6), 49.2 (C-2), 64.0 and 64.3 (OCH_2), 103.3 (C-4), 111.6 (Ar-C3), 114.5 (Ar-C8), 117.4 (Ar-C6), 128.8 (Ar-C7), 134.4 (Ar-C5), 139.4 (Ar-C8a). Anal. Calcd for $C_{14}H_{17}N_3O_2$·2HCl: C, 50.60; H, 5.72; N, 12.65. Found: C, 50.57; H, 5.68; N, 12.62.

2-(Pyrido[1,2-*a*]imidazo-3-yl)-4-piperidone Ethylene Acetal (10). Operating as for the preparation of iminoacetal (**7**), from aldehyde (**5**)[10] (2.50 g, 17.1 mmol) and aminoacetal (**6**)[6] (2.74 g, 20.9 mmol) in benzene (150 ml), a 1:5 mixture of imines *cis*- and *trans*-**8** was obtained as a red oil, which was flash chromatographed (97:3, CH_2Cl_2-MeOH) to yield imine *trans*-**8** (3.36 g, 78%) as an oil: Ir ($CHCl_3$)1663 cm^{-1} (C=N); ^1H nmr 1.43 (s, 3H, CH_3), 2.12 (t, J = 7 Hz, 2H, CH_2CH_2N), 3.75 (t, J = 7 Hz, 2H, NCH_2), 4.01 (s, 4H, OCH_2), 7.15 (t, J = 7 Hz, 1H, Ar-H6), 7.59 (t, J = 7 Hz, 1H, Ar-H7), 7.70 (d, J = 7 Hz, 1H, Ar-H8), 7.82 (d, J = 7 Hz, 1H, Ar-H5), 7.90 (s, 1H, Ar-H2), 9.00 (s, 1H, HC=N); ^{13}C nmr 23.8 (CH_3), 40.2 (CH_2CH_2N), 57.1 (CH_2N), 64.3 (CH_2O), 109.0 (OCO), 114.2 (Ar-C8), 117.8 (Ar-C6), 127.7 (Ar-C5), 129.4 (Ar-C7), 140.5 (Ar-C2), 150.1 (C=N); MS (*m/z*, %) 259 (M^+, 80), 145 (15), 118 (39), 90 (32), 78 (100).

Operating as for the preparation of piperidine (**9**), from iminoacetal (**8**) (4.4 g, 17 mmol) and anhydrous *p*-TsOH (6.5 g, 34.2 mmol) in dry benzene (250 ml), piperidine (**10**) was obtained, which was flash chromatographed (90:10, CH_2Cl_2-MeOH) to give a solid (3.44 g, 78%): mp 144°C (CH_2Cl_2); ir ($CHCl_3$) 3230 cm^{-1} (NH); ^1H nmr 1.68 (td, J = 12, 4 Hz, 1H, 5-Ha), 1.74-1.85 (m, 1H, 5-He), 2.00 (t, J = 12 Hz, 1H, 3-Ha), 2.05-2.15 (m, 1H, 3-He), 3.02 (td, J = 12, 2 Hz, 1H, 6-Ha), 3.18 (ddd, J = 12, 4, 2 Hz, 1H, 6-He), 4.00 (s, 4H, OCH_2), 4.25 (dd, J = 12, 2 Hz, 1H, 2-Ha), 6.80 (t, J = 7 Hz, 1H, Ar-H6), 7.15 (t, J = 7 Hz, 1H, Ar-H7), 7.43 (s, 1H, Ar-H2), 7.55 (d, J = 7 Hz, 1H, Ar-H8), 8.41 (d, J = 7 Hz, 1H, Ar-H5); ^{13}C nmr 35.9 (C-5), 39.4 (C-3), 43.6 (C-6), 50.0 (C-2), 64.1 and 64.2 (OCH_2), 107.4 (C-4), 111.6 (Ar-C8), 117.5 (Ar-C6), 124.1 (Ar-C5), 125.3 (Ar-C7), 125.7 (Ar-C3), 130.2 (Ar-C2), 146.1 (Ar-C8a); ms (*m/z*, %) 259 (M^+, 46), 228 (17), 214 (34), 198 (24), 172 (35), 158 (68), 144 (100), 131 (27), 118 (19), 87 (38). The hydrochloride (**10**·2HCl), mp 255-256°C (acetone); ^1H nmr (CD_3OD) 2.00 (br t, J = 12 Hz, 1H, 3-Ha), 2.05-2.21 (m, 1H, 3-He), 2.21-2.42 (m, 1H, 5-He), 2.55 (br t, J = 12 Hz, 1H, 5-Ha), 3.40-3.55 (m, 2H, 6-Ha and 6-He), 4.00 (s, 4H, OCH_2), 5.12 (br d, J= 12 Hz, 1H, 2-Ha), 7.74 (t, J = 7 Hz, 1H, Ar-H6), 8.16 (m, 2H, Ar-H7 and Ar-H8), 8.59 (s, 1H, Ar-H2), 9.26 (d, J = 7 Hz, 1H, Ar-H5); ^{13}C nmr (CD_3OD) 32.5 (C-5), 37.9 (C-3), 44.2 (C-6), 58.3 (C-2), 66.1 and 66.3 (OCH_2), 105.7 (C-4), 113.7 (Ar-C8), 119.0 (Ar-C6), 124.1 (Ar-C3), 125.55 (Ar-C7), 129.3 (Ar-C5), 136.3 (Ar-C2), 142.2 (Ar-C8a). Anal. Calcd for $C_{14}H_{17}N_3O_2$·2HCl: C, 50.60; H, 5.72; N, 12.65. Found:C, 50.85; H, 5.72; N, 12.22.

***N*-(2-Hydroxyethyl)-2-(pyrido[1,2-*a*]imidazo-2-yl)-4-piperidone Ethylene Acetal (11).** To a mixture of piperidine (**9**) (1.5 g, 5.83 mmol) and anhydrous Na_2CO_3 (0.6 g, 5.83 mmol) in absolute EtOH (85 ml), 2-bromoethanol (1.24 ml, 17.5 mmol) was slowly added. After refluxing until the reaction was complete (tlc, 3 days), the solvent was evaporated and the residue, dissolved in CH_2Cl_2, was washed with water. The organic extracts were dried, evaporated and flash filtered (93:7, CH_2Cl_2-MeOH) to obtain **9** (1.7 g, 77%), as a solid: mp 156°C (CH_2Cl_2); ir ($CHCl_3$) 3450-3100 cm^{-1}

(OH); ^{1}H nmr 1.59 (dd, J = 12, 2 Hz, 1H, 3-He), 1.75 (dt, J = 12, 2 Hz, 1H, 5-He), 1.80-2.15 (m, 2H, 3-Ha and 5-Ha), 2.40 (td, J = 12, 3 Hz, 1H, 6-Ha), 2.68 (ddd, J = 12, 8, 4 Hz, 2H, CH_ACH$_2$OH), 3.01 (ddd, J = 12, 5, 2 Hz, 1H, 6-He), 3.22 (ddd, J = 12, 8, 4 Hz, 2H, CH_BCH$_2$OH), 3.26-3.42 (m, 1H, C*H*OH), 3.45 (td, J = 10, 4 Hz, 1H, C*H*OH), 3.68 (dd, J = 12, 2 Hz, 1H, 2-Ha), 3.72-3.82 (br s, 4H, CH$_2$O), 6.58 (t, J = 7 Hz, 1H, Ar-6H), 6.95 (t, J = 7 Hz, 1H, Ar-7H), 7.35 (s, 1H, Ar-3H), 7.40 (d, J = 7 Hz, 1H, Ar-8H), 7.90 (d, J = 7 Hz, 1H, Ar-5H); ^{13}C nmr 34.4 (C-5), 42.3 (C-3), 50.0 (C-6), 54.8 (N*C*H$_2$CH$_2$OH), 58.8 (C-2), 59.5 (CH$_2$OH), 64.3 (OCH$_2$), 107.1 (C-4), 109.9 (Ar-C3), 112.2 (Ar-C8), 117.5 (Ar-C6), 124.6 (Ar-C2), 124.7 (Ar-C5), 125.8 (Ar-C7), 148.5 (Ar-C8a); ms (*m/z*, %) 303 (M$^+$, 2), 285 (14), 272 (19), 258 (8), 243 (16), 215 (8), 199 (8), 171 (12), 158 (12), 145 (100), 128 (29), 99 (31). Anal. Calcd for $C_{16}H_{21}N_3O_3$: C, 63.36; H, 6.93; N, 13.86. Found: C, 63.27; H, 6.98; N, 13.85. The hydrochloride (**11**·2HCl) was extremely hygroscopic. ^{1}H Nmr 1.98 (br d, J = 12 Hz, 1H, 3-He), 2.20 (br d, J = 12 Hz, 1H, 5-He), 2.75-3.10 (m, 2H, 3-Ha and 5-Ha), 3.29 (br s, 1H, OH), 3.41-3.70 (m, 2H, 6-H), 3.70-3.89 (m, 2H, N$^+$CH$_2$), 3.90-4.09 (m, 2H, CH$_2$OH), 4.09 (s, 4H, CH$_2$O), 5.40 (br d, J = 12 Hz, 1H, 2-Ha), 7.35 (s, 1H, Ar-3H), 7.40 (t, J = 7 Hz, 1H, Ar-6H), 7.90 (t, J = 7 Hz, 1H, Ar-7H), 8.10 (d, J = 7 Hz, Ar-8H), 8.69 (d, J = 7 Hz, 1H, Ar-5H), 9.00 (br s, NH$^+$); ^{13}C nmr (CD$_3$OD) 33.1 (C-5), 47.0 (C-3), 52.8 (C-6), 57.7 (N$^+$CH$_2$), 59.4 (C-2), 63.3 (OCH$_2$), 67.8 (CH$_2$OH), 103.9 (C-4), 115.4 (Ar-C8), 120.1 (Ar-C3), 130.2 (Ar-C6), 132.9 (Ar-C5), 137.8 (Ar-C7), 141.5 (Ar-C8a).

***N*-(2-Hydroxyethyl)-2-(pyrido[1,2-*a*]imidazo-3-yl)-4-piperidone Ethylene Acetal (12).** Operating as for the preparation of alcohol (**11**), from piperidine (**10**) (2.20 g, 8.5 mmol), 2-bromoethanol (2.43 ml, 34 mmol), and anhydrous K_2CO_3 (6.60 g, 61 mmol) in absolute ethanol (100 ml), aminoethanol (**12**) (1.64 g) was obtained, which was flash chromatographed (90:10 CH_2Cl_2-MeOH) to yield, together with aldehyde (**14**) (140 mg, 5%), pure **12** (810 mg, 32%) as a solid: mp 190°C (CH_2Cl_2); ir ($CHCl_3$) 3400-3250 cm^{-1} (OH); ^{1}H nmr 1.64 (br d, J = 12 Hz, 1H, 5-He), 1.68 (br d, J = 12 Hz, 1H, 3-He), 2.00 (td, J = 12, 4 Hz, 1H, 5-Ha), 2.24 (t, J = 12 Hz, 1H, 3-Ha), 2.31 (br t, J = 12 Hz, 1H, 6-Ha), 2.58 (br dd, J = 12, 4 Hz, 1H, 6-He), 2.62 (br d, J = 12 Hz, 1H, CH_ACH$_2$OH), 3.21 (br d, J = 12 Hz, 1H, CH_BCH$_2$OH), 3.36-3.48 (m, 2H, CH$_2$OH), 4.00 (s, 4H, CH$_2$O), 4.18 (dd, J = 12, 2 Hz, 1H, 2-Ha), 5.30 (br s, 1H, OH), 6.81 (t, J = 7 Hz, 1H, Ar-H6), 7.17 (t, J = 7 Hz, 1H, Ar-H7), 7.46 (s, 1H, Ar-H2), 7.54 (d, J = 7 Hz, 1H, Ar-H8), 8.62 (d, J = 7 Hz, 1H, Ar-H5); ^{13}C nmr 33.9 (C-5), 38.1 (C-3), 50.0 (C-6), 54.0 (C-2), 57.3 (NCH$_2$), 59.6 (CH$_2$OH), 64.9 (CH$_2$O), 107.7 (C-4), 112.6 (Ar-C8), 118.3 (Ar-C6), 124.7 (Ar-C3), 125.1 (Ar-C5), 126.3 (Ar-C7), 132.8 (Ar-C2), 146.9 (Ar-C8a); ms (*m/z*, %) 303 (M$^+$, 1), 272 (12), 186 (10), 149 (15), 128 (15), 111 (20), 97 (37), 95 (29), 86 (56), 84 (80), 57 (100). Anal. Calcd for $C_{15}H_{21}N_3O_3$: C, 63.36; H, 6.93; N, 13.86. Found: C, 63.37; H, 6.95; N, 13.77.

***N*-Formylmethyl-2-(pyrido[1,2-*a*]imidazo-2-yl)-4-piperidone Ethylene Acetal (13).** To a solution of oxalyl chloride (0.63 ml, 7.46 mmol) in dry CH_2Cl_2 (25 ml) cooled at -60°C, a solution of DMSO (1.2 ml, 18 mmol) was added dropwise. After stirring for 20 min at -60°C, a solution of alcohol (**11**) (1.13 g, 3.7 mmol) in dry CH_2Cl_2 (25 ml) was added dropwise. After 5 h at -60°C, Et_3N (5.83 ml, 40.8 mmol) was added, and the reaction mixture was allowed to reach room temperature before the addition of H_2O (75 ml). The mixture was stirred for 30 min, the layers separated, and the aqueous phase extracted with CH_2Cl_2. The organic extracs were dried, evaporated and flash chromatographed (93:7, CH_2Cl_2-MeOH) to obtain, together with pyridoimidazoquinolizidine (**15**) (lower Rf, 40 mg, 27%), aldehyde (**13**) (higher Rf, 0.75 g, 67%) as a solid: mp 113°C (CH_2Cl_2); ir ($CHCl_3$) 1720 cm^{-1} (C=O); ^1H nmr 1.78 (dd, J = 12, 2 Hz, 1H, 3-He), 1.88 (br d, J = 12 Hz, 1H, 5-He), 2.14 (td, J = 12, 5 Hz, 1H, 5-Ha), 2.40 (t, J = 12 Hz, 1H, 3-Ha), 2.75 (td, J = 12, 2 Hz, 1H, 6-Ha), 2.92 (dd, J = 15, 2 Hz, 1H, CH_ACHO), 3.00 (m, 1H, 6-He), 3.12 (dd, J = 15, 2 Hz, 1H, CH_BCHO), 3.89 (dd, J = 12, 2 Hz, 1H, 2-Ha), 3.98 (s, 4H, CH_2O), 6.98 (t, J = 7 Hz, 1H, Ar-H6), 7.28 (t, J = 7 Hz, 1H, Ar-H7), 7.55-7.70 (m, 2H, Ar-H3 and Ar-H8), 8.05 (d, J = 7 Hz, 1H, Ar-H5), 9.25 (br s, 1H, CHO);^{13}C nmr 34.5 (C-5), 40.1 (C-3), 52.5 (C-6), 57.1 (C-2), 64.2 (NCH_2), 64.5 (OCH_2), 106.7 (C-4), 113.2 (Ar-C8), 117.8 (Ar-C6), 122.8 (Ar-C5), 125.2 (Ar-C7), 125.4 (Ar-C2), 143.7 (Ar-C8a), 201.1 (br s, CHO); ms (*m/z*, %) 301 (M^+, 0.5), 258 (M^+-CH_2CHO, 13), 248 (56), 206 (20), 142 (12), 179 (100), 128 (17), 99 (54). Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.78; H, 6.31; N, 13.95. Found: C, 63.73; H, 6.50; N, 13.86.

***N*-Formylmethyl-2-(pyrido[1,2-*a*]imidazo-3-yl)-4-piperidone Ethylene Acetal (14).** Operating as for the preparation of aldehyde (**13**), from oxalyl chloride (0.74 ml, 8.66 mmol), DMSO (1.28 ml, 18.5 mmol), alcohol (**12**) (750 mg, 2.47 mmol) and Et_3N (3.86 ml, 27 mmol), in dry CH_2Cl_2 (70 ml), and water (50 ml), an oil was obtained which was flash chromatographed (93:7, CH_2Cl_2-MeOH) to give aldehyde (**14**) (440 mg, 60 %) as a solid: mp 68°C (CH_2Cl_2); ir ($CHCl_3$) 1730 cm^{-1} (CO); ^1H nmr 1.76-1.95 (m, 2H, 3-He and 5-He), 2.08 (td, J = 12, 5 Hz, 1H, 5-Ha), 2.35 (t, J = 12 Hz, 1H, 3-Ha), 2.85 (td, J = 12, 2 Hz, 1H, 6-Ha), 2.92 (dd, J = 15, 2 Hz, 1H, CH_ACHO), 3.08 (dt, J = 12, 2 Hz, 1H, 6-He), 3.20 (dd, J = 15, 2 Hz, 1H, CH_BCHO), 4.00 (s, 4H, CH_2O), 4.25 (dd, J = 12, 2 Hz, 1H, 2-Ha), 6.86 (t, J = 7 Hz, 1H, Ar-H6), 7.22 (t, J = 7 Hz, 1H, Ar-H7), 7.55 (s, 1H, Ar-H2), 7.65 (d, J = 7 Hz, 1H, Ar-H8), 8.18 (d, J = 7 Hz, 1H, Ar-H5), 9.38 (CHO); ^{13}C nmr 32.7 (C-5), 36.8 (C-3), 50.2 (C-6), 55.1 (C-2), 61.6 (NCH_2), 63.6 (OCH_2), 106.0 (C-4), 111.6 (Ar-C8), 117.2 (Ar-C6), 122.5 (Ar-C3), 124.0 (Ar-C5), 124.9 (Ar-C7), 132.3 (Ar-C2), 145.8 (Ar-C8a), 200.1 (CHO); ms (*m/z*, %) 301 (M^+, 0.6), 272(M^+-CHO, 11), 186 (13), 128 (28), 84(100). Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.79; H, 6.31; N, 13.95. Found: C, 63.58; H, 6.39; N, 13.63.

7-Hydroxypyrido[1',2':1,2]imidazo[4,5-*a*]quinolizidin-2-one Ethylene Acetals (15 and 16). A solution of aldehyde (**13**) (780 mg, 2.59 mmol) in 4*N* HCl (40 ml) was stirred at 0°C for 8 h. The reaction mixture was poured on ice-water, basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and evaporated to obtain a 1:1 mixture of alcohols (**15**) and (**16**) (590 mg), which was separated by flash chromatography (95:5, CH_2Cl_2-MeOH), as two solids. Alcohol (**15**) (lower R_f, 290 mg, 37%): mp 79°C (CH_2Cl_2); ir (KBr) 3550-3220 cm^{-1} (OH); ^1H nmr 1.65 (t, J = 12 Hz, 1H, 1-Ha), 1.70-1.80 (m, 1H, 3-He), 2.00 (td, *J* = 12, 5 Hz, 1H, 3-Ha), 2.49-2.70 (m, 2H, 1-He and 4-Ha), 2.89 (t, *J* = 12 Hz, 1H, 6-Ha), 2.95-3.10 (m, 1H, 4-He), 3.48 (dd, *J* = 12, 5 Hz, 1H, 6-He), 3.70 (br d, *J* = 12 Hz, 1H, 12b-H), 4.00 (br s, 4H, CH_2O), 5. 29 (t, *J* = 5 Hz, 1H, 7-H), 6.80 (t, *J* = 7 Hz, 1H, 10-H), 7.20 (t, *J* = 7 Hz, 1H, 11-H), 7.55 (d, *J* = 7 Hz, 1H, 12-H), 8.30 (d,*J* =7 Hz, 1H, 9-H); ^{13}C nmr 34.2 (C-3), 37.1 (C-1), 52.3 (C-4), 57.4 (C-6), 59.5 (C-7), 62.5 (C-13b), 64.3 (CH_2O), 107.0 (C-2), 112.2 (C-12), 117.2 (C-10), 124.7 (C-11), 125.0 (C-9); ms (*m/z*, %) 301 (M^+, 24), 283 (28), 256 (14), 222 (22), 173 (53), 169 (51), 149 (88), 128 (62), 99 (100).

Alcohol (**16**) (higher R_f, 290 mg, 37%): mp 144°C (CH_2Cl_2); ir (KBr) 3500-3350 cm^{-1} (OH); ^1H nmr 1.71 (t,*J* = 12 Hz, 1H, 1-Ha), 1.30 (dd, *J* = 12, 2 Hz, 1H, 1-He), 1.89 (dt, *J* = 12, 3 Hz, 1H, 3-He), 2.08 (td, *J* = 12, 5 Hz, 1H, 3-Ha), 2.18 (dt, *J* = 12, 2 Hz, 1H, 4-He), 2.80 (td, *J* = 12, 2 Hz, 1H, 4-Ha), 2.90-3.10 (m, 2H, 6-Ha and 6-He), 3.52 (dd, *J* = 12, 2 Hz, 1H, 12b-Ha), 3.95-4.15 (m, 4H, CH_2O), 4.92 (s, 1H, 7-He), 6.88 (t, *J* = 7 Hz, 1H, 10-H), 7.22 (t, *J* = 7 Hz, 1H, 11-H), 7.60 (d, *J* = 7 Hz, 1H, 12-H), 8.19 (d, *J* = 7 Hz, 1H, 9-H); ^{13}C nmr 34.9(C-3), 37.6 (C-1), 52.6 (C-4), 58.6 (C-6), 60.5 and 60.9 (C-13b and C-7), 64.3 (OCH_2), 106.9 (C-2), 112.3 (C-12), 117.0 (C-10), 123.9 (C-11), 124.7 (C-9), 128.9 (C-7a), 131.0 (C-13a),145.5 (C-12a); ms (*m/z*, %) 301 (M^+, 24), 283 (28), 256 (14), 222 (22), 173 (53), 169 (51), 149 (88), 128 (62), 99 (100). Anal. Calcd for $C_{16}H_{19}N_3O_3$: C, 63.78; H, 6.31; N, 13.95. Found: C, 63.68; H, 6.28; N, 13.97.

7-Hydroxypyrido[1',2':1,2]imidazo[4,5-*a*]quinolizidin-2-ones (17 and 18). A solution of aldehyde (**13**) (400 mg, 1.32 mmol) in 4*N* HCl (30 ml) was strirred at 60 °C for 5.5 h. The reaction mixture was poured on ice-water, basified with Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and evaporated yielding a 1:1 mixture of keto alcohols (**17**) and (**18**) (330 mg), which was separated by flash chromatography (90:10, CH_2Cl_2-MeOH). Keto alcohol (**17**) (higher Rf, 34 mg, 10%): ir ($CHCl_3$) 3450-3200 (OH), 1713 cm^{-1} (CO); ^1H nmr 2.40-3.70 (m, 8H), 4.40 (dd, *J* = 12, 3 Hz, 1H, 13b-H), 5.55 (s, 1H, 7-H), 6.90 (t, *J* = 7 Hz, 1H, 10-H), 7.15 (t, *J* = 7 Hz, 1H, 11-H), 7.50 (d, *J* = 7 Hz, 1H, 12-H), 8.00 (d, *J* = 7 Hz, 9-H); ^{13}C nmr 39.4 (C-3), 51.8 (C-1), 57.2 (C-6), 59.0 (C-4), 61.0 (C-13b), 73.5 (C-7), 113.5, 117.9, 118.4, 122.9, 125.0, 143.4, 208.8 (C=O); ms (*m/z*,%) 258 (M^++1,16), 195 (10), 184 (11), 169 (13), 145 (17) 132 (43), 118 (27), 94 (100). Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35; H, 5.87; N, 16.33. Found: C, 65.75; H, 5, 85; N, 16.50.

Keto alcohol (**18**) (lower Rf, 37 mg, 11%): ir (KBr) 3430 (OH), 1712 (CO); ^{1}H nmr 2.40-3.20 (m, 8H), 4.55-4.70 (m, 1H, 7-H), 4.80-5.00 (m, 1H, 13b-H), 6.85 (t, *J*=7 Hz, 1H, 10-H), 7.15 (t, *J*=7 Hz, 1H, 11-H), 7.50 (d, *J*=7 Hz, 1H, 12-H), 8.00 (d, *J*=7 Hz, 1H, 9-H); ^{13}C nmr ($CDCl_3$-CD_3OD) 34.7 (C-3), 46.6 (C-1), 58.2 and 58.9 (C-4 and C-6), 60.0 (C-13b), 69.8 (C-7), 113.4, 118.0, 123.0, 125.3, 134,2, 143.6, 203.7 (C=O).

Pyrido[1',2':1,2]imidazo[4,5-*a*]quinolizidin-2-one (1). A solution of the equimolecular mixture of alcohols (**17**) and (**18**) (140 mg, 0.46 mmol) and triethylsilane (0.22 ml, 1.4 mmol) in freshly distilled trifluoroacetic acid (1.03 ml, 14 mmol) was refluxed for 24 h. Once cooled at room temperature, an excess of anhydrous K_2CO_3 was added and the mixture was stirred for 30 min, before slow addition of H_2O (15 ml). The mixture was extracted with CH_2Cl_2, and the organic extracts, washed with 10% aqueous Na_2CO_3, were dried and evaporated to give an oil which was flash chromatographed (95:5, CH_2Cl_2-MeOH), thus isolating **1** as a yellow gum (45 mg, 38%): Ir (NaCl)1720 cm^{-1} (CO); ^{1}H nmr ($CDCl_3$-CD_3OD) 1.10-1.90 (m, H), 2.10 (td, *J*=12, 3 Hz, 1H), 2.95 (dt, *J*=12, 3 Hz, 1H), 3.15 (td, *J*=12, 3 Hz, 1H), 4.25 (t, *J*=12 Hz, 1H), 4.45 (dd, *J*=12, 3Hz, 1H), 6.85 (t, *J*= 7 Hz, 1H, 7-H), 7.15 (t, *J*=7 Hz, 1H, 6-H), 7.50 (d, *J*=7 Hz, 1H, 5-H), 8.00 (d, *J*=7 Hz, 1H, 8-H); ^{13}C nmr (CD_3OD) 22.6, 30.2,38.9, 39.2, 46.9, 61.2 (C-13b), 115.4 (C-12), 118.7 (C-10), 124.9 (C-11), 127.9 (C-9), 130.1 (C-7a), 132.6 (C-13a), 213.5 (C=O). Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.26; N, 17.41. Found: C, 70.06; H, 6.21; N, 17.43.

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