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MERCURIC ACETATE CYCLIZATION OF 4-(ARYLMETHYL)PIPERIDINES: SYNTHESIS OF INDOLO[2,3-g]MORPHANS (TETRACYCLIC RING SYSTEM OF *STRYCHNOS* INDOLE ALKALOIDS) AND 7,8-BENZOMORPHANS.

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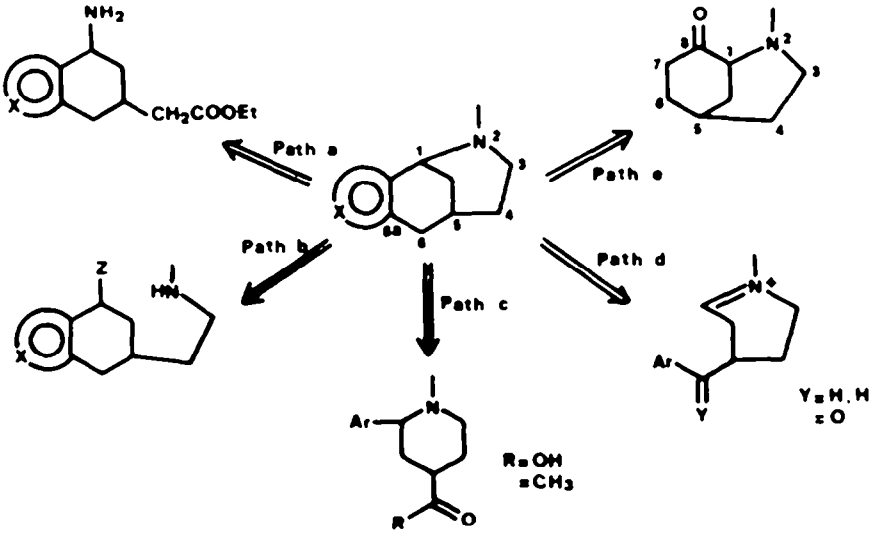
Abstract - A new synthetic route to indolo[2,3-g]morphans and 7,8-benzomorphans is reported. The key step in these syntheses is the mercuric acetate oxidation of appropriate 2-(4-piperidylmethyl)indoles or 4-benzylpiperidines, respectively. An alternative synthetic entry to 2-(4-piperidylmethyl)indoles, consisting in Wadsworth-Emmons condensation of a suitable 4-piperidone with diethyl 2-oxopropylphosphonate followed by catalytic hydrogenation and Fischer indolization of the resulting 4-acetonylpiperidine, is described.

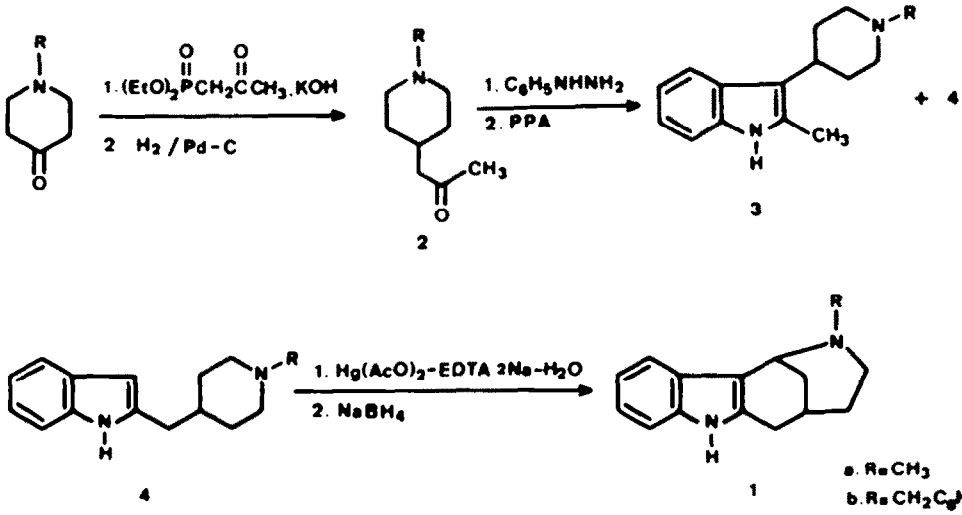
The framework of 2-azabicyclo[3.3.1]nonane (morphan)[2] is a common feature of many natural (morphine and *Strychnos* indole alkaloids) and synthetic products (6,7-benzomorphans[3] and related groups of analgesics[4]), in which this nucleus is fused to an aromatic ring. The synthesis of compounds having an aromatic ring condensed with the g side (C_7-C_8) of the morphan system has been accomplished through five different approaches, that differ in the bond formed in the last step: a) Closure of the piperidine ring by lactamization of 4-amino-1,2,3,4-tetrahydronaphthalene 2-acetic acid derivatives, as in the first synthesis[5] of 7,8-benzomorphans. b) Elaboration of the piperidine ring implying formation of C_1-N bond in the last step, such as occurs in the synthesis of indolo[3,2-g]-,[6] and thiazolo[4,5-g]morphans.[7]



c) Formation of the C_6-C_{6a} bond either by PPA cyclization of 2-(3-indolyl)-4-piperidinecarboxylic acids[8] or by treatment of 4-acetyl-2-(3-indolyl)piperidines with boron trifluoride-etherate or p-toluenesulfonic acid.[9] These processes have been frequently used in the synthesis of the indole alkaloids uleine and dasycarpidone, and in that of related compounds having the indolo[2,3-g]morphan skeleton. The first procedure has also been applied to the synthesis of 7,8-benzomorphans,[10] pyrrolo[2,3-g]-,[11] and pyrrolo[3,2-g]morphans.[11] d) Cyclization of 4-(arylmethyl)- or 4-aroyl-2,3,4,5-tetrahydropyridinium salts generated either by isomerization of 4-benzoyl-[12] or 4-(indolylcarbonyl)-1,2,3,6-tetrahydropyridines[13] to the corresponding 1,2,3,4-tetrahydropyridines followed by acid treatment or, by mercuric acetate oxidation of 4-(2-pyrrolylmethyl)- or 4-(3-indolylmethyl)piperidines.[14] The latter have also been generated by acid treatment of 2-cyano-4-(3-indolylmethyl)piperidines.[15,16] e) Elaboration of the aromatic ring in the last step from an appropriate functionalized 2-azabicyclo[3.3.1]nonane. This methodology has received application to the synthesis of heteromorphans[17] such as indolo[3,2-g]-,[6] pyrazolo[4,3-g]-,[18] pyrimido[5,4-g]-,[18] pyrido[3,2-g]-,[18] pyrido[2,3-g]-[19] and thiazolo[5,4-g]morphans.[7]

In this paper we report the mercuric acetate cyclization of appropriate 4-(arylmethyl)piperidines as a new synthetic entry to indolo[2,3-g]morphans,[20] tetracyclic ring system present in the *Strychnos* indole alkaloids, and to 7,8-benzomorphans,[21] structural analogues of 6,7-benzomorphans.

Several synthetic routes towards 4-(2-indolylmethyl)piperidines have been reported.[22,23] However, in order to prepare piperidines 2 required for the synthesis of indolo[2,3-g]morphans 1 we have developed an alternative procedure consisting in the Fischer indole synthesis[24] from 1-(4-piperidyl)-2-propanones. The latter are easily accessible from 4-piperidones through Wadsworth-Emmons condensation with diethyl 2-oxopropylphosphonate and further catalytic hydrogenation according to our previously reported procedure.[25]

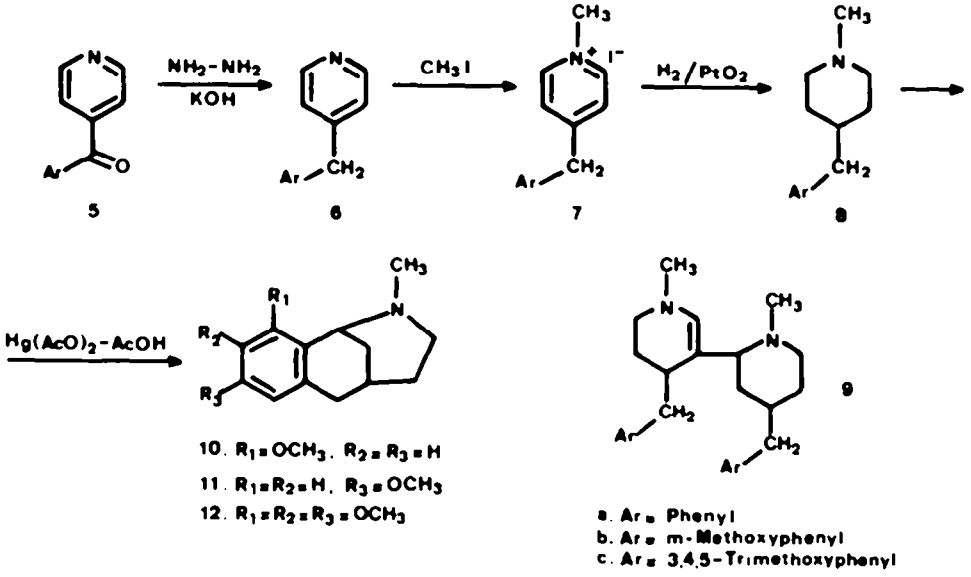


2 3 4 1

When the Fischer indolization of 4-piperidylpropanone 2a phenylhydrazone was effected with ethanolic hydrogen chloride, the 2,3-disubstituted indole 3a was isolated in 40% yield as the only product.[26] In an attempt to modify the regioselectivity of the above ring closure, we tried the use of PPA as cyclizing agent since it is well known that this reagent favors indolization onto the methyl group of methyl alkyl ketone arylhydrazones.[27] Under these conditions, an approximately equimolecular mixture of 3a and the desired 2-substituted indole 4a was obtained. Similarly, treatment of 2b phenylhydrazone with PPA afforded a 1:1 mixture of indole derivatives 3b and 4b. Piperidylmethylindoles 4a and 4b were isolated in 30% yield by column chromatography and were easily characterized by the signal at 66.2 due to the 3-indole

proton in the ^{1}H-NMR spectrum. In turn, ^{1}H-NMR spectra of 2,3-disubstituted indoles 3a and 3b showed, as the most significant signal, a singlet at δ2.1-2.3 due to the methyl group attached to the indole 2-position.

On the other hand, benzylpiperidines 8 required for the synthesis of 7,8-benzomorphans were conveniently prepared from 4-benzylpyridines 6, by quaternization with methyl iodide and further catalytic hydrogenation of the resulting pyridinium salts 7. In turn, methoxy substituted benzylpyridines 6b and 6c were synthesized by reaction of m-methoxyphenylmagnesium bromide with 4-cyanopyridine, as described for the preparation of 4-benzoylpyridine,[28] and by condensation of 4-pyridyllithium[29] with 3,4,5-trimethoxybenzonitrile, respectively, followed by Wolff-Kishner reduction of the resulting 4-benzoyl derivatives 5b and 5c.



Oxidative cyclization of 4a and 4b was effected with mercuric acetate,[30] in the presence of EDTA disodium salt to avoid the mercuriation of the indole nucleus, at pH 3-4 (hydrolysis of $Hg(AcO)_2$-EDTA.Na_2) in water as the solvent.[31,32] Subsequent addition of an excess of $NaBH_4$ in order to reduce the possible over oxidation products and to destroy the excess of $Hg(AcO)_2$ led to the cyclized compounds 1a[33] (36%) and 1b (30%), respectively.

In the benzene series, mercuric acetate cyclizations were effected in aqueous acetic acid solution, without adding EDTA.Na_2. Since it was expected that electrophilic attack of the iminium salt generated by oxidation of piperidine 8a upon the benzene nucleus would be slower than in the indole series, the reaction mixture was additionally refluxed in 50% aqueous acetic acid. However, cyclization did not occur, and the dimeric product 9a was isolated in 44% yield.[34]

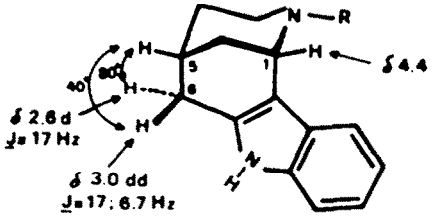
The presence of a molecular peak at m/e 374 in the mass spectrum of 9a supported the proposed structure. The NMR spectrum exhibited, as the most significant signals, two singlets (δ2.15 and 2.6) due to piperidine and enamine N-methyl groups, respectively, and a broad signal (δ5.9) corresponding to the enamine proton. Formation of 9a can be interpreted by considering that electrophilic attack of the iminium salt generated in the oxidation process occurs intermolecularly upon the corresponding enamine,[35,36] in equilibrium with the iminium salt, instead of intramolecularly upon the benzene ring.

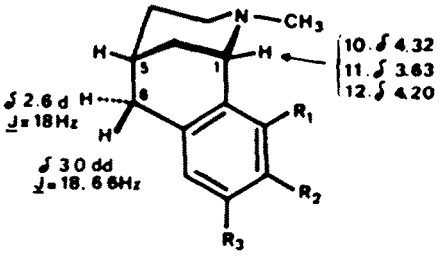
When oxidation was effected from the most activated compound 8b, besides the dimeric product 9b, 7,8-benzomorphans 10 and 11 were isolated in 13% yield. This result makes evident that the failure in the above cyclization must be attributed to the lower nucleophilic character of benzene ring as compared with indole. In

agreement with this interpretation, mercuric acetate cyclization of 4-(trimethoxybenzyl)piperidine 8c furnished exclusively the 7,8-benzomorphan 12 in 91% yield, thus clearly indicating that electronic factors influence the relative ratios of dimerization *versus* ring closure.

The molecular peak at *m/e* 217 for 10 and 11 and at *m/e* 277 for 12 in the mass spectra, the base peak at *m/e* 59 ($CH_3\overset{+}{N}HCH_2CH_3$) in all cases, as well as the major fragments at *m/e* 96 (*N*-methyldihydropyridinium ion), *m/e* 44 ($CH_3\overset{+}{N}H{=}CH_2$), and *m/e* 158 for 10 and 11 and *m/e* 218 for 12 (naphthalene type), confirm the benzomorphan nucleus and are in agreement with those reported for the basic skeleton.[37]

^{1}H-NMR Data of Indolomorphans 1 and 7,8-Benzomorphans 10-12.





1a. R = CH_3

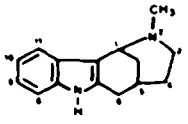
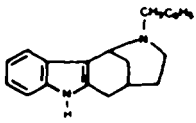
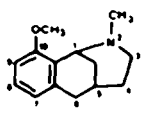
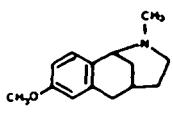
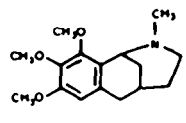
1b. R = $CH_2C_6H_5$

10. $R_1 = OCH_3$, $R_2 = R_3 = H$
11. $R_1 = R_2 = H$, $R_3 = OCH_3$
12. $R_1 = R_2 = R_3 = OCH_3$

The spectral data of bridged systems 1 (a,b), 10, 11, and 12 possess some common trends. Thus, in the ^{1}H-NMR spectra the methine proton at C-1 is the most deshielded of aliphatic protons and resonates at $\delta \sim 4.4$ in the indoloderivatives 1 and at δ 3.6 in the 7,8-benzomorphan 11 as usual in this structural type.[5] However, in 7,8-benzomorphans 10 and 12 this signal appears at $\delta \sim 4.3$ due to the anisotropy effect of the C-10 oxygen substituent. On the other hand, in all cyclized compounds the methylene protons at C-6 appear as diastereotopic, one of them as a doublet of doublets at $\delta \sim 3.0$ and the other as an isolated doublet at $\delta \sim 2.65$. The vicinal coupling constants between protons on the C_5-C_6 unit (J=6.6 and 0 Hz) correspond by the Karplus relation to dihedral angles which are consistent with those observed from Dreiding models.

The most noteworthy difference for the saturated carbons in the ^{13}C-NMR spectra of the above cyclized compounds is the high field position of C-6 in the indolomorphan systems as compared to 7,8-benzomorphans due to the high electrodensity of the indole nucleus.[38] This feature should as well be observed for C-1, also adjacent to the aromatic ring. Nevertheless, it is only observed in the benzene derivative 11, in which the signal for C-1 appears at a field (5.6 ppm) lower than in the indoloderivative 1a. The upfielding of C-1 in compounds 10 and 12 is caused by a γ-effect induced by the methoxy group attached to C-10. On the other hand, we have observed that aromatic methoxy groups flanked by two *ortho* substituents exhibit, as expected,[39] chemical shift values ($\sim$60.5 ppm) higher than those with one or no *ortho* substituents ($\sim$55 ppm).

^{13}C-NMR Chemical Shifts[a,b] of Indolomorphans 1 and 7,8-Benzomorphans 10-12.

Carbon No	 1a	 1b	 10	 11	 12
C-1	51.78	52.10	50.11	57.37	50.59
C-3	46.47	43.74	46.54	46.25	46.17
C-4	33.12[c]	32.39[c]	30.75	32.15[c]	31.00[c]
C-5	24.80	24.96	23.95	24.71	24.07
C-6	29.27	29.07	34.55	34.95	34.44
C-6a	135.98	135.88	140.83	140.24	134.64
C-7a or C-7	137.06	136.46	120.75	110.42	106.37
C-8	110.56	110.77	128.42	158.71	151.45[c]
C-9	120.57	121.72	107.33	112.82	139.30
C-10	119.27	119.89	157.59	131.26	152.71[c]
C-11 or C-10a	118.20	118.13	118.06	123.77	116.58
C-11a	128.58	128.06	--	--	--
C-11b	105.79	105.49	--	--	--
CH_2 bridge	32.89[c]	32.10[c]	32.52	33.13[c]	32.47[c]
NCH_3	44.76	--	42.94	43.30	43.00
CH_2Ar	--	60.48[d]	--	--	--
OCH_3	--	--	55.18	55.13	55.61[e] 60.42[f] 60.75[f]

[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. [d] Phenyl ring carbons were found at 137.79, 129.54, 128.36, and 127.51 ppm. [e] Methoxy group attached to C-8. [f] Methoxy group attached to C-9 or C-10.

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^{1}H-NMR spectra were recorded in $CDCl_3$ with TMS as internal standard (60 MHz: Perkin-Elmer R-24B; 200 MHz: Varian XL-200). ^{13}C-NMR spectra were recorded with a Varian XL-200 spectrometer (50.3 MHz). Chemical shifts are reported in ppm downfield (δ) from TMS. IR spectra were taken on a Perkin-Elmer 1430 spectrophotometer. Mass spectra were recorded on a Hewlett-Packard 5930A mass spectrometer. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous $MgSO_4$ powder. TLC and column chromatography were carried out on SiO_2 (silica gel 60, Merck, 63-200 μm) or Al_2O_3 (aluminoxid 90, Merck, activity I), and the spots were located with UV light or iodoplatinate reagent. Preparative TLC was performed on silica gel plates $60F_{254}$ (Merck), layer thickness 2 mm. All distillations were effected using a Büchi GKR-50 Kugelrohr apparatus. The temperature cited are the temperature of the oven during the distillation. Microanalyses were performed by Instituto de Química Bio-Orgánica, Barcelona.

1-(1-Methyl-4-piperidyl)-2-propanone (2a) was prepared from 1-methyl-4-piperidone in a 0.12 mol scale in 76% yield by the published procedure.[25]

1-(1-Benzyl-4-piperidyl)-2-propanone (2b) was prepared from 1-benzyl-4-piperidone in a 0.09 mol scale in 90% yield by the published procedure.[25]

2-(1-Methyl-4-piperidylmethyl)indole (4a). A mixture of ketone 2a (500 mg, 32 mmol) and phenylhydrazine (349 mg, 3.2 mmol) was heated on a steam bath for 30 min. Polyphosphoric acid (8 g) was added to the crude hydrazone and the reaction mixture was stirred under nitrogen at 135 °C for 30 min. The mixture was poured into crushed ice, and the solution was basified with aqueous sodium hydroxide solution and extracted with benzene. Evaporation of the extracts gave a syrup which was chromatographed on silica gel. Elution with 1:4 benzene-chloroform left 123 mg (25%) of *2-methyl-3-(1-methyl-4-piperidyl)indole* (3a): m.p. 165-166 °C (hexane); NMR (CCl_4) 2.3 (s, 6H, NCH_3 and In-CH_3), 1.6-2.4 (m, 6H, 2-Ha and 3-H), 2.6-3.1 (m, 3H, 2-He and 4-H), 6.75-7.6 (m, 4H, ArH), 7.9 (s, 1H, NH). (Found: C, 78.69; H, 8.91; N, 12.09. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.82; N, 12.26). By a gradual increase in concentration of eluant from 0% to 2% methanol in chloroform, 152 mg (30%) of the indole derivative 4a were obtained: m.p. 135-136 °C (hexane) [Lit. 141-142 °C (ethanol),[22a] 137-139 °C[23a]]; NMR (200 MHz) 1.40 (qd, J=4, 12 Hz, 2H, 3- and 5-Ha), 1.4-1.7 (m, 1H, 4-H), 1.74 (br d, J=12 Hz, 2H, 3- and 5-He), 1.94 (td, J=12, 12, 2 Hz, 2H, 2- and 6-Ha), 2.28 (s, 3H, NCH_3), 2.66 (d, J=6.7 Hz, 2H, $InCH_2$), 2.87 (br d, J=12 Hz, 2H, 2- and 6-He), 6.23 (dd, J=2.1, 0.8 Hz, 1H, indole 3-H), 7.1-7.15 (m, 2H, indole 5- and 6-H), 7.2-7.3 (m, 1H, indole 7-H), 7.5-7.55 (m, 1H, indole 4-H), 8.0 (br s, 1H, NH).

When a solution of the ketone 2a (500 mg, 3.2 mmol) and phenylhydrazine hydrochloride (466 mg, 3.2 mmol) in 7 ml of absolute ethanol saturated with dry hydrogen chloride was refluxed for 2 h 30 min and then stirred at room temperature overnight, the 2,3-disubstituted indole 3a (284 mg, 40%) was isolated as the only product after the usual work-up.

2-(1-Benzyl-4-piperidylmethyl)indole (4b). Operating as above from ketone 2b (1 g, 4.3 mmol) a crude mixture of indole derivatives 3b and 4b was obtained and chromatographed on silica gel. Elution with benzene-chloroform (1:0 to 1:1 eluent) gave *3-(1-benzyl-4-piperidyl)-2-methylindole* (3b): 290 mg (22%): m.p. 130-131 °C (ethanol-ether); NMR (CCl_4) 2.1 (s, 3H, CH_3), 1.4-3.0 (m, 9H, piperidine), 3.35 (s, 2H, $ArCH_2$), 6.7-7.4 (m, 4H, indole), 7.1 (s, 5H, ArH), 7.6 (m, 1H, NH). (Found: C, 82.84; H, 8.02; N, 9.18. Calcd. for $C_{21}H_{24}N_2$: C, 82.89; H, 7.89; N, 9.21). Elution with chloroform-benzene (1:1 to 1:0 eluent) gave 4b: 407 mg (31%); m.p. 105-106 °C (ethanol-water) [Lit.[23a] 112-114 °C (ethanol-water)]; NMR (200 MHz) 1.3-1.6 (m, 3H, 3-, 4-, and 5-Ha), 1.65 (br d, J=12 Hz, 2H, 3- and 5-He), 1.98 (td, J=12, 12, 2 Hz, 2H, 2- and 6-Ha), 2.59 (d, J=6.4 Hz, 2H, $InCH_2$), 2.90 (br d, J=12 Hz, 2H, 2- and 6-He), 3.54 (s, 2H, $ArCH_2$), 6.17 (dd, 1H, indole 3-H), 6.9-7.5 (m, 4H, indole), 8.46 (br s, 1H, NH).

2-Methyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (1a). A solution of 4a (433 mg, 1.89 mmol) in methylene chloride (5 ml) was added to a solution of mercuric acetate (3.03 g, 9.49 mmol) and EDTA.Na_2.$2H_2O$ (3.6 g, 9.63 mmol) in water (65 ml). Methylene chloride was evaporated by heating the mixture at 40 °C under a stream of nitrogen and the resulting solution was refluxed for 1 h. After addition of methanol (22 ml) and sodium borohydride (64 mg), the whole was stirred at room temperature for 20 min and filtered. The filtrate was concentrated under reduced pressure, basified with aqueous ammonium hydroxide, and extracted with methylene chloride. Evaporation of the dried organic extracts gave an oil which was chromatographed through alumina. On elution with 9:1 chloroform-methanol, 153 mg (36%) of 1a were obtained: m.p. 185-187 °C (ether-ethanol); NMR (200 MHz) 1.68 (dd, J=12, 2 Hz, 1H, 3-Ha), 2.1-2.7 (m, 5H, 4-H, 5-H and 12-H), 2.41 (s, 3H, NCH_3), 2.72 (d, J=17 Hz, 1H, 6-H), 3.13 (dd, J=17, 6.3 Hz, 1H, 6-H), 4.37 (br, 1H, 1-H), 7.1-7.5 (m, 4H, indole), 8.40 (br, 1H, NH); (Found: C, 79.23; H, 8.12; N, 12.36. Calcd. for $C_{15}H_{18}N_2$: C, 79.60; H, 8.01; N, 12.37).

2-Benzyl-1,2,3,4,5,6-hexahydro-1,5-methanoazocino[4,3-b]indole (1b). Operating as above from the indole derivative 4b (0.5 g, 1.64 mmol), mercuric acetate (2.62 g, 82 mmol) and EDTA.Na_2.$2H_2O$ (3.12 g, 8.3 mmol) at 90-100 °C for 1h, the tetracyclic base 1b (150 mg, 30%) was isolated after column chromatography through silica gel (99:1 chloroform-ethanol as eluent); NMR (200 MHz) 1.57 (d, J=12.5 Hz, 1H, 4-He), 1.85 (dd, J=12.5, 2.8 Hz, 1H, 12-Ha), 2.05 (tt, J=14.5, 14.5, 4.8, 4.8 Hz, 1H, 4-Ha), 2.16 (td, J=14.5, 14.5, 3.2 Hz, 1H, 3-Ha), 2.36-2.58 (m, 3H, 3-He, 5-He and 12-He), 2.63 (d, J=17 Hz, 6-H), 3.08 (dd, J=17, 6.7 Hz, 1H, 6-H), 3.31 and 4.11 (2d, J=13 Hz, 1H each, $ArCH_2N$), 4.48 (br, 1H, 1-H), 7.09-7.48 (m, 9H, ArH), 8.43 (br, 1H, NH). For the hydrochloride: m.p. 200-202 °C (acetone-ethanol). (Found: C, 73.44; H, 7.00; N, 7.77; Cl, 10.15. Calcd. for $C_{21}H_{23}ClN_2$.$1/3C_3H_6O$: C, 73.76; H, 7.03; N, 7.82; Cl, 9.89).

4-(3-Methoxybenzoyl)pyridine (5b). A solution of 4-cyanopyridine (6 g, 57 mmol) in tetrahydrofuran (50 ml) was added dropwise under nitrogen to the Grignard reagent prepared from m-bromomethoxybenzene (10.1 ml, 80 mmol) and magnesium (1.92 g, 0.08 mmol) in anhydrous ether (50 ml). The resulting mixture was refluxed for 5 h, the solvent was evaporated, and the residue was treated with 1:1 aqueous sulfuric acid (25 ml). The solution was basified with 20% aqueous sodium hydroxide and extracted with ether. The organic extracts were dried and evaporated to give 5b (7.42 g, 87%). IR (KBr) 1660 (C=O); NMR 3.8 (s, 3H, OCH_3), 7.0-7.4 (m, 4H, ArH), 7.5 (d, J=6 Hz, 2H, Pyr-H), 8.7 (d, J=6 Hz, 2H, Pyr-H). The picrate derivative had m.p. 144-146 °C (ethanol). (Found: C, 51.31; H, 3.05; N, 12.57. Calcd. for $C_{19}H_{14}N_4O_9$: C, 51.59; H, 3.19; N, 12.66).

4-(3,4,5-Trimethoxybenzoyl)pyridine (5c). To a cooled (-70°C) solution of 4-bromopyridine hydrochloride[29a] (6.7 g, 34.6 mmol) in anhydrous ether (10 ml) was added dropwise under nitrogen a solution of *n*-butyl-lithium (43.3 ml, 69.3 mmol) in anhydrous ether (30 ml) also cooled at -70 °C. The mixture was stirred at -70 °C for 1 h and at -30 °C for 30 min. Then, a cooled (0 °C) solution of 3,4,5-trimethoxybenzonitrile (6.7 g, 34.6 mmol) in anhydrous benzene (40 ml) was slowly added. The reaction mixture was stirred at -30 °C for 30 min, poured into ice-water (100 ml), acidified with 2N hydrochloric acid, and extracted with benzene. The aqueous layer was refluxed for 2 h, cooled, basified with 20% aqueous sodium carbonate, and extracted with chloroform. Evaporation of the solvent left 5c (2.5 g, 27%). A sample recrystallized from ethanol melted at 103-105 °C; IR ($CHCl_3$) 1655 (C=O); NMR 3.8 (s, 6H, OCH_3), 3.9 (s, 3H, OCH_3), 6.95 (s, 2H, ArH), 7.45 (d, J=6 Hz, 2H, Pyr-H), 8.7 (d, J=6 Hz, 2H, Pyr-H); MS *m/e* (relative abundance) 273 (M^+, 67), 258 (21), 202 (22), 195 (100), 116 (15), 109 (16), 106 (62), 78 (67), 66 (23), 51 (26). (Found: C, 65.96; H, 5.57; N, 4.96. Calcd. for $C_{15}H_{15}NO_4$: C, 65.93; H, 5.53; N, 5.12).

4-(3-Methoxybenzyl)pyridine (6b). To a solution of potassium hydroxide (22.7 g, 0.4 mol) in ethylene glycol (400 ml), ketone 5b (20 g, 93.8 mmol) and 80% hydrazine hydrate (28 ml, 0.435 mol) were added. The resulting mixture was refluxed for 2 h 30 min, distilled to raise the temperature to 190 °C, and refluxed again for 3 h. The reaction mixture was poured into ice-water and extracted with chloroform. The organic extracts were washed with water, dried, and evaporated to give benzylpiperidine 6b (15.1 g, 81%) as a clear oil, b.p. 135-136 °C/0.06 mm Hg (Lit.[40] b.p. 140 °C/0.4 mmHg).

4-(3,4,5-Trimethoxybenzyl)pyridine (6c). Following the above procedure, from ketone 5c (2.42 g, 8.35 mmol), 80% hydrazine hydrate (2.49 ml, 38.7 mmol), and potassium hydroxide (2.02 g, 35.6 mmol) in ethylene glycol (36 ml), benzylpyridine 6c (1.1 g, 49%) was obtained; NMR 3.65 (s, 2H, $ArCH_2$), 3.7 (s, 9H, OCH_3), 6.2 (s, 2H, ArH), 6.9 (d, J=6 Hz, 2H, Pyr-H), 8.3 (d, J=6 Hz, 2H, Pyr-H); MS *m/e* (relative abundance) 260 (18), 259 (M^+, 100), 244 (87), 216 (32), 182 (47), 181 (48), 167 (35), 156 (68), 155 (35), 129 (41), 93 (32). The picrate melted at 165-167 °C (ethanol); NMR 3.85 (s, 9H, OCH_3), 4.15 (s, 2H, $ArCH_2$), 6.35 (s, 2H, ArH), 7.65 (d, J=6 Hz, 2H, Pyr-H), 8.75 (d, J=6 Hz, 2H, Pyr-H). (Found: C, 51.81; H, 4.04; N, 11.26. Calcd. for $C_{21}H_{20}N_4O_{10}$: C, 51.64; H, 4.12; N, 11.47).

1-Methyl-4-(3,4,5-trimethoxybenzyl)pyridinium Iodide (7c). Freshly distilled methyl iodide (3 ml, 44.5 mmol) in anhydrous acetone (5 ml) was added dropwise to a solution of pyridine 6c (0.97 g, 3.74 mmol) in anhydrous acetone (50 ml). The resulting mixture was stirred at room temperature for 15 h. The solid was filtered and crystallized from ethanol to give 7c (0.98 g, 65%); m.p. 259-260 °C; NMR (DMSO-d_6) 3.55 (s, 3H, OCH_3), 3.7 (s, 6H, OCH_3), 4.1 (s, 2H, ArH), 4.25 (s, 3H, NCH_3), 6.6 (s, 2H, ArH), 7.9 (d, J=6 Hz, 2H, Pyr-H), 8.7 (d, J=6 Hz, 2H, Pyr-H); MS *m/e* (relative abundance) 274 (M^+, 1), 259 (20), 245 (34), 142 (100), 127 (41). (Found: C, 47.82; H, 5.01; N, 3.94; I, 31.41. Calcd. for $C_{16}H_{20}INO_3$: C, 47.89; H, 5.02; N, 3.49; I, 31.63).

4-Benzyl-1-methylpiperidine (8a). A mixture of 4-benzyl-1-methylpyridinium iodide[41] (7a; 5.5 g, 17.6 mmol) in absolute methanol (200 ml) and platinum dioxide (200 mg) was shaken at room temperature under hydrogen at atmospheric pressure for 48 h. The catalyst was filtered off and the solution was evaporated. The residue was dissolved in water, basified with 20% aqueous potassium carbonate, and extracted with chloroform. Evaporation of the dried organic extracts yielded 8a (3 g, 90%); NMR (200 MHz) 1.37 (dq, J=12, 12, 12, 3.7 Hz, 2H, 3-Ha and 5-Ha), 1.4-1.5 (m, 1H, 4-Ha), 1.63 (br d, J=12.5 Hz, 2H, 3-He and 5-He), 1.85 (td, J=12, 12, 2.5 Hz, 2H, 2-Ha and 6-Ha), 2.23 (s, 3H, NCH_3), 2.53 (d, J=6.5 Hz, 2H, Ar-CH_2), 2.81 (dt, J=12 Hz, 2H, 2-He and 6-He), 7.06-7.34 (m, 5H, ArH); MS *m/e* (relative abundance) 190 (5), 189 (M^+, 24), 188 (29), 111 (23), 98 (36), 96 (26), 91 (57), 83 (63), 70 (74), 65 (39), 55 (58), 44 (100), 43 (57), 42 (98). The picrate melted at 173-175 °C (ethanol). (Found: C, 54.56; H, 5.38; N, 13.28. Calcd. for $C_{19}H_{22}N_4O_7$: C, 54.54; H, 5.30; N, 13.39).

4-(3-Methoxybenzyl)-1-methylpiperidine (8b).[40] A mixture of pyridinium salt 7b[41] (5 g, 14.6 mmol) in absolute methanol (100 ml) and platinum dioxide (167 mg) was hydrogenated as above. After the usual workup, piperidine 8b (3.05 g, 95%) was obtained; NMR (200 MHz) 1.34 (qd, J=12, 12, 12, 3.7 Hz, 2H, 3-Ha and 5-Ha), 1.3-1.5 (m, 1H, 4-Ha), 1.64 (br d, J=12 Hz, 2H, 3-He and 5-He), 1.86 (td, J=12, 12 and 2.5 Hz, 2H, 2-Ha and 6-Ha), 2.23 (s, 3H, NCH_3), 2.51 (d, J=6.5 Hz, 2H, $ArCH_2$), 282 (br d, J=12 Hz, 2H, 2-He and 6-He), 3.79 (s, 3H, OCH_3), 6.6-7.3 (m, 4H, ArH); MS m/e (relative abundance) 220 (9), 219 (M^+, 46), 218 (51), 111 (18), 98 (22), 97 (12), 96 (47), 91 (17), 83 (39), 70 (26), 55 (23), 44 (39), 43 (100), 42 (31). ^{13}C-NMR 32.29 (t, 3- and 5-C), 37.23 (d, 4-C), 43.22 (t, $ArCH_2$), 46.43 (q, NCH_3), 55.09 (q, OCH_3), 55.92 (t, 2-C and 6-C), 110.91 (d, Ar 4-C), 114.34 (s, Ar 2-C), 121.57 (d, Ar 6-C), 129.05 (d, Ar 5-C), 142.34 (s, Ar 1-C), 159.50 (s, Ar 3-C). A sample of 8b hydroiodide resulting from hydrogenation melted at 142-145 °C (ether-acetone). (Found: C, 48.23; H, 6.31; N, 3.93; I, 36.85. Calcd. for $C_{14}H_{22}INO$: C, 48.42; H, 6.38; N, 4.03; I, 36.54).

1-Methyl-4-(3,4,5-trimethoxybenzyl)piperidine (8c). Operating as above, from pyridinium iodide 7c (1.21 g, 3.01 mmol), platinum dioxide (61 mg), and absolute methanol (50 ml), piperidine 8c (0.71 g, 84%) was obtained. A sample recrystallized from acetone melted at 105-107 °C; NMR (200 MHz) 1.34 (qd, J=12, 12, 12 and 3.7 Hz, 2H, 3-Ha and 5-Ha), 1.3-1.5 (m, 1H, 4-Ha), 1.59 (br d, J=12 Hz, 2H, 3-He and 5-He), 1.84 (td, J=12, 12 and 2.5 Hz, 2H, 2-Ha and 6-Ha), 2.21 (s, 3H, NCH_3), 2.41 (d, J = 6 Hz, 2H, $ArCH_2$), 3.76 (s, 3H, OCH_3), 3.80 (s, 6H, OCH_3), 6.29 (s, 2H, ArH); ^{13}C NMR 32.05 (t, 3-C and 5-C), 37.23 (d, 4-C), 43.53 (t, $ArCH_2$), 46.24 (q, NCH_3), 55.85 (q, OCH_3), 55.99 (t, 2-C and 6-C), 60.84 (q, OCH_3), 105.98 (d, Ar 2-C and 4-C), 136.34 (s, Ar 1-C), 152.95 (s, Ar 3-C and 5-C); MS m/e (relative abundance) 280 (5), 279 (M^+, 21), 278 (10), 264 (33), 248 (34), 181 (14), 111 (30), 98 (24), 96 (100), 83 (67), 70 (32), 44 (30). (Found: C, 68.41; H, 9.03; N, 5.00; Calcd. for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01).

Mercuric Acetate Oxidation of 4-Benzyl-1-methylpiperidine (8a). A mixture of piperidine 8a (1.5 g, 7.9 mmol), mercuric acetate (23.3 g, 79 mmol), and 5% acetic acid (100 ml) was refluxed for 7 h. The precipitate formed during the reaction was filtered and washed with 5% acetic acid. The combined filtrates were saturated with hydrogen sulfide for 30 min. Mercuric sulfide was removed by filtration through "Hyflo Super-Cel" and washed with 5% acetic acid. To the combined filtrate and washings was added an equal volume of glacial acetic acid. The resulting solution was refluxed under nitrogen for 72 h, cooled, basified with 20% aqueous sodium hydroxide, and extracted with ether. Evaporation of the dried organic extracts gave an oil which was purified by column chromatography using chloroform as eluent to give *4-benzyl-3-[4-benzyl-1-methyl-2-piperidyl]-1-methyl-1,2,3,4-tetrahydropyridine* (9a) (0.64 g, 44%); IR (NaCl) 1650 cm^{-1} (C=C); NMR 2.15 (s, 3H, NCH_3), 2.6 (s, 3H, enamine NCH_3), 5.9 (m, 1H, =C-H), 7.15 (br s, 10H, ArH); MS m/e (relative abundance) 374 (M^+, 1), 283 (1), 226 (1), 187 (5), 97 (12), 96 (100), 94 (16), 91 (17), 44 (11), 42 (33), 39 (13).

Mercuric Acetate Oxidation of 4-(3-Methoxybenzyl)-1-methylpiperidine (8b). A solution of piperidine 8b hydroiodide (5 g, 14.4 mmol), mercuric oxide (38.8 g, 0.18 mol), and 40% acetic acid (200 ml) was refluxed for 7 h. The usual workup gave 1.1 g of an oil which was chromatographed. On elution with chloroform, *4-(3-methoxybenzyl)-3-[4-(3-methoxybenzyl)-1-methyl-2-pyridyl]-1-methyl-1,2,3,4-tetrahydropyridine* (9b) was obtained: 0.21 g (7%); IR (NaCl) 1635 cm^{-1} (C=C); NMR 2.25 (s, 3H, NCH_3), 2.6 (s, 3H, enamine NCH_3), 3.7-3.8 (br s, 6H, OCH_3), 6.0 (br, 1H, 2-H), 6.6-7.2 (m, 8H, ArH); MS m/e (relative abundance) 434 (M^+, 1), 325 (1), 218 (1), 121 (5), 115 (2), 96 (100), 81 (10), 78 (12), 42 (38). On elution with 97:3 chloroform-methanol, a (1:1) mixture of *8-methoxy-2-methyl-1,5-methano-1,2,3,4,5,6-hexahydro-2-benzazocine* (11) and *10-methoxy-2-methyl-1,5-methano-1,2,3,4,5,6-hexahydro-2-benzazocine* (10) was obtained: 0.42 g (13%). Pure 11 (lower R_f value) was separated by preparative TLC using 9:1 ether-acetone as developing solvent. NMR (200 MHz) 2.15 (s, 3H, NCH_3), 2.43 (dd, J=12.6, 3 Hz, 1H, 3-He), 2.65 (d, J=18 Hz, 1H, 6-H), 3.05 (dd, J=18, 6.6 Hz, 1H, 6-H), 3.63 (t, J=3 Hz, 1H, 1-He), 3.79 (s, 3H, OCH_3), 6.6-6.9 (m, 2H, ArH), 7.10 (t, J=8 Hz, 1H, ArH); EM m/e (relative abundance) 217 (M^+, 10), 174 (4), 160 (9), 159 (17), 158 (10), 115 (16), 96 (20), 91 (10), 78 (6), 77 (11), 63 (10), 59 (100), 44 (60), 42 (56). The picrate melted at 192-195 °C (ethanol). (Found: C, 53.42; H, 4.97; N, 12.58. Calcd. for $C_{20}H_{22}N_4O_8$: C, 53.80; H, 4.96; N, 12.55). Benzazocine 10 (higher R_f value) was obtained contamined with 11 and showed the following spectroscopic data: NMR (200 MHz) 2.15 (s, 3H, NCH_3), 2.67 (d, J=18 Hz, 1H, 6-H), 3.02 (dd, J=18, 6.6 Hz, 1H, 6-H), 3.77 (s, 3H, OCH_3), 4.32 (t, J=3 Hz, 1H, 1-He), 6.70 (d, J=8 Hz, 1H, ArH), 6.75 (d, J=8 Hz, 1H, ArH), 7.16 (d, J=8 Hz, 1H, ArH); MS m/e (relative abundance) 217 (M^+, 36), 203 (30), 160 (18), 159 (38), 158 (17), 145 (40), 144 (38), 115 (34), 96 (37), 74 (31), 59 (100), 44 (45).

8,9,10-Trimethoxy-2-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocine (12). A mixture of piperidine 8c (0.53 g, 1.89 mmol), mercuric oxide (4.12 g, 19 mmol), and 40% acetic acid (30 ml) was refluxed for 7 h. After the usual workup, the resulting acetic acid solution was refluxed under nitrogen for 72 h, basified, and extracted with ether to give pure benzazocine 12: (0.39 g, 91%); NMR (200 MHz) 2.20 (s, 3H, NCH_3), 2.60 (d, J=18 Hz, 1H, 6-H), 3.00 (dd, J=18, 6.6 Hz, 1H, 6-H), 3.84 (s, 9H, OCH_3), 4.20 (br, 1H, 1-H), 6.42 (s, 1H, ArH); EM m/e (relative abundance) 277 (M^+, 6), 220 (21), 219 (5), 218 (6), 115 (11), 96 (12), 91 (12), 77 (12), 59 (100), 44 (46). The picrate melted at 138-140 °C (ethanol). (Found: C, 52.06; H, 5.26; N, 11.14. Calcd. for $C_{22}H_{26}N_4O_{10}$: C, 52.17; H, 5.17; N, 11.06).

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