SYNTHESIS OF AROMATIC CHLOROBERBINES

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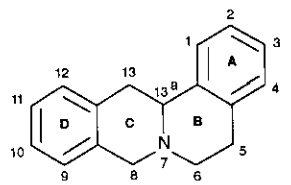
Abstract - The introduction of chlorine atoms into aromatic rings of berbines was effected from an ethoxycarbamido group which does not undergo decomposition under the conditions of the Bischler-Napieralski reaction. At the end of the synthesis of the berbine ring system this group was transformed into a primary aromatic amine which was converted into chlorine by the Sandmeyer reaction. Thus berbines ***6a,b*** *chlorinated in the aromatic ring A and berbines* ***10a,b*** *chlorinated in the aromatic ring D were prepared. The preparation of the starting β-phenethylamines* ***1a,b*** *with an ethoxycarbamido group was also discussed.*

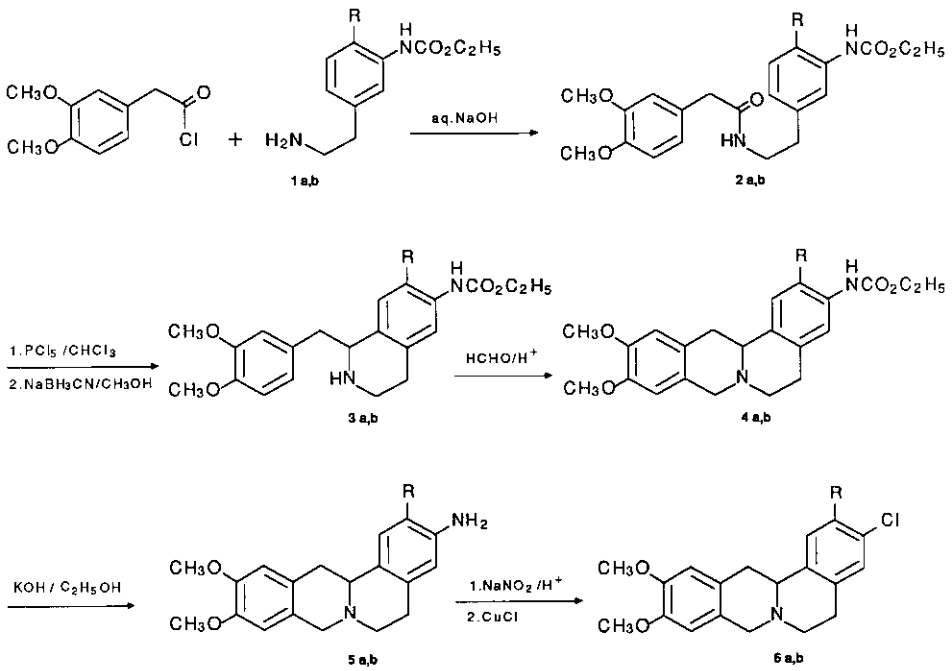
Berbine or 5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine and its derivatives have natural or synthetic origins and several thousand publications on their chemical and pharmacological properties have been reported.[1-5]



Berbine or 5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine

All known berbines contain generaly only oxygen function (OH, OMe, O-CH_2O...) into aromatic rings. A small number of compounds containing other functions has been described.[6-9] In fact the direct introduction of a withdrawing group on the aromatic rings prevents the B and C ring closure under the Bischler-Napieralski reaction conditions. Previous studies in our laboratory have shown the importance of aromatic substitution for the α-adrenergic antagonist activity of berbines.[10-12] In a further extension of our studies in this area we describe here the synthesis of some chlorinated derivatives of the berbine heterocycle.

Chlorination of the ring A -The introduction of a chlorine atom in the aromatic ring A was realized by using an ethoxycarbamido group as precursor (Scheme 1).

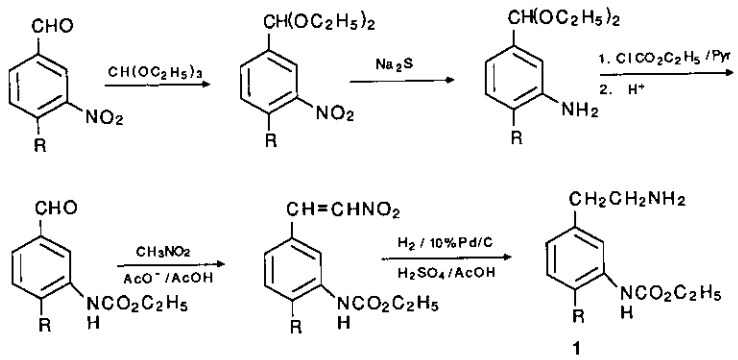


Scheme 1. Chlorination of berbine in the ring A (**a** : R=H, **b** : R=Cl)

As has been described[13] this group promotes the Bischler-Napieralski reaction and the cyclization occurs selectively at the para position. The starting material **2** in this reaction was synthetized by condensation of β-phenethylamines **1** with 3,4-dimethoxyphenylacetyl chloride under the Schotten-Baumann reaction conditions. Dehydrative cyclization of **2** under the Bischler-Napieralski conditions followed by reduction with sodium cyanoborohydride in methanolic solution afforded tetrahydroisoquinolines **3**.

The Mannich reaction [14, 15] of these bases with 36 % formaldehyde solution in the presence of a strong acid yielded the berbines **4**. Hydrolysis of the ethoxycarbamido group with KOH in ethanolic solution gave **5** and the Sandmeyer reaction of these bases afforded the chloroberbines **6** .

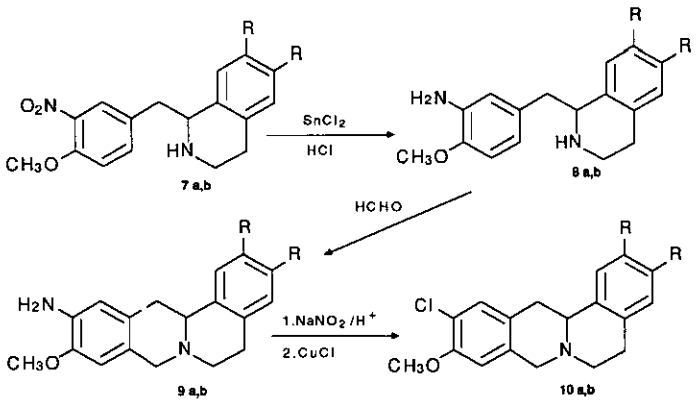
The starting β-phenethylamines **1** were prepared, as described previously by Ishiwata and Itakura,[16] from m-nitrobenzaldehydes (Scheme 2).



Scheme 2. Synthesis of phenethylamines **1** (R=H, Cl)

The most important modification in this Scheme concerns the reduction of the 3-ethoxycarbamido-β-nitrostyrenes. Usually lithium aluminum hydride is used for this reduction.[16] But in this case the carbamate group would be easily reduced to amine. Furthermore catalytic hydrogenation under basic conditions [18] (e.g. pyridine) is not applicable because of the instability of the carbamate group. Thus, this reduction was effected by catalytic hydrogenation over 10 % Pd/C, (at 70 °C, 80 bar, 2 h), in highly acidic solution (AcOH + 5 % H_2SO_4),[19] in order to avoid the dimerization of these compounds occurring in less acidic (AcOH) or neutral (EtOH) solutions.[20,21] (Scheme 2).

Chlorination of the ring D -In a similar manner the bases **10** chlorinated in the ring D were synthetized (Scheme 3).



Scheme 3. Chlorination of berbines in the ring D (**a** : R=OMe, **b** : R=H)

Reduction of 1-(3-nitro-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinolines **7** with stannous chloride dihydrate in acidic solution yielded the corresponding amino compounds **8**. The Mannich reaction of these bases with 36 % formaldehyde solution in ethanol (without acid) afforded the 11-aminoberbines **9**.[22] Their treatment according to the Sandmeyer reaction conditions gave the 11-chloroberbines **10**.

In conclusion, this method using an ethoxycarbamido group as precursor of chlorine atoms is an efficient route to introduce electron-withdrawing atoms into berbine ring system.
Furthermore, this method should allow the introduction of a wide variety of substituents into the aromatic rings of berbines : F, I, NO_2, CF_3, ..., by using the Sandmeyer reaction at the end of the synthesis.

EXPERIMENTAL

Melting points (uncorrected) were determined on a KOFFLER hot-stage apparatus. Spectral data were obtained with a Beckman IR4230 spectrophotometer and a Bruker AC 200 nmr spectrometer. Analyses were performed by Cent. Serv. Microan., Vernaison. All tlc were performed on Merck Silica Gel F-254 plates ($CHCl_3$-MeOH, 18 : 2).

4-Chloro-3-nitrobenzaldehyde Diethyl Acetal -A mixture of 4-chloro-3-nitrobenzaldehyde (50 g, 0.269 mol), triethyl orthoformate (80.2 g, 0.54 mol), NH_4Cl (2.24 g) and EtOH (90 ml) was stirred at room temperature for 30 h. After evaporation of the solvent the mixture was extracted with Et_2O (3 x 100 ml). The combined organic solutions were washed with water, dried ($MgSO_4$) and evaporated to give 68.3 g (97 %) of a pale yellow oil, bp 130-133 °C (3-4 mmHg). Ir ($CHCl_3$) : ν NO_2 1555 and 1345 cm^{-1}. ^1H-Nmr ($CDCl_3$) : δ 1.25 (t, J= 6.6 Hz, 6H, 2 x $CH_2\underline{CH_3}$), 3.58(q , J= 6.6 Hz,4H, 2 x $\underline{CH_2}CH_3$), 5.54 (s, 1H, CH), 7.58 (m, 2H, H_5 + H_6), 8.00 (d, J = 1.2 Hz,1H, H_2). Anal. Calcd for $C_{11}H_{14}NO_4Cl$: C, 50.87; H, 5.39; N, 5.39. Found: C, 50.58; H, 5.25; N, 5.33.

3-Amino-4-chlorobenzaldehyde Diethyl Acetal -In accordance with the method described previously,[23] 200 g (0.83 mol) of Na_2S. 9 H_2O were dissolved in 200 ml of water and 85 ml of concentrated HCl were added dropwise during 30 min. To this acid solution 68.3 g (0.263 mol) of the previous described compound dissolved in EtOH (330 ml) were added and the whole mixture was refluxed for 6 h. After evaporation of the solvent the mixture was extracted with Et_2O (3 x 100 ml). The ethereal solution was washed with water, dried ($MgSO_4$) and evaporated to give 38.6 g (64 %) of a reddish oil, bp 118-120 °C (3-4 mm Hg). Ir ($CHCl_3$) : ν NH_2 3490 and 3400 cm^{-1}. ^1H-Nmr ($CDCl_3$) : δ 1.22(t, J= 6.9 Hz, 6H, 2 x $CH_2\underline{CH_3}$), 2.78 (s, 2H, NH_2), 3.68 (m, 4H, 2 x $\underline{CH_2}CH_3$), 5.56 (s, 1H, CH), 7.5 (m, 3H, arom.). Anal. Calcd for $C_{11}H_{16}NO_2Cl$: C, 57.49; H, 6.97; N, 6.10. Found: C, 57.28; H, 6.89; N, 6.05.

4-Chloro-3-ethoxycarbamidobenzaldehyde -To a stirred solution of the previous described amine (36 g, 0.157 mol) in pyridine (85 ml), cooled to 0-5 °C, was added dropwise ethyl chloroformate (27.24 g, 0.25 mol). After the addition was completed the reaction mixture was heated at 60 °C for 30 min, then was cooled to room temperature, diluted with H_2O (85 ml) and acidified with 15 % aq. HCl (340 ml). The

mixture was stirred overnight and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and evaporated to afford 26.05 g (73 %) of white needles recrystallized from petroleum ether (80-100 °C), mp 60-61 °C. Ir ($CHCl_3$) : ν NH 3430, ν C=O (carbamate) 1740, ν C=O (aldehyde)1710cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 1.36 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 4.29 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 7.23 (m, 1H, NH), 7.53 (m, 2H, H_3 • H_4), 8.73 (d, J = 1.3 Hz, 1H, H_6), 9.98 (s, 1H, CHO). Anal. Calcd for $C_{10}H_{10}NO_3Cl$: C, 52.75; H, 4.39; N, 6.15. Found: C, 52.58; H, 4.36; N, 6.09.

4-Chloro-3-ethoxycarbamido-β-nitrostyrene -A mixture of the previous described benzaldehyde (10.2 g, 45 mol), $AcONH_4$ (5.31 g), Ac_2O (1.37 ml), and $MeNO_2$ (15.5 ml) in AcOH (40 ml) was refluxed for 2 h. The mixture was cooled in ice-cold bath and the yellow precipitate was filtered. Recrystallization from ethanol gave 8.24 g (68 %) of yellow needles, mp 106-107 °C. Ir ($CHCl_3$) : ν NH 3430, ν C=O (carbamate) 1735, ν C=C 1635, ν NO_2 1345 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 7.19 (m, 1H, NH), 7.59 (d, J trans = 13.7 Hz, 1H, $\underline{CH}$=$CHNO_2$), 7.95 (d, J trans = 13.7 Hz, 1H, CH=$\underline{CH}$ NO_2). Anal. Calcd for $C_{11}H_{11}N_2O_4Cl$: C, 48.79; H, 4.06; N, 10.35. Found: C, 48.69; H, 4.03; N, 10.31.

3-Ethoxycarbamido-β-phenethylamine (1a) -3-Ethoxycarbamido-β-nitrostyrene (10 g, 42 mmol), in glacial acetic acid (200 ml) containing conc. H_2SO_4 (10.6 ml) was hydrogenated over 10% Pd/C (3 g) at 70°C/80 bar for 2 h in a stainless steel bomb. The mixture was filtered, the filtrate was evaporated in vaccuum, the residue was basified with 10 % aq. NH_4OH solution and extracted with Et_2O. The extract was dried ($MgSO_4$) and treated with gaseous HCl to give 6.73 g (65 %) of **1a**.HCl as a white powder, mp 184-185 °C (MeOH-Et_2O) [lit. 183-185 °C].[16] Ir (KBr) : ν NH 3270, ν NH_3^+ 3170-2700 (broad), ν C=O 1695 cm^{-1}. ^{1}H-Nmr (DMSO - d_6) : δ 2.90 (m, 4H, $\underline{CH_2}$-$\underline{CH_2}$), 6.88 (d, J=7.2 Hz, 1H, H_5), 8.04 (broad, 3H, NH_3^+), 9.63 (s, 1H, NH).

4-Chloro-3-ethoxycarbamido-β-phenethylamine (1b) -In accordance with the method presented above this compound was prepared from 4-chloro-3-ethoxycarbamido-β-nitrostyrene (10 g) to give 6.19 g (60 %) of **1b**.HCl, mp 151-152 °C (MeOH-Et_2O). Ir (KBr) : ν NH 3270, ν NH_3^+ 3170-2700 (broad), ν C=O 1700 cm^{-1}. ^{1}H-Nmr (DMSO - d_6) : δ 2.92 (m, 4H, $\underline{CH_2}$-$\underline{CH_2}$), 7.05 (d, J = 7.4 Hz, 1H, H_5,), 8.02 (broad, 3H, NH_3^+), 8.91 (s, 1H, NH). Anal. Calcd for $C_{11}H_{16}N_2O_2Cl_2$: C, 47.31; H, 5.73; N, 10.0. Found: C, 47.22; H, 5.68; N, 9.89.

N-(3-Ethoxycarbamidophenethyl)-2-(3,4-dimethoxyphenyl)acetamide (2a) -To an ice cooled stirred mixture of **1a**.HCl (10 g, 40 mmol), $CHCl_3$ (100 ml) and 3 % aq. NaOH (500 ml) was added dropwise a solution of 3,4-dimethoxyphenylacetyl chloride (11.2g, 52 mmol) in $CHCl_3$ (70 ml). After 1 h stirring at room temperature the organic layer was washed with 5 % aq. HCl and water, dried ($MgSO_4$) and evaporated to yield 12.94 g (82 %) of white colorless needles, mp 109-110 °C (acetone-diisopropyl

ether). Ir ($CHCl_3$) : ν NH 3430, ν C=O (carbamate)1735, ν C=O (amide) 1660 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 1.31 (t, J = 7.2 Hz, 3H, $CH_2\underline{CH_3}$), 2.71 (t, J = 6.7 Hz, 2H, $\underline{CH_2}CH_2N$), 3.45 (m, 2H, $\underline{CH_2}CH_2N$), 3.47 (s, 2H, $COCH_2$), 3.82 and 3.88 (2s, 6H, 2 x OCH_3), 4.22 (q, J = 7.2 Hz, 2H, $\underline{CH_2}CH_3$), 5.42 (m, 1H, NH amide), 6.59 (m, NH carbamate). Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.28; H, 6.73; N, 7.25. Found: C, 65.18; H, 6.69; N, 7.28.

N-(4-Chloro-3-ethoxycarbamidophenethyl)-2-(3,4-dimethoxyphenyl)acetamide (2b) -In accordance with the method presented above this compound was prepared from **1b** (10 g) to give 11.6 g (77 %) of pale yellow needles, mp 85-86 °C (MeOH/Et_2O). Ir ($CHCl_3$) : ν NH 3430, ν C=O (carbamate) 1735, ν C=O (amide) 1660 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 1.34 (t, J = 6.7 Hz, 3H, $CH_2\underline{CH_3}$), 2.72 (t, J = 7.1 Hz, 2H, $\underline{CH_2}CH_2N$), 3.45 (m, 2H, $CH_2\underline{CH_2}N$), 3.48 (s, 2H, $COCH_2$), 3.82 and 3.87 (2s, 6H, 2 x OCH_3), 4.24 (q, J = 6.8 Hz, 2H, $\underline{CH_2}CH_3$), 5.40 (m, 1H, NH amide), 7.05 (m, NH carbamate). Anal. Calcd for $C_{21}H_{25}N_2O_5Cl$: C, 59.93; H, 5.94; N, 6.66. Found: C, 59.90; H, 5.82; N, 6.58.

1-(3,4-Dimethoxybenzyl)-6-ethoxycarbamido-1,2,3,4-tetrahydroisoquinoline (3a) -The amide **2a** (25 g, 64.7 mmol) was dissolved in $CHCl_3$ (125 ml) and PCl_5 (30 g, 144 mmol) was cautiously added. After stirring for 6 h at room temperature, Et_2O (120 ml) was slowly added and the precipitate was filtered. Recrystallization of the crude product from MeOH/Et_2O gave the 3,4-dihydroisoquinoline hydrochloride (20.43 g, 78 %) as pale yellow needles, mp 189-192 °C (dec.). Ir ($CHCl_3$) : ν NH^+ 2700-2400, ν $C=N^+$ 1645 cm^{-1} ^{1}H-Nmr ($CDCl_3$) : δ 3.00 (m, 2H, $\underline{CH_2}CH_2N$), 3.90 (m+s, 8H, CH_2N + 2 x OCH_3), 4.48 (s, 2H, $CH_2C=N$), 14.50 (m, 1H, NH^+). The above hydrochloride (10 g, 24.7 mmol) was suspended in a mixture of MeOH (50 ml) and THF (200 ml). $NaBH_3CN$ (3.4 g, 54 mmol) was added in several portions and stirring continued for 45 min at room temperature. The solvent was evaporated and the residue was made basic with 3 % aq. NaOH. The reaction mixture was extracted with $CHCl_3$, the organic phase was washed with water, dried ($MgSO_4$) and the solvent was removed. The slurry residue was triturated in diisopropyl ether and recrystallized from benzene/n-hexane to afford 7.5 g (82 %) of **3a** as a white powder, mp 127-129 °C. Ir ($CHCl_3$) : ν NH 3320, ν NH (carbamate) 3425, ν C=O 1730 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : 1.78 (s, 1H, NH), 3.77 (s, 6H, 2 x OCH_3), 4.00 (m, 3H, $\underline{CH_2}CH_3$ + CHN), 6.44 (m, 1H, NH carbamate). Anal. Calcd for $C_{21}H_{26}N_2O_4$: C, 68.11; H, 7.03; N, 7.57. Found: C, 68.08; H, 6.98; N, 7.49.

7-Chloro-1-(3,4-dimethoxybenzyl)-6-ethoxycarbamido-1,2,3,4-tetrahydroisoquinoline (3b) -A mixture of **2b** (20 g, 47.5 mmol) and P_2O_5 (40 g, 282 mmol) was refluxed in anhydrous toluene (100 ml) for 3 h. The solvent was decanted and ice was cautiously added. The aqueous layer was washed twice with $CHCl_3$, basified with 10 % aq. NaOH solution and extracted with $CHCl_3$. The organic layer was washed with water, dried ($MgSO_4$) and evaporated to give the 3,4-dihydroisoquinoline derivative as a yellow oil,

which was characterized as its hydrochloride (11.9 g, 57 %), mp 205-208 °C (dec.) (MeOH/Et_2O). Ir ($CHCl_3$) : ν NH 2700-2400, ν C=N 1650 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 3.04 (m, 2H, $C\underline{H}_2CH_2N$), 3.91 (m+s, 8H, CH_2N + 2 x OCH_3), 4.55 (s, 2H, CH_2C = N), 7.48 (s, 1H, NH carbamate), 15.53 (m, 1 H, NH^+).

The above hydrochloride (10 g) was reduced by the same procedure as described for 1-(3,4-dimethoxybenzyl)-6-ethoxycarbamido-3,4-dihydroisoquinoline to afford 7.18 g (78 %) of **3b** as a white powder, mp 100-102 °C (n-hexane). Ir ($CHCl_3$) : ν NH 3320, νNH (carbamate) 3420, ν C=O 1725 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 1.66 (s, 1H, NH), 3.87 (s, 6H, 2 x OCH_3), 4.24 (m, 3H, $C\underline{H}_2CH_3$ + $C\underline{H}N^+$), 7.03(m, 1H, NH carbamate), 7.91 (s, 1H, H5). Anal. Calcd for $C_{21}H_{25}N_2O_4Cl$: C, 62.30; H, 6.18; N, 6.92. Found: C, 62.20; H, 6.08; N, 6.82.

3-Ethoxycarbamido-5,6,13,13a-tetrahydro-10,11-dimethoxy-8H-dibenzo[a,g]quinolizine (4a) -The amine **3a** (5 g, 13.5 mmol) was dissolved in a 3.5 % aq. HCl solution (82 ml) and the solution was heated to 85-90 °C. 36 % Formol solution (10 ml, 111 mmol) was added dropwise and stirring was continued for 30 min at 40-50 °C. After cooling, the precipitate was filtered and recrystallized from MeOH/Et_2O. Treatment with 10 % aq. NaOH solution, extraction with $CHCl_3$ and recrystallization of the residue from ethanol afforded 4.64 g (90 %) of **4a** as a pale yellow powder, mp 140-142 °C. Ir ($CHCl_3$) : ν NH 3430 (carbamate), 2810-2760 (Bohlmann bands), ν C=O 1730 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 1.25 (t, J = 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 3.63 (d, J = 13.6 Hz, 1H, H_{8ax}), 3.85(s, 6H, 2 x OCH_3), 3.98 (d, J = 13.6 Hz, 1H, H_{8eq}), 4.21 (q, J = 6.75 Hz, 2H, $C\underline{H}_2CH_3$), 6.60 (m, 3H, NH + H_9 + H_{12}), 7.18 (m, 3H, H_1 + H_2 • H_4). Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.11; H, 6.80; N, 7.33. Found: C, 69.05; H, 6.75; N, 7.28.

2-Chloro-3-ethoxycarbamido-5,6,13,13a-tetrahydro-10,11-dimethoxy-8H-dibenzo[a,g]quinolizine (4b) - In accordance with the method presented above this compound was prepared from **3b** (5g) to give 4.37 g (85 %) of a pale yellow powder, mp 178-180 °C (EtOH). Ir ($CHCl_3$) : νNH 3420 (carbamate), 2810-2760 (Bohlmann bands), ν C=O 1730 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 3.84 (s, 6H, 2 x OCH_3), 4.25 (q, J = 6.8 Hz, 2H, $C\underline{H}_2CH_3$), 6.54 and 6.58 (2s, 2H, H_9 + H_{12}), 7.12 (m, 1H, NH), 7.26 (s, 1H, H_1), 7.95 (s, 1H, H_4). Anal. Calcd for $C_{22}H_{25}N_2O_4Cl$: C, 63.38; H, 6.00; N, 6.72. Found: C, 63.20; H, 6.08; N, 6.62.

3-Amino-5,6,13,13a-tetrahydro-10,11-dimethoxy-8H-dibenzo[a,g]quinolizine (5a) -A mixture of **4a** (4 g, 10.47 mmol) and 10% KOH-EtOH solution (100 ml, 178 mmol) was refluxed for 2 h in the presence of N_2. The solvent was evaporated and the resultant residue was acidified with conc. HCl and the acidic solution was basified with conc. NH_4OH. The product was extracted with $CHCl_3$ and the extract was dried ($MgSO_4$) and evaporated to give a slurry product which was recrystallized from ethanol to give 2.85 g (88 %) of **5a** as a white powder, mp 162-163 °C. Ir ($CHCl_3$) : ν NH_2 3480 and 3390, 2810-2760 (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$) : δ 3.48 (m, 2H, NH_2), 3.61 (d, J = 15.1 Hz, 1H, H_{8ax}), 3.83 (s, 6H, 2 x

OCH_3), 3.95 (d, J =15.1 Hz,1H, H_{8eq}), 6.53 (m, 4H, H_2 + H_4 • H_9 • H_{12}), 7.03 (d, J = 8.3 Hz,1H, H_1). Anal. Calcd for $C_{19}H_{22}N_2O_2$: C, 73.55; H, 7.10; N, 9.03. Found: C, 73.15; H, 6.98; N, 9.00.

3-Amino-2-chloro-5,6,13,13a-tetrahydro-10,11-dimethoxy-8H-dibenzo[a,g]quinolizine (5b) -In accordance with the method presented above this compound was prepared from **4b** (4 g) to give 2.65 g (80%) of a pale yellow powder, mp 148-150 °C (EtOH). Ir ($CHCl_3$) : v NH_2 3490 and 3390, 2810-2760 cm^{-1} (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$) : δ 3.58, (d, J = 14.3 Hz, 1H, H_{8ax}), 3.82 (s, 6H, 2 x OCH_3), 3.90 (m, 2H, NH_2), 3.95 (d, J =14.3 Hz, 1H, H_{8eq}), 6.52 (2s, 2H, H_4 + H_{12}), 6.64 (s, 1H, H_9), 7.13 (s, 1H, H_1). Anal. Calcd for $C_{19}H_{21}N_2O_2Cl$: C, 66.18; H, 6.09; N, 8.13. Found: C, 65.90 H, 5.98; N, 7.98.

3-Chloro-5,6,13,13a-tetrahydro-10,11-dimethoxy-8H-dibenzo[a,g]quinolizine (6a) -Berbine **5a** (500 mg, 1.6 mmol) was dissolved in 10% sulfuric acid (15 ml) at 0-5 °C. $NaNO_2$ (125 mg, 1.81 mmol) in water (1 ml) was added dropwise and stirring was continued for 30 min at this temperature. The orange-red solution was added to another solution of CuCl (350 mg) in conc. HCl (9 ml) and the whole was heated at 70-75 °C for a few minutes and then at room temperature for 1 h. The final solution was basified with 10 % aq. NH_4OH and extracted with $CHCl_3$. The organic layer was separated, washed with water, dried ($MgSO_4$) and evaporated. Chromatography on silica gel using a mixture of $MeOH/CH_2Cl_2$ afforded 276 mg (52 %) of a pale yellow powder, mp 136-138 °C (n-hexane). Ir ($CHCl_3$) : 2810-2750 cm^{-1} (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$) : δ 3.68 (d, J = 15.1 Hz, 1H, H_{8ax}), 3.90 (s, 6H, 2 x OCH_3), 4.03 (d, J = 15.1 Hz, 1H, H_{8eq}), 6.58 and 6.65 (2s, 2H, H_9 + H_{12}), 7.21 (m, 3H, H_1 + H_2 + H_4). Anal. Calcd for $C_{19}H_{20}NO_2Cl$: C, 69.19; H, 6.07; N, 4.25. Found: C, 69.03, H, 5.95; N, 4.15.

2,3-Dichloro-5,6,13,13a-tetrahydro-10,11-dimethoxy-8H-dibenzo[a,g]quinolizine (6b) -In accordance with the method presented above this compound was prepared from **5b** (500 mg) to afford 264 mg (50%) of a pale yellow powder, mp 122-124 °C (n-hexane). Ir ($CHCl_3$) : 2810-2750 (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$) : δ 3.85 (s, 6H, 2 x OCH_3), 3.96 (d, J = 15.8 Hz, 1H, H_{8eq}), 6.66 (s, 1H, H_9), 7.24 (s, 1H, H_4), 7.35 (s, 1H, H_1). Anal. Calcd for $C_{19}H_{19}NO_2Cl_2$: C, 62.64; H, 5.22; N, 3.84. Found: C, 62.18; H, 5.09; N, 3.75.

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(4-methoxy-3-nitrobenzyl)isoquinoline (7a) -This compound was prepared from 10 g (26.7 mmol) of N-(3,4-dimethoxyphenyl)-2-(4-methoxy-3-nitrophenyl)acetamide[22] as described for compound **3a** to give 7.18 g (75 %) of white crystals, mp 137-138 °C (benzene). Ir ($CHCl_3$) : v NH 3320 cm^{-1} (weak). ^{1}H-Nmr ($CDCl_3$) : δ 1.60 (s, 1H, NH), 2.85 (m, 4H, $NCHCH_2$ + NCH_2CH_2), 3.08 (m, 2H, CH_2N), 3.89 and 3.97 (2s, 9H, 3 x OCH_3), 4.12 (dd, J trans= 10.1 Hz, J cis = 3.6 Hz, 1H, CHN). Anal. Calcd for $C_{19}H_{22}N_2O_5$: C, 63.68; H, 6.14; N, 7.82. Found: C, 63.52; H, 6.08; N, 7.78.

1,2,3,4-Tetrahydro-1-(4-methoxy-3-nitrobenzyl)isoquinoline (7b) -This compound was prepared from 10 g of N-phenethyl-2-(4-methoxy-3-nitrophenyl)acetamide[22] as described for the compound **3b** to give 6.92 g (73 %) of white crystals, mp 132-133°C (benzene). Ir ($CHCl_3$) : ν NH 3320 cm^{-1} (weak). ^{1}H-NMR ($CDCl_3$) : δ 1.67 (s, 1H, NH), 2.87 (m, 4H, $NCHC\underline{H}_2$ + $NCH_2C\underline{H}_2$), 3.13 (m, 2H, CH_2N), 3.95 (s, 3H, OCH_3), 4.22 (dd, J trans = 10.4 Hz, J cis = 3.6 Hz, 1H, CHN,). Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.45; H, 6.04; N, 9.39. Found: C, 68.12; H, 5.95; N, 9.28.

1-(3-Amino-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (8a) -Base **7a** (10 g) was dissolved in glacial acetic acid (40 ml) and heated to reflux. A second solution was prepared by dissolving stannous chloride dihydrate (18 g) in conc. HCl (24 ml) and also heated. This solution was added slowly to the first solution and stirring was continued out of heat for 1h. The precipitate was filtered, washed with cold EtOH, basified with 10 % aq. NH_4OH and extracted with $CHCl_3$.The organic layer was washed with water, dried ($MgSO_4$) and evaporated to afford 6.6 g (72 %) of a reddish oil, which was used for the next step without further purification. Ir ($CHCl_3$) : ν NH_2 3480 and 3390 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 2.17 (s, 1H, NH), 2.75 (m, 4H, $NCHC\underline{H}_2$ + $NCH_2C\underline{H}_2$), 3.12 (m, 2H, CH_2N), 3.83 (s + m, 11H, 3 x OCH_3 + NH_2), 4.02 (dd, J trans = 10.4 Hz, J cis = 3.6 Hz, 1H, CHN).

1-(3-Amino-4-methoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (8b) -In accordance with the method presented above this compound was prepared from **7b** (10 g) to afford 6.74 g (75 %) of reddish oily product, which was used for the next step without further purification. Ir ($CHCl_3$): ν NH_2 3480 and 3390 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) : δ 1.95 (s, 1H, NH), 2.87 (m, 4H, $NCHC\underline{H}_2$ + $NCH_2C\underline{H}_2$), 3.16 (m, 2H, CH_2N), 3.84 (s+m, 5H, OCH_3 + NH_2), 4.15 (dd, J trans = 10.4 Hz, J cis = 3.6 Hz, 1H, CHN).

11-Amino-5,6,13,13a-tetrahydro-2,3,10-trimethoxy-8H-dibenzo[a,g]quinolizine (9a) -A mixture of **8a** (2 g, 6.1 mmol), 36 % formol solution (6 ml, 66 mmol) and 50 ml of EtOH was refluxed for 1 h. The solvent was evaporated and the mixture was extracted with CH_2Cl_2. The organic phase was washed with water, dried ($MgSO_4$) and evaporated to give a slurry product. Crystallization from methanol gave 1.55 g (75 %) of colorless plates, mp 232-234 °C (lit. 225-228 °C).[22] Ir ($CHCl_3$) : ν NH_2 3450 and 3370, 2810-2760 cm^{-1} (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$) : δ 3.74 (m, 2H, NH_2), 3.82 (s, 9H, 3 x OCH_3), 6.51 and 6.54 (2s, 2H, H_9+ H_{12}), 6.61 (s, 1H, H_4), 6.74 (s, 1H, H_1). Anal. Calcd for $C_{20}H_{24}N_2O_3$: C, 70.59; H, 7.06; N, 8.23. Found: C, 70.41; H, 7.06; N, 8.15.

11-Amino-5,6,13,13a-tetrahydro-10-methoxy-8H-dibenzo[a,g]quinolizine (9b) -In accordance with the method presented above this compound was prepared from **8b** (2 g) to afford 1.46 g (70 %) of a white powder, mp 200-201 °C (MeOH). Ir ($CHCl_3$) : ν NH_2 3450 and 3370, 2810-2760 cm^{-1} (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$) : δ 3.69 (m, 4H, H_{8ax} + H_{13a} + NH_2), 3.82 (s, 3H, OCH_3), 3.93 (d, J = 14.4 Hz, 1H, H_{8eq}),

6.50 (s, 1H, H_{12}), 6.52 (s, 1H, H_9). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.14; H, 7.14; N, 10.00. Found: C, 76.80; H, 7.06; N, 9.95.

11-Chloro-5,6,13,13a-tetrahydro-2,3,10-trimethoxy-8H-dibenzo[a,g]quinolizine (10a) -Using the same procedure as described for the conversion of **5a** to **6a**, 500 mg of **9a** gave 317 mg (60 %) of **10a** as colorless needles, mp 177-178 °C (EtOH). Ir ($CHCl_3$) : 2810-2760 cm^{-1} (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$): δ 3.24 (dd, $J_{13eq,13a}$ = 3.6 Hz, $J_{13eq,13ax}$ = 16.1 Hz, 1H, H_{13eq}), 3.58 (dd, $J_{13eq,13a}$ = 3.6 Hz, $J_{13ax,13a}$ = 10.4 Hz, 1H, H_{13a}), 3.69 (d, J = 15.3 Hz, 1H, H_{8ax}), 3.87 (s, 9H, 3 x OCH_3), 3.99 (d, J = 15.3 Hz, 1H, H_{8eq}), 6.60 and 6.66 (2s, 2H, H_4 + H_9), 6.72 (s, 1H, H_1), 7.18 (s, 1H, H_{12}). Anal. Calcd for $C_{20}H_{22}NO_3Cl$: C, 66.76; H, 6.12; N, 3.89. Found: C, 66.49; H, 6.08; N, 3.85.

11-Chloro-5,6,13,13a-tetrahydro-10-methoxy-8H-dibenzo[a,g]quinolizine (10b) -Using the same procedure as described for the conversion of **5a** to **6a**, 500 mg of **9b** gave 337 mg (63 %) of **10b** as colorless needles, mp 202-204 °C (MeOH). Ir ($CHCl_3$) : 2810-2760 cm^{-1} (Bohlmann bands). ^{1}H-Nmr ($CDCl_3$) : δ 3.29 (dd, $J_{13eq,13a}$ = 3.6 Hz, $J_{13ax,13eq}$ = 15.3 Hz, 1H, H_{13eq}), 3.66 (m, 2H, H_{8ax} + H_{13a}), 3.88 (s, 3H, OCH_3), 3.99 (d, J = 15.3 Hz, 1H, H_{8eq}), 6.64 (s, 1H, H_9). Anal. Calcd for $C_{18}H_{18}NOCl$: C, 72.12; H, 6.01; N, 4.67. Found: C, 71.68; H, 5.97; N, 4.45.

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Received, 30th October, 1989