SYNTHESIS OF WEBERINE AND NORWEBERINE AND THEIR 1-METHYL CONGENERS

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Abstract - The synthesis of 2-methyl-5,6,7,8-tetramethoxy-1,2,3,4-tetrahydroisoquinoline (weberine) 5 from 2,3,4,5-tetramethoxy-β-phenylethylamine via norweberine 4 is described. The synthesis of their 1-methyl homologs was also accomplished.

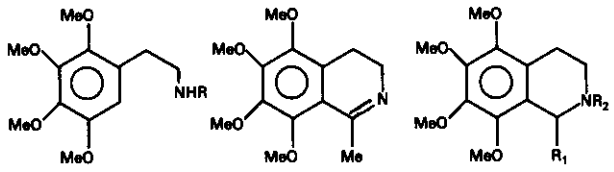
INTRODUCTION

The aromatic tetramethoxy-substituted tetrahydroisoquinoline (TIQ) alkaloid weberine 5 has been isolated from extracts of the Mexican Cactus Pachycereus weberi[1], and reported to occur also in Pachycereus pringlei[2]. The natural source is limited. This alkaloid has now been synthesized from the known aromatic tetramethoxy-substituted β-phenethylamine 1[3] by direct reductive methylation, and via norweberine 4 using a Pictet-Spengler reaction. The preparation of the 1-methyl analogs 6 and 7 which might be of diagnostic interest, was also accomplished by standard procedures.

RESULTS AND DISCUSSION

The β-phenethylamine 1,[3] readily prepared from 2,3,4,5-tetramethoxybenzaldehyde[3,4] by standard procedures underwent the expected Pictet-Spengler reaction with formaldehyde, to afford norweberine 4. Reductive N-methylation of 4 gave weberine 5, isolated as its hydrochloride, mp 165-166°C. This material proved to be identical with a sample of natural origin isolated by McLaughlin et al.[1] by ^{1}H NMR, IR, mp, and MS. The doublet in ^{1}H NMR for the N-CH_3 proton collapses to a singlet when +NH-CH_3 was exchanged with D_2O. Reductive N-methylation of 1 afforded directly weberine 5. The 1-methyl analog 6 could also be obtained by a Pictet-Spengler reaction with acetaldehyde as the reactant. A better procedure to prepare the 1-methyl-substituted

Figure 1



1 R = H
2 R = Ac

3

4 $R_1 = H, R_2 = H$
5 $R_1 = H, R_2 = Me$
6 $R_1 = Me, R_2 = H$
7 $R_1 = Me, R_2 = Me$

analogs 6 and 7 was provided with the Bischler-Napieralski method, giving from the amide 2 first the 3,4-dihydroisoquinoloine 3, then 6 upon reduction, and 7 after N-methylation of 6.

EXPERIMENTAL

Mps were taken on a Fisher-Johns melting point apparatus and are uncorrected. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this Laboratory. IR spectra were obtained on a Beckman 4230 instrument. NMR spectra were determined by using a Varian HR-220 spectrometer with Me_4Si as an internal reference. CI-MS spectra were obtained by using a Finnigan 1015 D spectrometer, and EI-MS spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV). Thin-layer chromatography plates were purchased from Analtech, Inc.

2,3,4,5-Tetramethoxy-β-phenethylamine (1). 2,3,4-Trimethoxybenzaldehyde (Aldrich) was oxidized with m-chloroperbenzoic acid in CH_2Cl_2 to give 1-hydroxy-2,3,4-trimethoxybenzene (98%, bp 95-100° C/1mm Hg) [5]. This phenolic compound was methylated with dimethyl sulfate and K_2CO_3 in refluxing acetone to give 1,2,3,4-tetramethoxybenzene (87%, mp 87-89°C from MeOH, lit.[4] mp 88-91°C). Treatment of the tetramethoxybenzene with N-methyl-N-phenylformamide and $POCl_3$ afforded 2,3,4,5-tetramethoxybenzaldehyde (92%, bp 115-125°C/2mmHg, lit.[4] bp 147°C/5mmHg). Condensation of the tetramethoxybenzaldehyde with nitromethane in the presence of ammonium acetate in refluxing AcOH yielded the corresponding nitrostyrene (60%, mp 57-59°C from CH_2Cl_2-n-hexane, lit.[3] mp 63-64°C from MeOH). Reduction of the nitrostyrene with $LiAlH_4$ in refluxing THF gave the amine 1 (63%, as hydrochloride, mp 167-168°C from MeOH-Et_2O, lit.[3] mp 155-156°C).

N-Acetyl-2-(2,3,4,5-tetramethoxyphenyl)ethylamine (2). AcCl (0.07 ml, 1 mmol) was added dropwise to a stirred solution of the amine hydrochloride (1.HCl) (276 mg, 1 mmol) and Et_3N (0.28 ml, 2 mmol) in CH_2Cl_2 (10 ml). The mixture was stirred at 25°C for 1 h, washed with 10% HCl and brine, dried ($MgSO_4$) and evaporated to leave an oil (275 mg, 97%), bp 155-160°C/0.5 mmHg; IR ν_{max}^{film} cm^{-1}: 3290, 3080, 2940, 1650, 1540, 1490, 1465, 1410, 1230, 1125, 1090, 1050; ^1H NMR ($CDCl_3$): δ 5.82 (bs, 1H, NH), 3.85 and 3.80 (each s, each 3H, 2 x OMe), 3.75 (s, 6H, 2 x OMe), 3.45-3.31 (m, 2H, N-CH_2), 2.80-2.68 (m, 2H, ArCH_2), and 1.92 (s, 3H, Ac); CI-MS m/z 284 (M^+ + 1); EI-MS m/z 283 (M^+).

3,4-Dihydro-5,6,7,8-tetramethoxy-1-methylisoquinoline (3). A mixture of the amide (2) (283 mg, 1 mmol), $POCl_3$ (0.1 ml, 1 mmol), and MeCN (3 ml) was refluxed for 1 h. The mixture was evaporated and the residue was basified with 10% NH_4OH, extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated to give 3. ^1H NMR ($CDCl_3$): δ 3.89, 3.82, 3.77, and 3.70 (each s, each 3H, 4 x OMe), 3.41 (t, J=7Hz, 2H, CH_2-3), 2.50 (t, J=7Hz, 2H, CH_2-4), 2.41 (s, 3H, C_1-Me); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1620, 1465, 1410, 1355, 1335, 995; Hydrochloride of 3: 258 mg (85%); mp 141-143°C (MeOH-Et_2O); IR ν_{max}^{KBr} cm^{-1}: 2980, 2930, 2825, 2760, 2600, 1670, 1575, 1470, 1410, 1355, 1335, 1110, 1085, 1055, 1005, 950; ^1H NMR ($CDCl_3$): δ 4.00, 3.91, 3.81, and 3.74 (each s, each 3H, 4 x OMe), 3.72-3.62 (m, 2H, CH_2-3), 2.96 (s, 5H, C-CH_3 and CH_2-4); CI-MS m/z 266 (M^+ +1); EI-MS m/z 265 (M^+); (Found: C, 55.75; H, 6.71; N, 4.65. Calcd. for $C_{14}H_{20}NO_4Cl$: C, 55.72; H, 6.68; N, 4.64%).

1,2,3,4-Tetrahydro-5,6,7,8-tetramethoxyisoquinoline (4). A mixture of the amine hydrochloride (1.HCl) (278 mg, 1 mmol) and formaldehyde (37%, 3 ml) was stirred at 25°C for 18 h. The mixture was basified with 10% NH_4OH, extracted with Et_2O, and the organic layer was dried ($MgSO_4$) and evaporated. ^1H NMR ($CDCl_3$): δ 3.80 (bs, 2H, CH_2-1), 3.78 and 3.70 (each s, each 6H, 4xOMe), 3.02-2.89 and 2.65-2.53 (each m, each 2H, CH_2-3 and CH_2-4); Hydrochloride of 4: 225 mg (78%), mp 172-173°C (MeOH-Et_2O), ^1H NMR ($CDCl_3$): δ 9.82 (bs, 2H, NH and HCl), 4.16 (bs, 2H, CH_2-1), 3.84, 3.81, 3.78 and 3.75 (each s, each 3H, 4xOMe), 3.45-3.35 (m, 2H, CH_2-3), 3.12-2.92 (m, 2H, CH_2-4): IR ν_{max}^{KBr} cm^{-1}: 2950, 2780, 2720, 2640, 2550, 1470, 1420, 1385, 1365, 1350, 1120, 1075, 1005; CI-MS m/z 254 (M^+ +1), EI-MS m/z 253 (M^+); (Found: C, 53.70; H, 6.85, N, 4.75. Calcd. for $C_{13}H_{20}NO_4Cl$: C, 53.89; N, 6.96; N, 4.83%).

1,2,3,4-Tetrahydro-5,6,7,8-tetramethoxy-2-methylisoquinoline (weberine) (5). (a) A mixture of the amine hydrochloride (4.HCl) (290 mg, 1 mmol) and formaldehyde (37%, 2 ml) in MeOH (2ml) was stirred

for 5 h at 25°C. $NaCNBH_3$ (126 mg, 2 mmol) was added and the mixture was stirred for 0.5 h. The mixture was basified with 10% NH_4OH, extracted with Et_2O and the Et_2O layer was dried ($MgSO_4$) and evaporated. ^1H NMR ($CDCl_3$) δ 3.79 (s, 6H, 2xOMe), 3.72 and 3.70 (each s, each 3H, 2xOMe), 3.58 (s, 2H, CH_2-1), 2.90-2.66 (m, 4H, CH_2-3 and CH_2-4), and 2.48 (s, 3H, NMe). Hydrochloride of 5 (252 mg, 83%), mp 165-166°C (AcOEt); IR ν_{max}^{KBr} cm^{-1}: 2940, 2840, 2670, 2590, 2550, 2390, 1465, 1360, 1110, 1085, 1040, 950. ^1H NMR ($CDCl_3$): δ 4.55-4.25 (m, 2H, CH_2-1), 3.84, 3.78, 3.76 and 3.74 (each s, each 3H, 4xOMe), 3.50-2.95 (m, 4H, CH_2-3 and CH_2-4), 2.91 (d, J=7Hz, 3H, NMe); CI-MS m/z 268 ($M^+ + 1$); EI-MS m/z 267 (M^+); (Found: C, 55.12; H, 7.51; N, 4.76. Calcd. for $C_{14}H_{22}NO_4Cl$: C, 55.35; H, 7.30; N, 4.61%). (b) A mixture of the amine hydrochloride (1.HCl) (278 mg, 1 mmol) and formaldehyde (37%, 1ml) was stirred at 25°C for 15 h. MeOH (3 ml) and $NaCNBH_3$ (100 mg, 1.59 mmol) was added to the mixture and stirred for 0.5 h. The mixture was basified with 10% NH_4OH, and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated to afford 5 (240 mg, 79%), which was identical in every respect with the sample described in (a).

1,2,3,4-Tetrahydro-5,6,7,8-tetramethoxy-1-methylisoquinoline (6). (a) $NaCNBH_3$ (126 mg, 2 mmol) was added to a stirred solution of 3.HCl (302 mg, 1 mmol) and the mixture was stirred at 25°C for 1 h. The mixture was basified with 10% NH_4OH and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated. ^1H NMR ($CDCl_3$): δ 4.13 (q, 1H, CH-1), 3.77, 3.76, 3.73 and 3.72 (each s, each 3H, 4xOMe), 3.18-2.41 and 2.68-2.50 (each m, each 2H, CH_2-3 and CH_2-4), 1.79 (bs, 1H, NH), 139, (d, J=7Hz, 3H, C_1-Me); Hydrochloride of 6 (263 mg, 88%), mp 152-153°C; IR ν_{max}^{KBr} cm^{-1}: 3060, 2940, 2840, 2760, 2460, 1580, 1470, 1415, 1370, 1355, 1345, 1080, 1055, 1035, 1005, 955; ^1H NMR ($CDCl_3$): δ 9.65 (bs, 2H, NH and HCl), 4.60 (bs, 1H, CH-1), 3.86 (s, 9H, 3xOMe), 3.71 (s, 3H, OMe), 3.55-2.94 (m, 4H, CH_2-3 and CH_2-4), and 1.68 (d, J=7Hz, 3H, CH_3-1); CI-MS m/z 268 (M^+); EI-MS 267 (M^+); (Found: C, 55.41; H, 7.27; N, 4.44. Calcd.for $C_{14}H_{22}NO_4Cl$: C, 55.35; H, 7.30; N, 4.61%).

(b) A mixture of the amine hydrochloride (1.HCl) (278 mg, 1 mmol), acetaldehyde (1 ml) and 10% HCl (2 ml) was refluxed for 5 h. The mixture was washed with Et_2O, and the acidic layer was basified with 10% NH_4OH, and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and evaporated to give 6 (56 mg, 21%), which was identical in every respect with the sample described in (a).

1,2,3,4-Tetrahydro-5,6,7,8-tetramethoxy-1,2-dimethylisoquinoline (7). A mixture of the amine hydrochloride (6.HCl) (304 mg, 1 mmol) and formaldehyde (37%, 3 ml) was stirred for 5 h at 25°C. $NaCNBH_3$ (126 mg, 2mmol) and MeOH (5 ml) were added and stirring was continued for 0.5 h. The

mixture was basified with 10% NaOH and extracted with Et_2O. The organic phase was dried and evaporated to leave an oil. IR ν_{max}^{film} cm^{-1}: 2940, 2840, 2800, 1470, 1415, 1375, 1355, 1335, 1200, 1160, 1115, 1080, 1065, 1030, 1005, 960, 870; ^1H NMR ($CDCl_3$): δ 3.80, 3.77, 3.75, 3.70 (each s, each 3H , 4xOMe), 2.95-2.41 (m, 4H, N-CH_2CH_2-Ar), 2.39 (s, 3H, NMe), 1.20 (d, J=7Hz, 3H, C-Me). Hydrochlodride of 7: (241 mg, 76%), mp 149-151°C (EtOAc); IR ν_{max}^{KBr} cm^{-1}: 2940, 2600, 2550, 2530, 2480, 2340, 1470, 1410, 1355, 1115, 1095, 1065, 975; ^1H NMR (CD_3OD): δ 4.48 (q, J=7Hz, 1H, CH-1), 3.80, 3.77, 3.75, 3.73 (each s, each 3H, 4xOMe), 3.63-3.09 (m, 2H, NCH_2), 3.00-2.91 (m, 2H, $ArCH_2$), 2.84 (s, 3H, NMe), 1.52 (d, J=7Hz, C-Me); CI-MS m/z 282 (M^+ +1); EI-MS m/z 281 (M^+); (Found: C, 56.56; H, 7.54; N, 4.26. Calcd. for $C_{15}H_{23}NO_4$.HCl: C, 56.69; 7.61; N, 4.41%).

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