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NEW SYNTHESIS OF BENZO[*a*]QUINOLIZIDIN-2-ONES *via* PROTECTED 2-ARYL-4-PIPERIDONES[1]

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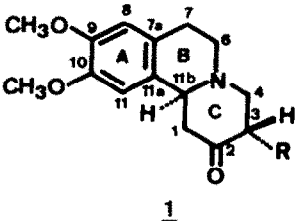
Abstract- A new synthesis of 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizin-2-one (1a) and its 3-ethyl derivative 1b *via* the corresponding 2-(3,4-dimethoxyphenyl)-4-piperidone ethylene acetals 7 is reported. Alkylation of 2-arylpiperidines 7 with 2-bromoethanol followed by oxidation of the resulting amino alcohols 9 with oxalyl chloride and dimethyl sulfoxide afforded the aldehydes 10, which were cyclized with hydrochloric acid to give 7-hydroxybenzo[*a*]quinolizidines 11. The reduction of 11 with triethylsilane and subsequent acid hydrolysis led to benzo[*a*]quinolizidin-2-ones 1.

The benzo[*a*]quinolizidin-2-one ring system[2,3] is a common synthetic intermediate in the preparation of emetine[4,5] and other related ipecac alkaloids as well as of reserpine-like activity analogues.[6,7] The synthesis of the key intermediates 1 has been previously accomplished through three different general approaches that differ in the bond formed in the key step: a) closure of the piperidine ring by Dieckmann cyclization of tetrahydroisoquinoline diesters;[8] b) closure of ring B by formation of C_{11a}-C_{11b} bond by Bischler-Napieralski reaction of *N*-phenethyl-2-piperidones;[9] c) elaboration of the piperidine ring by formation of C_1-C_{11b} bond by Mannich cyclization of a dihydroisoquinolinium ion upon the α-position of a keto group.[10,11]

In this paper we report a new synthetic entry to the benzo[*a*]quinolizidin-2-one ring system involving closure of ring B by formation of C_7-C_{7a} bond from appropriately *N*-substituted 2-aryl-4-piperidone ethylene acetals, a class of compounds for which we have recently reported a short, efficient method of preparation by Mannich-type cyclization of appropriate imino acetals.[12] The utility of 2-aryl-4-piperidones as intermediates in the synthesis of polycyclic compounds having a 2-arylpiperidine moiety, such as B-norbenzomorphans,[13] 7,8-benzomorphans,[14] the indole alkaloid uleine,[15] and analogues of the indole alkaloid ervitsine,[16] has already been established.

The required 4-piperidone ethylene acetals 7 were prepared in excellent yield by cyclization of imino acetals 6 with *p*-toluenesulfonic acid in anhydrous benzene. In turn, imines 6 were obtained by condensation of 3,4-dimethoxybenzaldehyde with the amino acetals 5. Compound 5a had been previously prepared,[12b] while 5b was conveniently obtained



a. R=H
b. R=Et

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through a three-step sequence involving reaction between ammonium salt 2[10b] and potassium phthalimide,[17] ketalisation of the resulting phthalimido ketone 3, and hydrazinolysis.

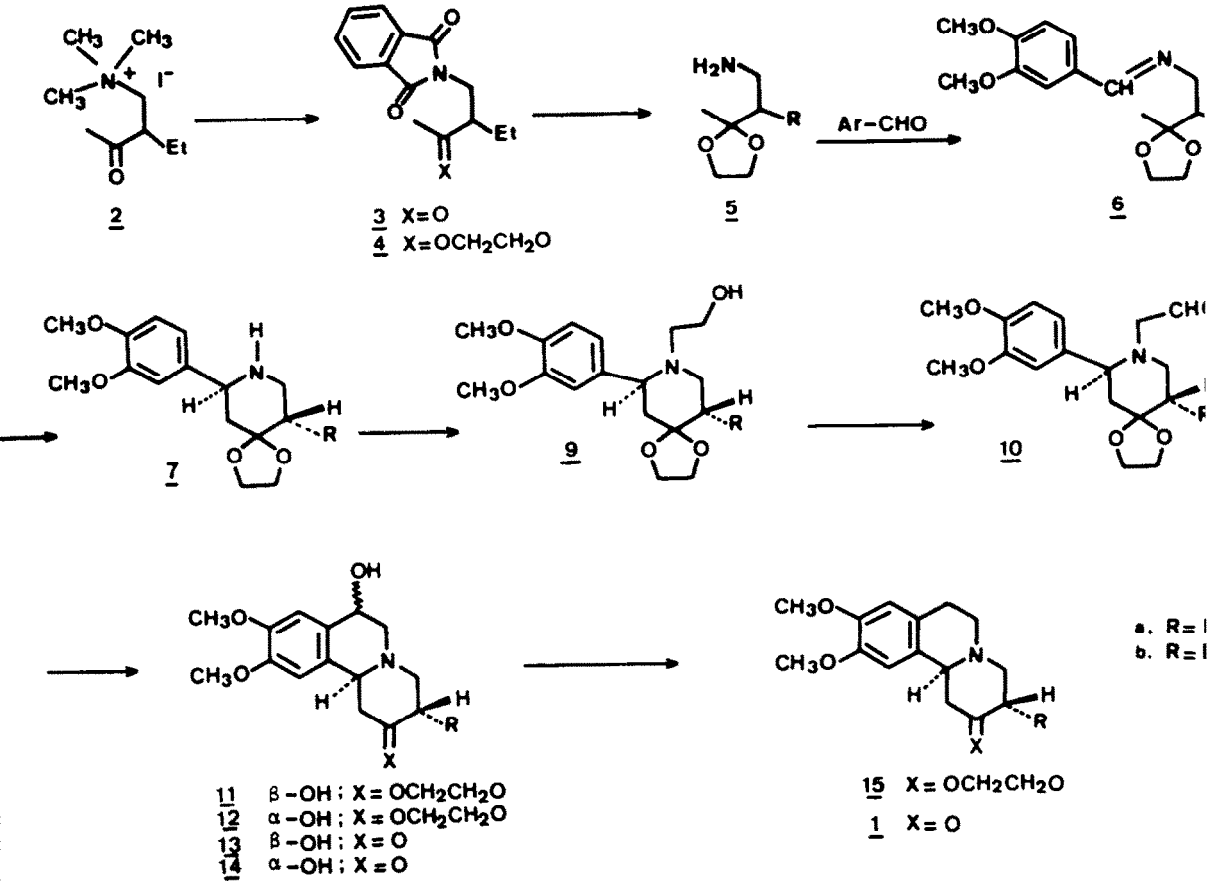
The expected[12b] *trans*-relationship between aryl and ethyl groups in 7b was established from the NMR data. In the ^{1}H-NMR spectrum the axial proton at C-6 appeared at δ 2.68 as a triplet with J=12 Hz, thus indicating a *trans*-diaxial relationship with 5-H, while the axial proton at C-2 appeared at δ 3.80 as a doublet of doublets (J=12 and 2.8 Hz) in accordance with an equatorial aryl group. Moreover, the non-observance of a "γ-gauche" effect upon C-3 in the ^{13}C-NMR spectrum of 7b, as compared with 7a, confirmed the equatorial disposition of the ethyl group.

Alkylation of piperidine 7a with methyl 2-bromoacetate followed by alkaline hydrolysis of the resulting methyl ester 8a with aqueous 2% barium hydroxide furnished an α-amino acid which, without further purification, was treated with PPA under several reaction conditions (1 h 30 min at 90 °C to 5 h at 140 °C). In no case the cyclization product could be detected. Such failure was interpreted taking into account that, under acidic conditions, α-amino acids can undergo decarbonylation.[18] However, there are some examples of PPA induced cyclizations of α-amino acids upon aromatic rings.[19] The above interpretation is in accordance with the fact that cyclization of the corresponding acyl chloride with aluminium trichloride furnished the secondary amine 7 as the sole isolable product. In this case, the iminium salt formed by decarbonylation undergoes hydrolysis to give 7.

Next, we planned to transform piperidines 7 into benzo[a]quinolizidines 15 by the Bobbit modification[20,21] of the Pommeranz-Fritsch cyclization.[22] However, the alkylation of 7a with bromoacetaldehyde ethylene (or diethyl) acetal or chloroacetaldehyde dimethyl acetal failed under a variety of experimental conditions. On the contrary, alkylation of piperidines 7 with 2-bromoethanol in the presence of anhydrous sodium carbonate was satisfactorily accomplished to give in good yields the corresponding amino alcohols 9. These alcohols were oxidized by the Swern method[23] to the unstable aldehydes 10, which were identified by their IR absorption at 1720 cm^{-1} and, without further purification, were cyclized with 4*N* hydrochloric acid.[24] Thus, when aldehydes 10 were stirred for 3 hours in 4*N* hydrochloric acid at 0 °C, 7-hydroxybenzo[a]quinolizidines 11 were obtained in 75-80% yield. The constitution and stereochemistry of compounds 11 were inferred from elemental analysis and spectroscopic data. In the IR spectrum, an OH absorption at 3420-3450 cm^{-1} as well as Bohlmann bands, characteristic of a *trans* B/C relationship,[25] were observed. The ^{1}H-NMR spectrum of 11 showed, as the most significant signal, a doublet of doublets with J=12 and 2.5 Hz at δ 3.3 due to the methine proton at C-11b. This chemical shift value is characteristic of a *trans*-fused B/C benzo[a]quinolizidine system[26] whereas the magnitude of the coupling constants made evident the axial disposition of 11b-H. The relative configuration at C-7, having a pseudoaxial hydroxy group, was deduced on the basis of the coupling constants of the 7-H signal whereas the equatorial disposition of the ethyl substituent in 11b was evident from the multiplicity of 4-Hax, which appears as a triplet with J=11.4 Hz.

When the cyclization of aldehyde 10a was effected at room temperature for 15 hours, an epimeric mixture of 7-hydroxybenzo[a]quinolizidines 11a and 12a was obtained. Compound 12a, having the 7-hydroxy group in a pseudoequatorial disposition, showed the 7-H signal as a doublet of doublets (J=7 and 4.2 Hz) at lower field (δ 4.74) than 11a (δ 4.46) due to the deshielding effect of the nitrogen lone pair.

On the other hand, when the aldehyde 10b was refluxed in the presence of 20% hydrochloric acid an epimeric mixture of quinolizidin-2-ones 13b and 14b was obtained. Their IR spectra showed an intense absorption at ν1690 cm^{-1} due to the carbonyl group. Both ketones, epimeric at C-7, were easily recognized, as above, from the chemical shift value and



signal multiplicity of 7-H. A relevant feature in the NMR spectra of the epimeric alcohols 11-12 and 13-14 is the greater deshielding of 8-H as compared with 1 when the hydroxy group is pseudoequatorial.

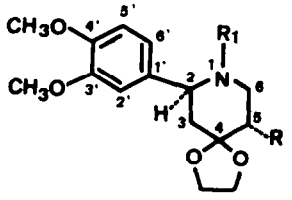
Finally, the reduction of alcohols 11 with triethylsilane in trifluoroacetic acid , followed by acid hydrolysis of the resultant acetals 15, led to the target benzo[*a*]quinolizidin-2-ones 1. Previous attempts to reduce 11a by hydrogenolysis using 10% palladium on charcoal under a variety of experimental conditions were unsuccessful.

The ^{13}C NMR data of arylpiperidines and benzo[*a*]quinolizidines[27] prepared in this work are showed in Tables 1 and 2, respectively.

EXPERIMENTAL

General- Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H-NMR spectra were recorded with a Varian XL-200 (200 MHz) spectrometer or, when indicated, on a Perkin-Elmer R-24B (60 MHz) instrument. ^{13}C-NMR spectra were recorded on a Varian XL-200 spectrometer (50.3 MHz). Unless otherwise indicated, NMR spectra were measured in $CDCl_3$, and chemical shifts are expressed in parts per million (δ) downfield from TMS as internal standard. IR spectra were taken with a Perkin-Elmer 1430 spectrophotometer, and only noteworthy absorptions (cm^{-1}) are listed. Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. Column chromatography was carried out on SiO_2 (silica gel 60, Merck, 63-200 μm). Thin layer chromatography was done on Merck silica gel 60 F_{254} aluminium precoated sheets, and the spots were located with UV light or iodoplatinate reagent. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous sodium sulfate. Microanalyses were preformed on a Carlo-Erba 1106 analyzer by Instituto de Química Bio-Orgánica, Barcelona.

Table 1. ^{13}C-NMR Chemical Shifts[a,b] of 2-(3,4-Dimethoxyphenyl)piperidines



7 R_1 = H
8 R_1 = CH_2COOCH_3
9 R_1 = CH_2CH_2OH
10 R_1 = CH_2CHO

a. R = H
b. R = CH_2CH_3

Carbon n°	7a	7b	8a	9a	9b	10b
C-2	59.1	59.3	64.1	66.1	66.0	65.4
C-3	42.9	44.1	44.0	44.4	44.8	44.3
C-4	107.4	109.7	107.0	107.0	108.8	108.7
C-5	34.5	46.6	34.8	34.8	45.7	45.8
C-6	44.1	49.2	51.0	50.0	54.8	55.9
C-1′	135.1	136.8	135.1	135.5	135.5	134.1
C-2′	110.3	109.9	110.3	110.6	110.4	110.4
C-3′[c]	149.1	149.0	149.3	149.3	149.2	149.1
C-4′[c]	148.5	148.2	148.4	148.4	148.3	148.2
C-5′	111.2	111.0	111.0	111.3	111.1	111.1
C-6′	119.1	118.8	120.0	119.9	119.9	120.3
OCH_3	55.9	55.9	55.8 55.9 51.3	55.9	55.9	55.9 56.0
OCH_2	64.3 64.6	64.9 65.2	64.2 64.4	64.3 64.4	65.1 64.9	65.2 64.9
NCH_2	----	----	55.5	54.7	54.8	57.2
XCH_2	----	----	----	58.4	58.4	----
CH_3CH_2	----	18.3	----	----	18.5	18.3
CH_2CH_3	----	12.0	----	----	12.1	12.0
C=O	----	----	171.4	----	----	201.7

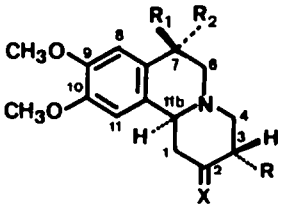
[a] In ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz. [b] The assignments are in agreement with off-resonance spectra. [c] The assignments may be interchanged.

3-(Phthalimidomethyl)-2-pentanone (3). To a solution of (2-ethyl-3-oxobutyl)trimethylammonium iodide[10b] (36.3 g, 0.13 mol) in anhydrous *N,N*-dimethylformamide (300 ml), potassium phthalimide (25.8 g, 0.14 mol) was added in small portions. The resulting suspension was refluxed for 14 h. The reaction mixture was poured into water-ice and extracted with chloroform. The organic extract was washed with aqueous sodium carbonate, dried, and evaporated to give phthalimide 3 (19.1 g, 60%): m.p. 43-44 °C (hexane-ether); IR (NaCl) 1710 and 1765 (C=O); ^{1}H-NMR (CCl_4, 60 MHz) 0.9 (t, 3H, CH_2CH_3), 1.6 (m, 2H, CH_2CH_3), 2.1 (s, 3H, $COCH_3$), 2.5-2.9 (m, 1H, COCH), 3.65 (d, J=6 Hz, 2H, NCH_2), 7.5-7.6 (m, 4H, ArH). (Found: C, 68.61; H, 6.12; N, 5.83. Calcd. for $C_{14}H_{15}NO_3$: C, 68.54; H, 6.16; N, 5.70).

3-(Phthalimidomethyl)-2-pentanone Ethylene Acetal (4). A stirred solution of the phthalimido ketone 3 (66.5 g, 0.27 mol), *p*-toluenesulfonic acid monohydrate (25.7 g, 0.13 mol), ethylene glycol (50.2 g, 0.81 mol), and anhydrous benzene (500 ml) was refluxed for 20 h with removal of water by a Dean-Stark trap. The reaction mixture was poured into ice-water and extracted with benzene. The extracts were washed with aqueous potassium carbonate, dried, and evaporated to give the phthalimido acetal 4 (57.7 g, 74%): m.p. 52-54 °C (hexane-ether); IR (NaCl) 1710 and 1770 (C=O); ^{1}H-NMR (CCl_4, 60 MHz) 1.0 (m, 3H, CH_2CH_3), 1.25 (s, 3H, $OCCH_3$), 3.5 (d, J=6 Hz, 2H, NCH_2), 3.73 (s, 4H, OCH_2), 7.6 (br s, 4H, ArH). (Found: C, 66.70; H, 6.61; N, 5.03. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84).

N-(3,4-Dimethoxybenzylidene)-3,3-ethylenedioxybutylamine (6a). A solution of the amino acetal 5a[12b] (9.2 g, 70 mmol) and 3,4-dimethoxybenzaldehyde (10.6 g, 64 mmol) in anhydrous benzene (200 ml) was stirred at 0 °C for 30 min, at room temperature overnight, and under

Table 2. ^{13}C-NMR Chemical Shifts[a,b] of Benzo[a]quinolizidines



a. R= H
b. R= CH_2CH_3

Carbon n°	11a	11b	13a	13b	14b	15a	15b	1a[c]	1b
C-1	41.0	41.4	47.3	47.6	46.5	40.8	40.4	47.6	47.6
C-2	107.7	109.7	208.3	209.1	210.0	107.9	109.3	208.7	209.7
C-3	34.7	46.4	41.3	51.6	50.1	34.3	45.0	41.1	51.1
C-4	53.2	59.4	54.5	60.4	60.4	53.5	57.9	54.8	60.8
C-6	59.3	57.9	58.8	58.7	56.4	51.5	51.1	50.8	50.5
C-7	66.8	67.0	66.7	66.9	66.5	29.3	28.6	29.3	29.4
C-7a	128.9	129.2	128.3	128.5	128.9	126.5	126.3	126.2	126.1
C-8	112.2	112.2	112.3	112.1	110.5	111.5	111.6	111.5	111.5
C-9[d]	148.9	148.8	149.3	148.4	148.4	147.5	147.6	147.9	147.8
C-10[d]	148.0	148.0	148.5	149.2	148.8	147.2	147.1	147.6	147.5
C-11	107.4	107.6	107.2	107.2	107.7	108.1	108.2	107.9	107.9
C-11a	129.9	130.2	129.0	128.9	129.4	129.6	129.0	128.6	128.6
C-11b	60.1	60.1	61.6	62.5	62.2	59.8	59.6	61.5	62.4
CH_2CH_3	----	18.3	----	19.3	19.3	----	18.1	----	19.3
CH_2CH_3	----	12.0	----	11.6	11.7	----	11.7	----	11.7
OCH_3	55.9 56.0	55.9 56.1	56.0 56.1	55.9 56.0	56.0 56.1	55.8 56.1	55.6 56.0	55.9 56.0	55.9 56.0
OCH_2	64.4 64.5	65.3 65.4	----	----	----	64.4 64.5	65.0 65.2	----	----

[a] In ppm relative to TMS. Measured in $CDCl_3$ solution at 50.3 MHz. [b] The assignments are in agreement with off-resonance spectra. [c] ^{13}C-NMR chemical shifts of 1a are the same (±0.5 ppm) than in reference 27a. [d] The assignments may be interchanged.

reflux for 4 h. After 16 h of additional refluxing with removal of water by a Dean-Stark trap, the solvent was evaporated to give the imine 6a (17 g, 98%): m.p. 35-36 °C (acetone); IR (NaCl) 1640 (C=N); ^{1}H-NMR (60 MHz) 1.25 (s, 3H, $OCCH_3$), 1.9 (t, 2H, $OCCH_2$), 3.5 (t, 2H, NCH_2), 3.6-3.7 (3 s, 9H, OCH_3), 3.8 (s, 4H, OCH_2), 6.5-7.0 (m, 2H, Ar-H), 7.2 (d, J=1 Hz, 1H, Ar-H), 7.9 (s, 1H, =CH); MS *m/e* (relative abundance) 279 (M^+, 23), 236 (36), 206 (82), 192 (22), 191 (100), 175 (23), 168 (45), 151 (28), 89 (32), 77 (22). (Found: C, 64.62; H, 7.31; N, 4.93. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.57; N, 5.01).

N-(3,4-Dimethoxybenzylidene)-2-ethyl-3,3-ethylenedioxybutylamine (6b). A solution of phthalimide 4 (62.4 g, 0.21 mol), 80% hydrazine hydrate (200 ml), and methanol (600 ml) was refluxed for 20 h, and then the solvent was distilled. The residue was cooled and aqueous 2*N* potassium hydroxide (150 ml) was added. After stirring for 30 min, the solution was extracted with methylene chloride. The extract was washed with water, dried, and the solvent distilled at atmospheric pressure to give *3-(aminomethyl)-2-pentanone ethylene acetal* (5b) (20 g, 60%): ^{1}H-NMR (60 MHz) 0.93 (m, 3H, CH_2CH_3), 1.16 (s, 3H, $OCCH_3$), 1.2-1.6 (complex signal, 5H, NH_2, CH_2CH_3, and CH), 2.4 (m, 2H, NCH_2), 3.73 (s, 4H, OCH_2). A mixture of amine 5b and 3,4-dimethoxybenzaldehyde (33.4 g, 0.14 mol) in anhydrous benzene (500 ml) was allowed to react as in the above deethyl series to give imine 6b (35 g, 90%): IR (NaCl) 1640 (C=N); ^{1}H-NMR (60 MHz) 0.96 (m, 3H, CH_2CH_3), 1.3 (s, 3H, $COCH_3$), 3.7 (s, 10H, OCH_2 and OCH_3), 6.5-7.4 (m, 3H, Ar-H), 8.03 (br s, 1H, =CH).

2-(3,4-Dimethoxyphenyl)-4-piperidone Ethylene Acetal (7a). A stirred mixture of the imino acetal 6a (19 g, 68 mmol) and anhydrous *p*-toluenesulfonic acid (25.8 g, 0.15 mol) in anhydrous benzene (450 ml) was refluxed under nitrogen for 1 h. The cooled mixture was poured into aqueous 5% hydrochloric acid. The aqueous phase was basified with sodium carbonate and extracted with methylene chloride. The extract was dried and evaporated to give piperidine 7a as a yellow solid (17.6 g, 93%): m.p. 78-79 °C (ether-acetone); IR (KBr) 3300 (NH); ^{1}H-NMR 1.6-2.0 (m, 3H, 3-He and 5-H), 1.76 (br t, *J*=12 Hz, 1H, 3-Ha), 2.99 (td, *J*=12, 12, 2.4 Hz, 1H, 6-Ha), 3.14 (ddd, *J*=12, 3.6, 1.6 Hz, 1H, 6-He), 3.6-3.9 (m, 1H, 2-Ha), 3.85 and 3.88 (2s, 3H each, OCH_3), 3.99 (br s, 4H, OCH_2), 6.80 (d, *J*=8 Hz, 1H, Ar-H_5), 6.93 (dd, J=8, 2 Hz, 1H, Ar-H_6), 7.02 (d, *J*=2 Hz, 1H, Ar-H_2); MS *m/e* (relative abundance) 279 (M^+, 81), 249 (25), 248 (92), 234 (100), 218 (44), 192 (36), 178 (36) 164 (73), 87 (29). The hydrochloride melted at 217-218 °C (acetone): ^{1}H-NMR (60 MHz) 3.7 (s, 3H, OCH_3), 3.8 (s, 3H, OCH_3), 3.9 (s, 4H, OCH_2), 4.2 (dd, *J*=12, 3 Hz, 1H, 2-Ha), 7.0-7.3 (m, 3H, Ar-H). (Found: C, 57.05; H, 7.15; N, 4.37; Cl, 11.20. Calcd. for $C_{15}H_{22}ClNO_4$: C, 57.05; H, 7.02; N, 4.43; Cl, 11.22).

trans-2-(3,4-Dimethoxyphenyl)-5-ethyl-4-piperidone Ethylene Acetal (7b). Operating as above, from imine 6b (41.7 g, 0.135 mol) and anhydrous *p*-toluenesulfonic acid (54 g, 0.315 mol) in anhydrous benzene (600 ml), ethylene acetal 7b (26 g, 67%) was obtained: m.p. 106-107 °C (ether); IR (KBr) 3280 (NH); ^{1}H-NMR 0.94 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.0-1.2 (m, 2H, CH_2CH_3), 1.66 (t, *J*=12.6 Hz, 1H, 3-Ha), 1.78 (m, 1H, 5-H), 1.90 (dd, *J*=12.6, 2.8 Hz, 1H, 3-He), 2.68 (t, *J*=12 Hz, 1H, 6-Ha), 3.28 (dd, *J*=12, 4.2 Hz, 1H, 6-He), 3.80 (dd, *J*=12, 2.8 Hz, 1H, 2-Ha), 3.86 and 3.89 (2s, 3H, OCH_3), 3.95-4.0 (m, 4H, OCH_2), 6.80 (d, *J*=8 Hz, 1H, Ar-H_5), 6.90 (dd, *J*=8, 2 Hz, 1H, Ar-H_6), 6.94 (d, *J*=2 Hz, 1H, Ar-H_2) MS *m/e* (relative abundance) 307 (M^+, 16), 262 (31), 172 (11), 178 (40), 164 (100), 115 (40), 99 (30), 87 (49). The hydrochloride melted at 205-206 °C (acetone-ether): ^{1}H-NMR 0.80 (t, *J*=7 Hz, 3H, CH_2CH_3), 0.9-1.1 (m, 2H, CH_2CH_3), 1.5-1.7 (m, 1H, 5-H), 1.90 (dd, *J*=14, 2.8 Hz, 1H, 3-He), 2.28 (t, *J*=12.6 Hz, 1H, 3-Ha), 2.75 (t, *J*=12.6 Hz, 1H, 6-Ha), 3.01 (dd, *J*=12.6, 4.2 Hz, 1H, 6-He), 3.83 and 3.89 (2s, 3H each, OCH_3), 3.9-4.0 (m, 4H, OCH_2), 4.16 (dd, *J*=12.6, 2.8 Hz, 1H, 2-Ha), 6.87 (d, *J*=8.3 Hz, 1H, Ar-H_5), 7.05 (dd, *J*=8.3, 2.2 Hz, 1H, Ar-H_6), 7.31 (d, *J*=2.2 Hz, 1H, Ar-H_2). (Found: C, 59.32; H, 7.50; N, 4.12. Calcd. for $C_{17}H_{26}ClNO_4$: C, 59.38; H, 7.62; N, 4.07).

2-(3,4-Dimethoxyphenyl)-1-(methoxycarbonylmethyl)-4-piperidone Ethylene Acetal (8a). To a mixture of piperidine 7a (8.5 g, 30 mmol) and anhydrous sodium carbonate (10 g) in absolute ethanol (250 ml), methyl 2-bromoacetate (2.8 ml, 30 mmol) was added dropwise. The resulting mixture was refluxed overnight and the ethanol was evaporated. The residue was dissolved in aqueous 5% hydrochloric acid and the resulting solution was washed with methylene chloride. The aqueous layer was basified with aqueous 20% potassium carbonate and extracted with methylene chloride. Evaporation of the dried organic extract yielded 8a (10.2 g, 98%): m.p. 105-106 °C (ethanol); IR (KBr) 1740 (C=O); ^{1}H-NMR 1.7-1.8 (m, 2H, 3- and 5-He), 1.94 (t, *J*=10.7 Hz, 3-Ha), 2.04 (td, *J*=11.6, 4.4 Hz, 5-Ha), 2.67 (td, *J*=11.2, 2.6 Hz, 1H, 6-Ha), 2.88 and 3.28 (AB, *J*=14 Hz, 2H, NCH_2CO), 3.08 (ddd, *J*=11.2, 4.5, 2.6 Hz, 1H, 6-He), 3.56 (dd, J=11.2, 2.2 Hz, 1H, 2-Ha), 3.57 (s, 3H, $COOCH_3$), 3.81 and 3.82 (2s, 3H each, OCH_3), 3.8-3.9 (m, 4H, OCH_2), 6.80 (d, J=8 Hz, 1H, Ar-H_5), 6.88 (dd, *J*=8, 1.6 Hz, 1H, Ar-H_6), 6.96 (d, *J*=1.6 Hz, 1H, Ar-H_2); MS *m/e* (relative abundance) 351 (M^+, 1), 294 (10), 128 (22), 99 (24), 87 (20), 42 (100). (Found: C, 61.78; H, 7.45; N, 3.90. Calcd. for $C_{18}H_{25}NO_6$: C, 61.50; H, 7.17; N, 3.98).

2-(3,4-Dimethoxyphenyl)-1-hydroxyethyl-4-piperidone Ethylene Acetal (9a). 2-Bromoethanol (4.3 ml, 60.8 mmol) was added dropwise to a mixture of piperidine 7a (8.5 g, 30.4 mmol) and anhydrous sodium carbonate (10 g) in absolute ethanol (250 ml). The resulting mixture was stirred at reflux under nitrogen for 15 h. The ethanol was evaporated and the residue was dissolved in aqueous 5% hydrochloric acid and washed with ether. The aqueous phase was basified with potassium carbonate and extracted with methylene chloride. The dried organic extract was evaporated to give an oil which was chromatographed. On elution with chloroform, product 9a (7 g, 71%) was obtained: IR (NaCl) 3600-3300 (OH); ^{1}H-NMR 1.6-2.0 (m, 2H, 3-He and 5-He), 1.84 (t, *J*=12 Hz, 1H, 3-Ha), 2.32 (td, *J*=12, 2.4 Hz, 1H, 5-Ha), 2.46 (br, 1H, OH), 2.64 and 2.70 (2 dd, J=10, 4.8 Hz, 2H, NCH_2), 3.12 (ddd, *J*=10, 4.2, 2.4 Hz, 1H, 6-He), 3.2-3.3 (m, 2H, OCH_2), 3.32 (dd, *J*=10, 3.6 Hz, 1H, 2-Ha), 3.56 (td, *J*=10, 3.6 Hz, 1H, 6-Ha), 3.79 and 3.81 (2s, 3H each, OCH_3), 3.9 (m, 4H, OCH_2), 6.7-6.8 (m, 3H, Ar-H); MS *m/e* (relative abundance) 323 (M^+, 4), 292 (60), 177 (10), 149 (18), 128 (78), 99 (78), 87 (60), 55 (22), 43 (37), 42 (100). The hydrochloride melted at 151-152 °C (ether-methanol). (Found: C, 56.89; H, 6.94; N, 3.70; Cl, 9.90. Calcd. for $C_{17}H_{26}ClNO_5$: C, 56.74; H, 7.28; N, 3.89; Cl, 9.85).

trans-2-(3,4-Dimethoxyphenyl)-5-ethyl-1-hydroxyethyl-4-piperidone Ethylene Acetal (9b). Operating as above, from piperidine 7b (5 g, 16.2 mmol), 2-bromoethanol (2.3 ml, 32.4 mmol), and anhydrous sodium carbonate (5 g) in absolute ethanol (100 ml), piperidine 9b (4.6 g, 81%) was obtained: m.p. 108-109 °C (ether-acetone); IR (KBr) 3000-3400 (OH); ^{1}H-NMR 0.96 (t, J=7 Hz, 3H, CH_2CH_3), 1.0-1.2 (m, 2H, CH_2CH_3), 2.6-2.8 (2 dd, J=10, 10, 5 Hz, 2H, NCH_2), 3.24 (dd, J=11, 3.7 Hz, 1H, 2-Ha), 3.3-3.4 (m, 3H, 6-He and OCH_2), 3.86 and 3.87 (2s, 3H each, OCH_3), 3.9-4.1 (m, 4H, OCH_2CH_2O), 6.8-6.86 (m, 3H, Ar-H); MS *m/e* (relative abundance) 351 (M^+, 1), 320 (16), 171 (19), 164 (14), 156 (63), 151 (10), 127 (54), 115 (65), 58 (52), 43 (100). (Found: C, 64.99; H, 8.59; N, 4.08. Calcd. for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.31; N, 3.98).

2-(3,4-Dimethoxyphenyl)-4,4-ethylenedioxy-1-piperidineacetaldehyde (10a). A solution of dimethyl sulfoxide (3.78 g, 50 mmol) in anhydrous methylene chloride (50 ml) was added dropwise under nitrogen to a solution of oxalyl chloride (2.78 g, 23 mmol) in anhydrous methylene chloride (50 ml). After stirring at -60 °C for 20 min, a solution of ethanolamine 9a (6.64 g, 20.5 mmol) in anhydrous methylene chloride (40 ml) was slowly added to the resulting mixture and stirring was continued for 3 h. Triethylamine (10.3 g, 0.1 mol) was added at -60 °C at a flow rate of 0.2 ml/min. The cooling bath was removed and the reaction was allowed to reach room temperature. Then, water (60 ml) was added and the mixture stirred for 30 min. The organic layer was separated, washed with water, dried, and evaporated to give a pale brown oil (80%) which was crystallized to an unstable solid: m.p. 58-60 °C (acetone); IR (NaCl) 1720 (C=O); ^{1}H-NMR (60 MHz) 1.6-2.1 (m, 4H, 3-H and 5-H), 2.65 and 3.15 (2d, J=17 Hz, 2H, NCH_2CO), 3.33 (br t, J=10 Hz, 1H, 6-Ha), 3.78 (s, 6H, OCH_3), 3.88 (br s, 4H, OCH_2CH_2O), 6.6-6.8 (m, 3H, Ar-H), 9.3 (br s, 1H, CHO).

trans-2-(3,4-Dimethoxyphenyl)-5-ethyl-4,4-ethylenedioxy-1-piperidineacetaldehyde (10b). Operating as above, from dimethyl sulfoxide (4.1 ml, 57.7 mmol), oxalyl chloride (2.3 ml 26.7 mmol), piperidine 9b (8.7 g, 24.7 mmol), and triethylamine (17 ml, 124 mmol) in methylene chloride (130 ml), aldehyde 10b was obtained (8.38 g, 97%) as a very unstable oil: IR (NaCl) 1718 (C=O); ^{1}H-NMR 0.97 (t, J=7 Hz, 3H, CH_2CH_3), 1.0-1.2 (m, 1H, CH_2CH_3), 1.6-1.8 (m, 1H, CH_2CH_3) , 2.32 (t, J=12 Hz, 1H, 3-Ha), 2.80 (dd, J=17, 2.4 Hz, 1H, NCH_2CO), 3.04 (dd, J=11, 4 Hz, 1H, 6-He), 3.24 (dd, J=17 Hz, 1.2 Hz, 1H, NCH_2CO), 3.39 (t, J=7 Hz, 1H, 6-Ha), 3.86 and 3.87 (2s, 3H each, OCH_3), 3.8-3.95 (m, 4H, OCH_2CH_2O), 6.7-7.1 (m, 3H, Ar-H), 9.50 (br s, 1H, CHO).

7-Hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-2-one Ethylene Acetal (11a). A solution of piperidine 10a (4.8 g, 15 mmol) in aqueous 4N hydrochloric acid (125 ml) was stirred at 0 °C for 3 h 15 min. The mixture was basified (pH=8) and extracted with methylene chloride. The organic layer provided benzo[*a*]quinolizidine 11a as an oil which was purified by "flash chromatography" on elution with 85:15 ether-acetone (3.6 g, 75%): IR (KBr) 3420 (OH), 2840-2800 (Bohlmann bands); ^{1}H-NMR 3.34 (dd, J=12, 2.5 Hz, 1H, 11b-H), 3.86 and 3.88 (2s, 3H each, OCH_3), 4.0-4.1 (m, 4H, OCH_2), 4.46 (t, J=2.4 Hz, 1H, 7-H), 6.62 (s, 1H, 11-H), 6.87 (s, 1H, 8-H); MS *m/e* (relative abundance) 321 (M^+, 9), 304 (M^+-OH, 20), 292 (26), 279 (24), 248 (24), 234 (38), 218 (22), 178 (54) 164 (35), 147 (33), 149 (100), 99 (17). The picrate melted at 168-170 °C (ethanol) (Found: C, 79.12, H, 7.32; N, 15.65. Calcd. for $C_{23}H_{26}N_4O_{12}$: C, 78.82; H, 7.47; N, 15.98) When the reaction was carried out at room temperature for 15 h, a 1:1 mixture of epimeric alcohols 11a and 12a was obtained. Pure isomer 12a was isolated by column chromatography on elution with 1:1 benzene-chloroform: IR (NaCl) 3300-3500 (OH), 2825-2910 (Bohlmann bands); ^{1}H-NMR 3.58 (dd, J=12.6, 2.8 Hz, 1H, 11b-H), 3.84 and 3.87 (2s, 3H each, OCH_3), 3.9-4.1 (m, 4H, OCH_2), 4.74 (dd, J=7, 4.2 Hz, 1H, 7-H), 6.53 (s, 1H, 11-H), 6.99 (s, 1H, 8-H). Operating at 40 °C, ketone 13a was also detected from the reaction mixture and separated by column chromatography on elution with chloroform: m.p. 199-200 °C (acetone-ether); IR (KBr) 3400 (OH), 2740-2840 (Bohlmann bands), 1680 (C=O); ^{1}H-NMR 3.45 (dd, J=12, 2.5 Hz, 1H, 11b-H), 3.85 and 3.90 (2s, 3H each, OCH_3), 4.54 (t, J=2.2 Hz, 1H, 7-H), 6.57 (s, 1H, 11-H), 6.92 (s, 1H, 8-H); MS *m/e* (relative abundance) 277 (M^+, 22), 260 (M^+-OH, 44), 178 (38), 167 (16), 149 (88), 127 (22), 84 (50), 71 (72), 57 (97), 44 (100), 43 (91), 42 (41). (Found: C, 64.51; H, 6.87; N, 4.82. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.90; N, 5.05).

3-Ethyl-7-hydroxy-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]quinolizin-2-one Ethylene Acetal (11b). Operating as above (0 °C, 4 h), from piperidine 10b (0.73 g, 2 mmol) and aqueous 4N hydrochloric acid (18 ml), alcohol 11b (0.6 g, 87%) was obtained after column chromatography (1:1 benzene-chloroform as eluent): m.p. 145-146 °C (ether-acetone); IR (KBr) 3450 (OH), 2750-2800 (Bohlmann bands); ^{1}H-NMR 0.94 (t, J=7 Hz, 3H, CH_2CH_3), 1.0-1.3 (m, 1H, CH_2CH_3), 2.36 (t, J= 11.4 Hz, 1H, 4-Ha), 3.30 (dd, J=12, 2.5

1H, 11b-H), 3.87 and 3.88 (2s, 3H each, OCH_3), 3.9-4.1 (m, 4H, OCH_2CH_2O), 4.44 (br s, 1H, 7-H), 6.60 (s, 1H, 11-H), 6.87 (s, 1H, 8-H); MS *m/e* (relative abundance) 350 (M^+, 1), 349 (3), 262 (6), 219 (4), 204 (5), 190 (7), 178 (16), 127 (18), 115 (9), 99 (14), 87 (30), 86 (60), 45 (81), 43 (100), 42 (93). (Found: C, 64.86: H, 8.16; N, 3.34. Calcd. for $C_{19}H_{27}NO_5.C_3H_6O$: C, 64.80; H, 8.10; N, 3.43). When the reaction was carried out from piperidine 10b (1.5 g, 4.3 mmol) and aqueous 4*N* hydrochloric acid (36 ml) at 50 °C for 5 h, a nearly equimolecular mixture of two isomeric ketones 13b and 14b (0.72 g, 55%) was obtained and separated by column chromatography. Elution with 1:1 benzene-chloroform furnished alcohol 13b (0.3 g) as a solid: m.p. 107-108 °C (ether-acetone); IR (KBr) 3420 (OH), 1685 (C=O); ^{1}H-NMR 0.98 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.3 (m, 1H, CH_2CH_3), 1.85 (m, 1H, CH_2CH_3), 3.42 (dd, *J*=12, 2.5 Hz, 1H, 11b-H), 3.87 and 3.91 (2s, 3H each, OCH_3), 4.56 (t, *J*=2.2 Hz, 1H, 7-H), 6.58 (s, 1H, 11-H), 6.92 (s, 1H, 8-H); MS *m/e* (relative abundance) 305 (M^+, 3), 288 (M^+-OH, 5), 190 (11), 178 (55), 91 (23), 70 (21), 54 (28), 41 (67), 42 (100), 43 (77). (Found: C, 66.89; H, 7.73; N, 4.49. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.58). Elution with 3:7 benzene-chloroform afforded alcohol 14b as a solid: m.p. 182-183 °C (acetone-ether); IR (KBr) 3170 (OH), 1690 (C=O); ^{1}H-NMR 0.96 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.22 (m, 1H, CH_2CH_3), 1.88 (m, 1H, CH_2CH_3), 3.40 (dd, *J*=11.5, 3.5 Hz, 1H, 11b-H), 3.85 and 3.89 (2s, 3H each, OCH_3), 4.75 (br s, 1H, 7-H), 6.50 (s, 1H, 11-H), 6.99 (s, 1H, 8-H); MS *m/e* (relative abundance) 306 (M^++1, 9), 305 (M^+, 46), 304 (27), 288 (M^+-OH, 74), 262 (43), 178 (100), 55 (21), 43 (21), 42 (22). (Found: C, 66.79; H, 7.66; N, 4.25. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.58).

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]*quinolizin-2-one Ethylene Acetal* (15a). To a solution of alcohol 11a (1.6 g, 4.98 mmol) in anhydrous methylene chloride (36 ml), trifluoroacetic acid (4.3 ml, 57 mmol) and triethylsilane (2.8 ml, 17.5 mmol) were successively added dropwise. The mixture was refluxed under nitrogen for 24 h, cooled, basified with anhydrous sodium carbonate, and poured into water (50 ml). The aqueous solution was extracted with methylene chloride and the organic extracts were washed with aqueous sodium bicarbonate, dried, and evaporated to give a brown oil which was chromatographed. On elution with chloroform, pure 15a (0.7 g, 50%) was obtained: IR (NaCl) 2740-2840 (Bohlmann bands); ^{1}H-NMR 3.34 (br d, *J*=12 Hz, 1H, 11b-H), 3.77 (s, 6H, OCH_3), 3.9-4.0 (m, 4H, OCH_2CH_2O), 6.52 and 6.55 (2s, 2H, 8-H and 11-H). The hydrochloride melted at 247-249 °C (acetone). (Found: C, 59.76; H, 6.95; N, 4.17. Calcd. for $C_{17}H_{24}ClNO_4$: C, 59.72; H, 7.07; N, 4.10).

3-Ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]*quinolizin-2-one Ethylene Acetal* (15b). Operating as above, from alcohol 11b (0.3 g, 0.86 mmol), trifluoroacetic acid (0.8 ml, 10.6 mmol), and triethylsilane (0.49 ml, 3.1 mmol) in methylene chloride (10 ml), benzo[a]quinolizidine 15b was obtained (87 mg, 30%) after column chromatography using chloroform as eluent: IR (NaCl) 2740-2840 (Bohlmann bands); ^{1}H-NMR 0.94 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.0-1.3 (m, 1H, CH_2CH_3), 1.6-1.7 (m, 1H, CH_2CH_3), 3.36 (br d, *J*=12 Hz, 1H, 11b-H), 3.84 and 3.86 (2s, 3H each, OCH_3), 3.8-4.1 (m, 4H, OCH_2CH_2O), 6.59 (s, 2H, 8-H and 11-H); MS *m/e* (relative abundance) 333 (M^+, 43), 332 (54), 290 (13), 288 (19), 246 (82), 218 (17), 205 (28), 191 (39), 176 (29), 146 (21), 86 (74), 84 (100), 55 (15) 49 (17). The hydrochloride melted at 235-236 °C (acetone). (Found: C, 59.78; H, 7.47; N, 3.28. Calcd. for $C_{19}H_{28}ClNO_4.1/2H_2O$: C, 60.15; H, 7.38; N, 3.69).

9,10-Dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]*quinolizin-2-one* (1a). A solution of acetal 15a (290 mg, 0.95 mmol) in methanol (10 ml) and aqueous 4*N* hydrochloric acid (20 ml) was stirred at 40 °C for 7 h. The resulting solution was basified with potassium carbonate and extracted with methylene chloride. The organic layer was dried and the solvent removed to leave a brown solid (220 mg, 89%): m.p. 149-150 °C (acetone) (lit.[8b] 150-151 ; CH_3OH); IR ($CHCl_3$) 2760-2840 (Bohlmann bands), 1710 (C=O); ^{1}H-NMR 3.52 (br d, *J*=12 Hz, 1H, 11b-H), 3.83 and 3.86 (2s, 3H each, OCH_3), 6.58 (s, 1H, Ar-H), 6.66 (s, 1H, Ar-H); MS *m/e* (relative abundance) 261 (M^+, 46), 260 (100), 218 (21), 191 (15), 176 (11), 84 (5), 49 (7), 42 (8).

3-Ethyl-9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2H-benzo[a]*quinolizin-2-one* (1b). Operating as above, from acetal 15b (0.5 g, 1.5 mmol), methanol (30 ml), and aqueous 4*N* hydrochloric acid (50 ml), compound 1b was obtained (360 mg, 83%) after column chromatography on elution with 80:20 benzene-chloroform: m.p. 106-107 °C (ether-acetone) (lit.[11a] 107-108 °C); IR (KBr) 2750-2820 (Bohlmann bands), 1710 (C=O); ^{1}H-NMR 0.96 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.27 (m, 1H, CH_2CH_3), 1.90 (m, 1H, CH_2CH_3), 3.48 (dd, *J*=12, 2.4 Hz, 1H, 11b-H), 3.83 and 3.86 (2s, 3H each, OCH_3), 6.56 (s, 1H, Ar-H), 6.63 (s, 1H, Ar-H); MS *m/e* (relative abundance) 289 (M^+, 12), 288 (18), 246 (18), 218 (5), 210 (40), 192 (18), 191 (31), 190 (18), 164 (58), 151 (100), 150 (91), 92 (66), 42 (38).

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