SYNTHESIS OF 7,7-DIMETHYLAPORPHINE ALKALOIDS

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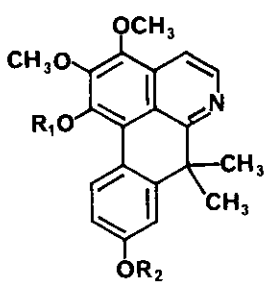
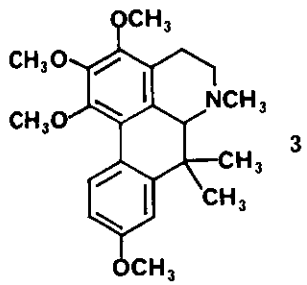
Abstract - The synthesis of N,O,O-trimethyltetrahydromelosmine (1,2,3,9-tetramethoxy-7,7-dimethylaporphine) (3) is described. The amide derivative (9), prepared from the appropriate acid (8) and amine (6) by condensation, was cyclized by a Bischler-Napieralski reaction to afford the 3,4-dihydroisoquinoline derivative (10). The N-methyltetrahydrobenzylisoquinoline (12) from the reduction of 10 and subsequent N-methylation, was cyclized with thalium trifluoroacetate/trifluoroacetic acid and boron trifluoride etherate to the target compound (3).

Two novel 7,7-dimethyltetradehydroaporphine alkaloids, melosmine (1) and melosmidine (2), have been recently isolated from Guatteria melosma[1]. In that investigation, reduction and subsequent N-methylation of these alkaloids afforded novel 7,7-dimethylaporphine alkaloids. This paper presents the total synthesis of one of these products, N,O,O-trimethyltetrahydromelosmine (1,2,3,9-tetramethoxy-7,7-dimethylaporphine) (3).



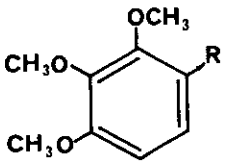
1 $R_1 = R_2 = H$

2 $R_1 = CH_3$; $R_2 = H$



3

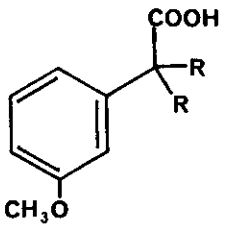
2,3,4 Trimethoxy-β-phenethylamine (6) was prepared from 2,3,4-trimethoxybenzaldehyde (4) (Aldrich) via 5 in 2 steps [i. CH_3NO_2/NaOH/5-10°/EtOH; ii. LAH/Et_2O/reflux] as previously described[2] in 65% yield. α-Methyl-α-(3-methoxyphenyl)propionic acid (8) was prepared from sodium 3-methoxyphenylacetate (Aldrich) (7) by treatment with 2 successive equivalents of lithium diisopropylamide (LDA) (prepared in situ: diisopropylamine/n-BuLi) and MeI in 61% yield[3]. The amine (6) and the acid (8) were condensed using a Schotten-Baumann reaction[4] and the resulting product (9) cyclized using the conditions of the Bischler-Napieralski reaction ($POCl_3$) in 57% yield[5]. The resulting imine (10) was reduced ($NaBH_4$) to afford the amine (11) in 82% yield. This product was N-methylated (CH_2O/$NaBH_4$) in 73% yield to give 12 which was subsequently cyclized using thalium trifluoroacetate/TFA/BF_3-Et_2O/-40°C to afford 3 in 9% yield.[6] The product was identical (UV, IR, MS) to N,O,O-trimethyltetrahydromelosmine (3).



4 R = CHO

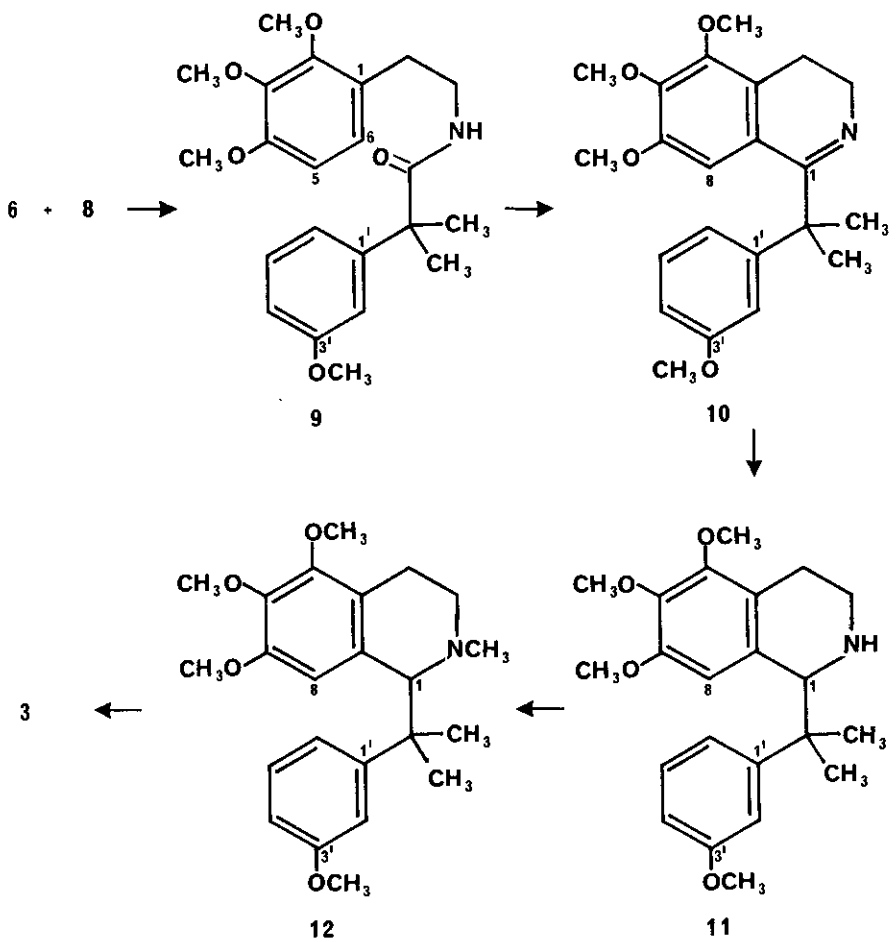
5 R = CH=CH−NO_2

6 R = CH_2−CH_2−NH_2



7 R = H

8 R = CH_3



EXPERIMENTAL

α-Methyl-α-(3-methoxyphenyl)proprionic Acid (8). 3-Methoxyphenylacetic acid (Aldrich) (10 g) was added to a slurry consisting of NaH (3 g) in mineral oil and diisopropylamine (9 ml) in anhydrous THF (200 ml). After briefly heating to reflux, the suspension was cooled to 0°C and N-butyllithium (4 g; 1 equivalent) was injected. The mixture was warmed to 30°C to complete the metallation, cooled to 0°C and MeI (9 g; 1 equivalent) was added. The mixture was stirred (2 hr) at 30°C, cooled to 0°C and a second equivalent of N-butyllithium (4 g) was injected. Following warming to 30°C to complete the metallation and subsequent cooling to 0°C, a second equivalent of MeI (9 g) was added dropwise with stirring. After stirring (3 hr) at 30°C, H_2O (250 ml) was added. The aqueous layer was collected, acidified with conc. HCl and extracted with Et_2O. The ether layer was dried over anhydrous Na_2SO_4 and evaporated to afford 8 (7.1 g) (61%) as colorless plates; mp 48-50°C (aqueous MeOH); ir ν max 3300-2500 (br), 1710 cm^{-1}; uv λ max (MeOH) 222 nm (log ε 3.05), 273 (2.39), 281 (2.31); ^{1}H-nmr ($CDCl_3$) δ 10.45 (1H,brs) (COOH), 7.35-6.7 (4H,m) (aromatic), 3.75 (3H,s) (C-3 methoxy), 1.52 (6H,s) (gem-dimethyl); ms m/z 194 (M^+,49%), 193(15), 166(8), 150(29), 149(100), 135(26), 133(10), 121(61), 115(10), 109(43), 108(14), 105(12), 91(41), 77(45), 65(21).

m-Methoxy-α-methyl-N-(2,3,4-trimethoxyphenethyl)hydratropamide[7] [N-2,3,4-Trimethoxyphenethyl)-α-methyl-α-(3'-methoxyphenyl)propionamide] (9). Thionyl chloride (5 ml) was added to 8 (3 g) in dry benzene (30 ml) and the mixture was heated (50°C) for 3 hours under anhydrous conditions. The acid chloride remaining after removal of volatile substances by evaporation of the reaction mixture, was dissolved in $CHCl_3$ (50 ml) and added dropwise to a well-stirred solution of 6 (3.3 g) and triethylamine (6 g) in chloroform (50 ml) at 0°C. The mixture was stirred for 2 hours at room temperature, washed successively with 100 ml portions of water, 2% HCl and 2% $NaHCO_3$, dried over anhydrous Na_2SO_4 and evaporated to afford 9 (5.1 g) (85%) as a colorless oil; ir ν max (film) 3400, 1655 cm^{-1}; uv λ max (MeOH) 238 nm (log ε 5.25), 280 (5.30); ^{1}H-nmr ($CDCl_3$) δ 7.16 (1H,d,J=8Hz) (C-6), 6.85 (1H,d,J=8Hz) (C-5), 6.82 (3H,m) (C-4',5',6'), 6.50 (1H,d,J=2Hz) (C-2'), 5.7 (1H,brs) (NH), 3.83 (6H,s), 3.79 (3H,s), 3.76 (3H,s) (4 x methoxy), 3.33 (2H,q,J=6Hz) (CH_2NH-), 2.63 (2H,t,J=6Hz) ($ArCH_2$-), 1.51 (6H,s) (gem-dimethyl); ms m/z 238(2%), 237(M^+,6), 195(16), 194(100), 179(23), 166(10), 149(20), 135(10), 121(16), 109(10), 91(18), 79(9), 65(5).

3,4-Dihydro-5,6,7-trimethoxy-1-(3'-methoxy-α,α-dimethylbenzyl)isoquinoline[7] (10). $POCl_3$ (5 ml) was added to 9 in dry benzene (50 ml) and refluxed for 1.5 hours. The brown residue left after evaporation of the mixture was triturated twice with petroleum ether, dissolved in Me_2CO (50 ml) and diluted with 2% aqueous HCl (200 ml). The aqueous acidic solution was washed twice with ether, cooled, basified with dilute NH_4OH and immediately extracted with Et_2O. The ether layer was dried over Na_2SO_4 and evaporated to afford 10 (2.2 g) (57%) as colorless plates; mp 121-2°C (ether); ir ν max (KBr) 2920, 2820, 1600, 1580, 1570, 1560 cm^{-1}; uv λ max (MeOH) 225 nm (log ε 4.03), 272 (3.61), 310 (2.60); ^{1}H-nmr ($CDCl_3$) δ 7.30-6.65 (4H,m) (C-2',4',5',6'), 6.28 (1H,s) (C-8), 3.83 (3H,s), 3.80 (3H,s), 3.75 (3H,s) (C-5,6,3' methoxys), 3.30 (3H,s) (C-7 methoxy), 2.59 (2H,t,J=7Hz) ($ArCH_2$-), 1.58 (6H,s) (gem-dimethyl); ms m/z 369(M^+,53%), 368(100), 354(27) 338(10), 206(10), 195(10) 194(60), 185(10), 169(13), 162(20), 156(10), 149(30), 136(32), 121(40), 109(26), 91(41), 77(29), 65(13).

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-(3'-methoxy-α,α-dimethylbenzyl)isoquinoline[7] (11). $NaBH_4$ (4g) and 10 (2g) in EtOH (50 ml) were stirred at room temperature for 2 hours. After evaporation, the residue was dissolved in H_2O and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhydrous Na_2SO_4 and evaporated to afford 11 (1.7 g) (82%) as an oil; mp of N-acetate 135-6°C ($CHCl_3$); ir ν max (film) 3420, 1600, 1585, 1500 cm^{-1}; uv λ max (MeOH) 228 nm (log ε 4.20), 275 (3.56), 283 (3.54); ^{1}H-nmr ($CDCl_3$) δ 7.20-6.70 (4H,m) (C-2',4',5',6'), 5.88 (1H,s) (C-8), 4.42 (1H,brs) (NH), 3.86 (3H,s), 3.83 (3H,s), 3.80 (3H,s) (C-5,6,3' methoxys), 3.44 (3H,s) (C-7 methoxy), 1.35 (3H,s) (C-CH_3), 1.24 (3H,s) (C-CH_3); ms m/z 222(100), 206(12), 192(7), 161(8), 149(6), 121(8), 91(8), 77(6), 65(4).

1,2,3,4-Tetrahydro-5,6,7-trimethoxy-1-(3'-methoxy-α,α-dimethylbenzyl)-2-methylisoquinoline[7] (12). Formalin (37%) (10 ml) was added to 11 (1 g) in EtOH and stirred at room temperature for 0.5 hours. After cooling in ice, $NaBH_4$ (3 g) was gradually added and the mixture stirred for 2 hours. The reaction mixture was evaporated, H_2O added and subsequently extracted with Et_2O. The Et_2O layer was dried over anhydrous Na_2SO_4 and evaporated to yield 12 (0.76 g) (73%) as plates; mp 170-1°C (ether); ir ν max (KBr) 2960, 1635, 1600, 1510 cm^{-1}; uv λ max (MeOH) 228 nm (log ε 4.30), 262 (4.29), 320 (2.80); ^{1}H-nmr ($CDCl_3$) δ 7.20-6.60 (4H,m) (C-2',4',5',6') 5.65 (1H,s) (C-8), 3.80 (3H,s), 3.75 (3H,s), 3.69 (3H,s) (C-5,6,3' methoxys), 3.42 (3H,s) (C-7 methoxy), 2.49 (3H,s) (N-CH_3), 1.41 (3H,s) (C-CH_3), 1.20 (3H,s) (C-CH_3); ms m/z 236(100), 220(10), 206(9), 194(8), 175(5), 149(6), 121(5), 91(5).

N,O,O-Trimethyltetrahydromelosmine (1,2,3,9-Tetramethoxy-7,7-dimethylaporphine (3). Thalium trifluoroacetate (TTFA) (150 mg) in TFA (120 ml) was cooled to -40°C and a solution of 12 (60 mg) in CH_2Cl_2 (5ml) and BF_3-Et_2O (1 ml) added in one batch. The reaction mixture was stirred (3 hr) at -40°C. After evaporation, H_2O was added and the pH adjusted to 9 with 5% NH_4OH. The solution was extracted with chloroform, dried over anhydrous Na_2SO_4 and evaporated to afford 3 (5 mg) (9%). The product was identical (UV, IR, MS) to the target compound[1].

ACKNOWLEDGEMENTS AND REFERENCES

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7. The authors are grateful to Kurt L. Loening, Nomenclature Director, Chemical Abstracts Service, Columbus, Ohio for providing the correct IUPAC name of this compound.

Received, 13th September, 1982