

## 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- $\beta$ -phenylethylamine via norweberine **4** is described. The synthesis of their 1-methyl homologs was also accomplished.

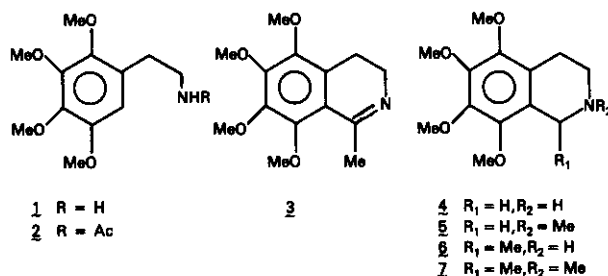
## INTRODUCTION

The aromatic tetramethoxy-substituted tetrahydroisoquinoline (TIQ) alkaloid weberine **5** has been isolated from extracts of the Mexican Cactus *Pachycereus weberi*<sup>1</sup>, and reported to occur also in *Pachycereus pringlei*<sup>2</sup>. The natural source is limited. This alkaloid has now been synthesized from the known aromatic tetramethoxy-substituted  $\beta$ -phenethylamine **1**<sup>3</sup> 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  $\beta$ -phenethylamine **1**,<sup>3</sup> readily prepared from 2,3,4,5-tetramethoxybenzaldehyde<sup>3,4</sup> 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.<sup>1</sup> by <sup>1</sup>H NMR, IR, mp, and MS. The doublet in <sup>1</sup>H NMR for the N-CH<sub>3</sub> proton collapses to a singlet when +NH-CH<sub>3</sub> was exchanged with D<sub>2</sub>O. 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



analogs  $6$  and  $7$  was provided with the Bischler-Napieralski method, giving from the amide  $2$  first the 3,4-dihydroisoquinoline  $3$ , 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<sub>4</sub>Si 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- $\beta$ -phenethylamine ( $1$ ). 2,3,4-Trimethoxybenzaldehyde (Aldrich) was oxidized with *m*-chloroperbenzoic acid in CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>CO<sub>3</sub> in refluxing acetone to give 1,2,3,4-tetramethoxybenzene (87%, mp 87-89°C from MeOH, lit.<sup>4</sup> mp 88-91°C). Treatment of the tetramethoxybenzene with N-methyl-N-phenylformamide and POCl<sub>3</sub> afforded 2,3,4,5-tetramethoxybenzaldehyde (92%, bp 115-125°C/2mmHg, lit.<sup>4</sup> 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<sub>2</sub>Cl<sub>2</sub>-*n*-hexane, lit.<sup>3</sup> mp 63-64°C from MeOH). Reduction of the nitrostyrene with LiAlH<sub>4</sub> in refluxing THF gave the amine  $1$  (63%, as hydrochloride, mp 167-168°C from MeOH-Et<sub>2</sub>O, lit.<sup>3</sup> 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 ( $\underline{1}$ .HCl) (276 mg, 1 mmol) and Et<sub>3</sub>N (0.28 ml, 2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 ml). The mixture was stirred at 25°C for 1 h, washed with 10% HCl and brine, dried (MgSO<sub>4</sub>) and evaporated to leave an oil (275 mg, 97%), bp 155-160°C/0.5 mmHg; IR $\nu_{\text{max}}^{\text{film}}$  cm<sup>-1</sup>: 3290, 3080, 2940, 1650, 1540, 1490, 1465, 1410, 1230, 1125, 1090, 1050; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  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<sub>2</sub>), 2.80-2.68 (m, 2H, ArCH<sub>2</sub>), and 1.92 (s, 3H, Ac); CI-MS  $m/z$  284 (M<sup>+</sup> + 1); EI-MS  $m/z$  283 (M<sup>+</sup>).

3,4-Dihydro-5,6,7,8-tetramethoxy-1-methylisoquinoline (3). A mixture of the amide (2) (283 mg, 1 mmol), POCl<sub>3</sub> (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<sub>4</sub>OH, extracted with Et<sub>2</sub>O. The organic layer was dried (MgSO<sub>4</sub>) and evaporated to give 3. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.89, 3.82, 3.77, and 3.70 (each s, each 3H, 4 x OMe), 3.41 (t, J=7Hz, 2H, CH<sub>2</sub>-3), 2.50 (t, J=7Hz, 2H, CH<sub>2</sub>-4), 2.41 (s, 3H, C<sub>1</sub>-Me); IR $\nu_{\text{max}}^{\text{CHCl}_3}$  cm<sup>-1</sup>: 1620, 1465, 1410, 1355, 1335, 995; Hydrochloride of 3: 258 mg (85%); mp 141-143°C (MeOH-Et<sub>2</sub>O); IR $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 2980, 2930, 2825, 2760, 2600, 1670, 1575, 1470, 1410, 1355, 1335, 1110, 1085, 1055, 1005, 950; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  4.00, 3.91, 3.81, and 3.74 (each s, each 3H, 4 x OMe), 3.72-3.62 (m, 2H, CH<sub>2</sub>-3), 2.96 (s, 5H, C-CH<sub>3</sub> and CH<sub>2</sub>-4); CI-MS  $m/z$  266 (M<sup>+</sup> + 1); EI-MS  $m/z$  265 (M<sup>+</sup>); (Found: C, 55.75; H, 6.71; N, 4.65. Calcd. for C<sub>14</sub>H<sub>20</sub>NO<sub>4</sub>Cl: 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 ( $\underline{1}$ .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<sub>4</sub>OH, extracted with Et<sub>2</sub>O, and the organic layer was dried (MgSO<sub>4</sub>) and evaporated. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  3.80 (bs, 2H, CH<sub>2</sub>-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<sub>2</sub>-3 and CH<sub>2</sub>-4); Hydrochloride of 4: 225 mg (78%), mp 172-173°C (MeOH-Et<sub>2</sub>O), <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  9.82 (bs, 2H, NH and HCl), 4.16 (bs, 2H, CH<sub>2</sub>-1), 3.84, 3.81, 3.78 and 3.75 (each s, each 3H, 4xOMe), 3.45-3.35 (m, 2H, CH<sub>2</sub>-3), 3.12-2.92 (m, 2H, CH<sub>2</sub>-4); IR $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 2950, 2780, 2720, 2640, 2550, 1470, 1420, 1385, 1365, 1350, 1120, 1075, 1005; CI-MS  $m/z$  254 (M<sup>+</sup> + 1), EI-MS  $m/z$  253 (M<sup>+</sup>); (Found: C, 53.70; H, 6.85, N, 4.75. Calcd. for C<sub>13</sub>H<sub>20</sub>NO<sub>4</sub>Cl: C, 53.89; H, 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 ( $\underline{4}$ .HCl) (290 mg, 1 mmol) and formaldehyde (37%, 2 ml) in MeOH (2ml) was stirred

for 5 h at 25°C. NaCNBH<sub>3</sub> (126 mg, 2 mmol) was added and the mixture was stirred for 0.5 h. The mixture was basified with 10% NH<sub>4</sub>OH, extracted with Et<sub>2</sub>O and the Et<sub>2</sub>O layer was dried (MgSO<sub>4</sub>) and evaporated. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 3.79 (s, 6H, 2xOMe), 3.72 and 3.70 (each s, each 3H, 2xOMe), 3.58 (s, 2H, CH<sub>2</sub>-1), 2.90-2.66 (m, 4H, CH<sub>2</sub>-3 and CH<sub>2</sub>-4), and 2.48 (s, 3H, NMe). Hydrochloride of 5 (252 mg, 83%), mp 165-166°C (AcOEt); IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 2940, 2840, 2670, 2590, 2550, 2390, 1465, 1360, 1110, 1085, 1040, 950. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 4.55-4.25 (m, 2H, CH<sub>2</sub>-1), 3.84, 3.78, 3.76 and 3.74 (each s, each 3H, 4xOMe), 3.50-2.95 (m, 4H, CH<sub>2</sub>-3 and CH<sub>2</sub>-4), 2.91 (d, J=7Hz, 3H, NMe); CI-MS  $m/z$  268 (M<sup>+</sup> + 1); EI-MS  $m/z$  267 (M<sup>+</sup>); (Found: C, 55.12; H, 7.51; N, 4.76. Calcd. for C<sub>14</sub>H<sub>22</sub>NO<sub>4</sub>Cl: 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<sub>3</sub> (100 mg, 1.59 mmol) was added to the mixture and stirred for 0.5 h. The mixture was basified with 10% NH<sub>4</sub>OH, and extracted with Et<sub>2</sub>O. The organic layer was dried (MgSO<sub>4</sub>) 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<sub>3</sub> (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<sub>4</sub>OH and extracted with Et<sub>2</sub>O. The organic layer was dried (MgSO<sub>4</sub>) and evaporated. <sup>1</sup>H NMR (CDCl<sub>3</sub>): 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<sub>2</sub>-3 and CH<sub>2</sub>-4), 1.79 (bs, 1H, NH), 1.39, (d, J=7Hz, 3H, C<sub>1</sub>-Me); Hydrochloride of 6 (263 mg, 88%), mp 152-153°C; IR  $\nu_{\text{max}}^{\text{KBr}}$  cm<sup>-1</sup>: 3060, 2940, 2840, 2760, 2460, 1580, 1470, 1415, 1370, 1355, 1345, 1080, 1055, 1035, 1005, 955; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 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<sub>2</sub>-3 and CH<sub>2</sub>-4), and 1.68 (d, J=7Hz, 3H, CH<sub>3</sub>-1); CI-MS  $m/z$  268 (M<sup>+</sup>); EI-MS 267 (M<sup>+</sup>); (Found: C, 55.41; H, 7.27; N, 4.44. Calcd. for C<sub>14</sub>H<sub>22</sub>NO<sub>4</sub>Cl: 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<sub>2</sub>O, and the acidic layer was basified with 10% NH<sub>4</sub>OH, and extracted with Et<sub>2</sub>O. The organic layer was dried (MgSO<sub>4</sub>) 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<sub>3</sub> (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<sub>2</sub>O. The organic phase was dried and evaporated to leave an oil. IR<sub>max</sub><sup>film</sup> cm<sup>-1</sup>: 2940, 2840, 2800, 1470, 1415, 1375, 1355, 1335, 1200, 1160, 1115, 1080, 1065, 1030, 1005, 960, 870; <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.80, 3.77, 3.75, 3.70 (each s, each 3H, 4xOMe), 2.95-2.41 (m, 4H, N-CH<sub>2</sub>CH<sub>2</sub>-Ar), 2.39 (s, 3H, NMe), 1.20 (d, J=7Hz, 3H, C-Me). Hydrochloride of **7**: (241 mg, 76%), mp 149-151°C (EtOAc); IR<sub>max</sub><sup>KBr</sup> cm<sup>-1</sup>: 2940, 2600, 2550, 2530, 2480, 2340, 1470, 1410, 1355, 1115, 1095, 1065, 975; <sup>1</sup>H NMR (CD<sub>3</sub>OD): 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<sub>2</sub>), 3.00-2.91 (m, 2H, ArCH<sub>2</sub>), 2.84 (s, 3H, NMe), 1.52 (d, J=7Hz, C-Me); CI-MS m/z 282 (M<sup>+</sup>+1); EI-MS m/z 281 (M<sup>+</sup>); (Found: C, 56.56; H, 7.54; N, 4.26. Calcd. for C<sub>15</sub>H<sub>23</sub>NO<sub>4</sub>·HCl: C, 56.69; 7.61; N, 4.41%).

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#### REFERENCES

1. R. Mata and J. L. McLaughlin, Phytochemistry, 1980, 19, 673.
2. R. Mata and J. L. McLaughlin, Planta medica, 1980, 38, 180.
3. F. Benington, R. D. Morin, and L. C. Clark, Jr., J. Org. Chem. 1955, 20, 102.
4. L. Syper, K. Kloc, and J. Mlochowski, Tetrahedron, 1980, 36, 123.
5. N. Minami and S. Kijima, Chem. Pharm. Bull. (Japan), 1980, 28, 1648.

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