SYNTHESIS OF PHENETHYLAMINES FROM PHENYLACETONITRILES OBTAINED BY ALKYLATION OF CYANIDE ION WITH MANNICH BASES FROM PHENOLS AND OTHER BENZYLAMINES*

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(Received in USA 5 June 1972; Received in UK for publication 20 February 1973)

Abstract — Benzylamines, obtained by the Mannich reaction on phenols or by reductive alkylation of aldehydes, have been used in place of benzyl chlorides to alkylate cyanide ion to obtain nitriles which may be reduced to phenethylamines. Yields of 4-hydroxy-3-methoxyphenylacetonitriIe were about the same from the primary, secondary, and tertiary amines. Benzylamines not having either an ortho or para OH group did not function as alkylating agents. With such compounds it was necessary to prepare the quaternary salts before alkylation could be achieved. 6-Hydroxydopamine was prepared from 2,4,5-trimethoxybenzaldehyde utilizing the latter approach. 3,5-Dimethoxy-4-hydroxyphenethylamine was cyclized to the corresponding dihydroisoquinoline. The isoquinoline and tetrahydroisoquinoline analogs were also prepared. 4-Hydroxy-3-methoxyphenylacetonitrile was hydrolysed to homovanillic acid, the naturally occurring metabolite of dopamine.

Many methods have been developed for the preparation of derivatives of phenethylamine because of their biological importance. Patel¹ has recently reviewed the methods for synthesis of mescaline (6) and other phenethylamines. The nitrostyrene method has probably been the most widely used, although it is not always successful. In some cases the nitrostyrenes themselves are difficult to prepare, while in other cases reduction with lithium aluminium hydride is troublesome, and catalytic reduction usually is unsatisfactory. Reduction of phenylacetonitriles, on the other hand, may be effected by catalytic reduction as well as by chemical means.

The nitriles are obtained from the corresponding benzyl chlorides which are often difficult to prepare as well as being unstable and unpleasant substances to handle. Further, OH groups on the benzene ring must be protected, adding two additional steps to the overall procedure. We have found that benzylamines may be used in place of benzyl chlorides to alkylation cyanide ion. The amines are easy to make and are stable, and it is not necessary to protect OH groups.

The Mannich reaction on phenols offers a convenient source of benzylamines. The reaction of 2,6-dimethoxyphenol (1) with formaldehyde and dimethylamine gave the expected Mannich base, 2,6-dimethoxy-4-dimethylaminomethylphenol (2) in good yield. Alkylation of cyanide ion with 2 was successful and 3,5-dimethoxy-4-hydroxyphenylacetonitrile (3) was obtained. Catalytic reduction of 3 proceeded smoothly to give 4-hydroxy-3,5-dimethoxyphenethylamine hydrochloride (4). The amine had previously been prepared by reduction of the appropriate nitrostyrene.²

Demethylation of 4 with hydrobromic acid led to 3,4,5-trihydroxyphenethylamine hydrobromide (5) which had previously been prepared by demethylation of 3,4,5-trimethoxyphenethylamine (6).³

The nitrile, 3, was hydrolysed to 4-hydroxy-3,5-dimethoxyphenylacetic (homosyringic) acid (7), and the acid could be converted to the acid chloride by the action of phosphorus pentachloride. The latter yielded the corresponding amide upon treatment with ammonia. This method is worth noting, since the customary procedure for converting phenolic acids to acid chlorides involves a preliminary reaction to protect the OH group.†

The amide, 8, was obtained from the acid, 7 and the amine 4. Cyclization of 8 by the Bischler-Napieralski method gave 3,4-dihydro-6,8-dimethoxy-1-(3,5-dimethoxy-4-hydroxybenzyl)-4-hydroxyisoquinoline (9). Hydrolysis of 9 with hydrobromic acid gave 3,4-dihydro-6,7,8-trihydroxy-1-(3,4,5-trihydroxybenzyl)isoquinoline (10).
Reduction of 9 gave the tetrahydroisoquinoline 11 while oxidation of 9 failed to give the papaverine analog, 6,8-dimethoxy-1-(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxyisoquinoline (14). The latter was obtained, however, by concurrent debenzylation and oxidation of 13, which in turn was obtained by benzylation of 9 or cyclization of the amide, 12. The nitrile, 3, also served as an intermediate for a new synthesis of mescaline hydrochloride (6). Reaction of 3 with dimethyl sulfate gave 3,4,5-trimethoxyphenylacetonitrile which then could be reduced to 6.
The ultimate product of this scheme depended, of course, upon the orientation of the Mannich side chain. For example, starting with 2-methoxy-phenol, we obtained 2-hydroxy-3-methoxyphenethylamine hydrochloride (15), and not 4-hydroxy-3-methoxyphenethylamine hydrochloride (21). The latter compound, however, can be obtained by this procedure starting with vanillin (16). Reductive alkylation of 16 with methylamine gave N-methylvanillylamine (18), which could be transformed to 4-hydroxy-3-methoxyphenylacetonitrile (20). Reduction of 20 proceeded smoothly to give 21.

Both 15 and 21 could be hydrolysed to, respectively, 2,3-dihydroxyphenethylamine hydrobromide and 3,4-dihydroxyphenethylamine (dopamine) hydrobromide. This method appears to be a practical procedure for large-scale preparation of dopamine.

Hydrolysis of 20 gave 4-hydroxy-3-methoxyphenylacetic acid (homovanillic acid), a naturally occurring metabolite of dopamine. This method of synthesis of homovanillic acid was superior to the reported oxidation of eugenol,4-6 or from vanillin through the rhodanine derivative,7 or via benzyl chloride.8

Certain mono- and di-methyl ethers of 1,2,4-benzenetriol appeared to offer some promise, utilizing the procedures described above, for a practical large-scale synthesis of 2,4,5-trihydroxyphenethylamine (6-hydroxydopamine).

The reaction of 2,5-dimethoxyphenol (22) with formaldehyde and dimethylamine gave, depending on the conditions of reaction, either the bis-methylene derivative or 3,6-dimethoxy-2,5-dimethylaminomethylphenol (23). No compound containing only one dimethylaminomethyl group was isolated.

2-Methoxyhydroquinone (27) underwent the Mannich reaction to give 2-dimethylaminomethyl-5-methoxyhydroquinone (28). Again we failed to obtain the desired nitrile, 29. In this case oxidation of the hydroquinone moiety may be responsible for the failure.

A successful approach started with 2,4,5-trimethoxybenzaldehyde (30). Reductive alkylation of 30 was accomplished with methylamine. The secondary amine was allowed to react with formaldehyde to give the tertiary amine which was quaternized with methyl iodide. The latter alkylated cyanide ion to give 2,4,5-trimethoxyphenyl-
acetonitrile (31). Reduction of the nitrile group followed by hydrolysis with hydrobromic acid gave 6-hydroxydopamine hydrobromide (32) in 22% yield overall.

As noted above we had to use the quaternary salt as the alkylating agent. The primary and secondary amines failed to react with cyanide ion to give the desired nitrile, 31. Amines could be used as alkylating agents only when OH groups were present in the \textit{para} or \textit{ortho} positions. Although most alkylations were carried out with tertiary amines, primary or secondary amines could also be used. For example 4-hydroxy-3-methoxybenzylamine (vanillylamine, 17), its N-Me (18) and its N,N-dimethyl (19) derivative gave rise to 4-hydroxy-3-methoxyphenylacetonitrile (20) in 64%, 58%, and 56% yield, respectively. The corresponding quaternary salt gave a 41% yield of the nitrile.

As might be expected a OH group in the \textit{meta} position failed to promote this reaction. None of the corresponding nitrile was isolated when 3-hydroxy-4-methoxybenzylamine (isovanillylamine) was allowed to react with cyanide ion in the usual manner. The only product isolated was the transamination product, N-(3-hydroxy-4-methoxybenzyl)formamide.

It seemed reasonable, then, to postulate that the quaternary salts reacted in the typical SN\textsubscript{2} type of reaction, while those amines which did react probably go through a quinone methide (33) intermediate. The quinone methide mechanism has been proposed by Von Auwers\textsuperscript{9-11} and others\textsuperscript{12,13} for related reactions. Gardner et al.\textsuperscript{14} have discussed the reaction of phenolic Mannich bases (but as the methiodides) with various nucleophiles. Andrisano et al.\textsuperscript{15} invoke this type of elimination—addition reaction for the preparation of thioethers from aminomethylnapthols (as the hydrochlorides) and benzenethiols.

\begin{center}
\begin{tikzpicture}
  \node (a) [draw, circle] {CH\textsubscript{2}NH\textsubscript{2}};
  \node (b) [draw, circle, above of=a] {H};
  \node (c) [draw, circle, below of=a] {OMe};
  \node (d) [draw, circle, right of=a] {MeO};
  \node (e) [draw, circle, right of=d] {CHO};
  \node (f) [draw, circle, below of=e] {MeO};

  \draw [->] (a) -- (b);
  \draw [->] (a) -- (c);
  \draw [->] (a) -- (d);
  \draw [->] (a) -- (e);
  \draw [->] (a) -- (f);

  \node at (1.5,0) {4 steps};
  \node at (3,0) {2 steps};
  \node at (4.5,0) {2 steps};

  \node at (5,0) {EXPERIMENTAL};

  \node at (5.5,0.5) {M.ps were determined on a Thomas-Hoover Unimelt apparatus and are corrected. Spectral data were obtained from a Perkin-Elmer 521 IR spectrometer and a Varian A-60 NMR spectrometer.}

  \node at (5.5,1) {2,6-Dimethoxy-4-dimethylaminomethylphenol (2). A soln of 2,6-dimethoxyphenol (154 g; 1 mole) in 225 ml (2.0 mole) 40% aqueous dimethylamine was stirred for 100 min (1-25 mole) of formalin was added dropwise during 1 hr, and then the soln was heated on the steam bath for 3 hr. The soln was evaporated and the oil was taken up in the minimum amount of ether, and chilled to give 211 g (100%) of amine, m.p. 82-84°. Recrystallization from ether raised the m.p. to 84-85°; IR (CHCl\textsubscript{3}): 3570 (OH), 2890-2850 (Me), 2800 (N-Me); 8(CDC\textsubscript{3}): 6-58 (2H, s, aromatic-H), 6-22 (H, br s, OH), 3-86 (6H, s, OMe x 2), 3-36 (2H, s, NCH\textsubscript{3}), 2-25 (6H, s, NMe x 2); (Found: C, 62-27; H, 8-29; N, 6-45. Calc. for C\textsubscript{11}H\textsubscript{17}N\textsubscript{3}O\textsubscript{5}: C, 62-56; H, 8-71; N, 6-63%).}

  \node at (5.5,2) {2-Dimethylaminomethyl-6-methoxyphenol (15). From 2-methoxyphenol (62 g; 0-5 mole) was obtained 47 g (52%) of the amine, b.p. 129-138° (8-0 mm). n\textsubscript{D} 1.5342; m.p. 47-48°, utilizing the procedure of Decombe\textsuperscript{16} who reported m.p. 46-47°.}

  \node at (5.5,3) {2-Dimethylaminomethyl-4,5-methylenedioxyphenol (25). A soln of 3,4-methylenedioxyphenol (27 g; 0-2 mole) and paraformaldehyde (6 g; 0-2 mole) in 44 ml of 40% aqueous dimethylamine and 100 ml EtOH was allowed to stand overnight at room temp. The soln was evaporated and the residue was crystallized from ether to give 31-5 g (81%) of the amine, m.p. 86-89°; IR (CHCl\textsubscript{3}): 3300-2400 cm\textsuperscript{-1} (superimposed OCH\textsubscript{3}, NMe and bonded OH stretching); 8(CDC\textsubscript{3}): 10-47 (H, s, OH), 6-47 (H, s, aromatic-H), 6-43 (H, s, aromatic-H), 5-80 (2H, s, OCH\textsubscript{3}), 3-55 (2H, s, NCH\textsubscript{3}), 2-31 (6H, s, NMe x 2); (Found: C, 61-52; H, 6-84; N, 6-98. Calc. for C\textsubscript{16}H\textsubscript{18}N\textsubscript{2}O\textsubscript{4}: C, 61-52; H, 6-71; N, 7-18%).}

  \node at (5.5,4) {Mannich reaction of 2,5-dimethoxyphenol. A soln of 2,5-dimethoxyphenol (32 g; 0-54 mole), formalin (5 ml; 0-06 mole) and dimethyamine (10-7 ml; 0-1 mole) in 50 ml EtOH was left overnight at room temp. The solvent was evaporated leaving a oil which crystallized from MeOH to give 4-7 g of material melting at 206-209°, presumably bis-(3,6-dimethoxy-2-hydroxyphenyl)methane; IR (Nujol): 3350 (bonded OH), 1600 and 1510 cm\textsuperscript{-1} (aromatic ring vibration); (t(dMSO): 8-57 (2H, br s, OH x 2), 6-40 (2H, s, aromatic-H), 6-30 (2H, s, aromatic-H); 3-37 (6H, s, OMe x 2), 3-31 (8H, s, OMe x 2 and CH\textsubscript{2}). (Found: C, 64-01; H, 6-03. Calc. for C\textsubscript{16}H\textsubscript{18}O\textsubscript{4}: C, 63-74; H, 6-29%).}

  \node at (5.5,5) {The reaction was repeated, but was heated under reflux for 4 hr. The oil obtained was converted to the hydrochloride and was crystallized from EtOH to give 2-8 g of 2,4-bis-(dimethylaminomethyl)-3,6-dimethoxyphenol, (23) m.p. 223-225°; IR (KB): Strong absorption between 3650-2300 cm\textsuperscript{-1} due to OH, NH, NMe stretch; (t(D\textsubscript{2}O): 7-35 (H, s, aromatic-H), 4-48 (2H, s, CH\textsubscript{2}N), 4-39 (2H, s, CH\textsubscript{2}N), 4-00 (3H, s, OMe), 3-89 (3H, s, OMe), 2-98 (6H, s, NMe x 2); 2-95 (6H, s, NMe x 2). (Found: C, 49-54; H, 6-18%).}

\node at (5.5,6) {\textcopyright 1934 J. H. Short, D. A. Dunnigan and C. W. Ours.}
\end{tikzpicture}
\end{center}
aqueous dimethylamine in 100 ml EtOH was left over.

The soln was allowed to stand at room temp for 1 hr before filtering off the catalyst. The filtrate was evaporated and the residue was crystallized from benzene to give 26 g (79%) of the desired amine, m.p. 111-113°. The recorded m.p. is 130-131°. 1R (Nujol): 3450-3000 (Complex absorption due to OH and NH stretch), 1675 cm⁻¹ (amide I). The recorded m.p. is 142-144°.

Preparation of phenylethylamines from phenylacetonitriles

Method A. The nitrile (0-1 mole) was dissolved in 250 ml of EtOH and 25 ml of conc HCl was added. Hydrogenation was effected at low pressure over PdC (3-5 g). If the product precipitated water was added to effect soln before filtering off the catalyst. The filtrate was evaporated and the residue was crystallized from MeOH, EtOH, or 2-ProH. In some cases it was necessary to add ether to induce the product to precipitate. The amines are described in Table 2.

Method B. The dihydroxy and trihydroxyphenylethylamines were prepared from the appropriate methyl ethers by allowing them to reflux for 4 hr in HBr and AcOH in the manner described by Senoh and Witkop. 19 The amines are described in Table 2.

Homovanillic acid. To 250 ml of 50% NaOH was added a soln of 4-hydroxy-3-methoxymethylmethylamine (85 g; 0-52 mole) in 200 ml 2-methoxyethanol. The soln was heated under reflux under N₂ for 3 hr. The soln was evaporated to half its initial volume; chilled, and neutralized carefully with conc HCl. The colorless cream-colored platelets were collected on a filter, washed thoroughly with water, and dried overnight at 80° under vacuum. The yield of the acid was 82 g (86%), m.p. 142-144°. 19 The recorded m.p. is 143°.

Homosyringic acid. Hydrolysis of 3,5-dimethoxy-4-hydroxyphenylacetonitrile (110 g; 0-57 mole) was accomplished in the manner described above to give 93.5 g (81%) of the acid melting at 130-132° after recrystallization from EtOAc. The recorded m.p. is 130-131°.

3,5-Dimethoxy-4-hydroxyphenylacetonitrile. A soln of homovanillic acid (11-8 g; 0-056 mole) in 200 ml anhyd ether was stirred in an ice bath as PCl₃ (14-7 g; 0-07 mole) was added. Stirring was continued for 3 hr. The solvent was removed and the residue was treated with aqueous ammonia. The crude product was crystallized from methyl ethyl ketone. The yield was 5-9 g (50%) of material melting at 132-134°. IR (Nujol): 3450-3000 (Complex absorption due to OH and NH stretch), 1675 cm⁻¹ (amide CO). 1R (CDCl₃): 6-50 (2H, s, aromatic-H), 5-43-5-20 (2H, br s, NH₂), 3-87 (6H, s, OMe X 2), 3-47 (2H, s, CH₂) (Found: C, 57-13; H, 6-26; N, 5-64. Calc. for C₁₃H₁₄ClN₂O₂: C, 56-86; H, 6-20; N, 6-63%).
Table 1. Phenylacetonitriles

![R^3 R^4 R^5 R^6]

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>R^3</th>
<th>B.p., °C (mm)</th>
<th>n_D</th>
<th>M.p., °C</th>
<th>Yield, %</th>
<th>Formula</th>
<th>C, %</th>
<th>H, %</th>
<th>N, %</th>
<th>C, %</th>
<th>H, %</th>
<th>N, %</th>
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<tbody>
<tr>
<td>H</td>
<td>MeO</td>
<td>HO</td>
<td>144–155 (0-3)</td>
<td>1.532</td>
<td>76</td>
<td>C_{10}H_{14}NO_3</td>
<td>62.16</td>
<td>62.12</td>
<td>5.57</td>
<td>5.71</td>
<td>7.25</td>
<td>7.32</td>
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<tr>
<td>H</td>
<td>MeO</td>
<td>MeO</td>
<td>140–155 (0-1)</td>
<td>77–78</td>
<td>88</td>
<td>C_{11}H_{18}NO_3</td>
<td>63.75</td>
<td>63.89</td>
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<td>HO</td>
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<td>H</td>
<td>140–145 (0-3)</td>
<td>102–104</td>
<td>23</td>
<td>C_{6}H_{12}N_3</td>
<td>66.24</td>
<td>66.50</td>
<td>5.56</td>
<td>5.76</td>
<td>8.58</td>
<td>8.64</td>
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<tr>
<td>HO</td>
<td>MeO</td>
<td>HO</td>
<td>140–140 (0-1)</td>
<td>1.5484</td>
<td>43</td>
<td>C_{11}H_{14}NO_3</td>
<td>63.75</td>
<td>63.53</td>
<td>5.56</td>
<td>5.62</td>
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<tr>
<td>MeO</td>
<td>H</td>
<td>MeO</td>
<td>160–165 (1-0)</td>
<td>83–86</td>
<td>43</td>
<td>C_{11}H_{14}NO_3</td>
<td>63.75</td>
<td>63.53</td>
<td>6.32</td>
<td>6.34</td>
<td>6.76</td>
<td>6.71</td>
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Spectral data table 1a

<table>
<thead>
<tr>
<th>IR (cm⁻¹) in CHCl₃</th>
<th>NMR CDCl₃ Chemical shifts (δ)</th>
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<td>3525</td>
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<tr>
<td>2</td>
<td>3550</td>
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<tr>
<td>3</td>
<td>3656</td>
</tr>
<tr>
<td>4</td>
<td>3656</td>
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</tbody>
</table>
Table 2. Phenethylamines

| R² | R³ | R¹ | R¹ | X | Method | M.p., °C | Yield, % | Formula | Calc. | Found | Calc. | Found | Calc. | Found | Notes |
|----|----|----|----|----|--------|---------|----------|---------|-------|-------|-------|-------|-------|-------|
| H  | MeO| HO | MeO| H  | Cl     | A       | 256-258° | 95      | C₁₀H₁₂N₂O₂.HCl | 51.40 | 51.66 | 6.90  | 6.77  | 5.99  |       |        |
| 2  | H  | MeO| HO | MeO| Me₂CH | Cl     | 216-218° | 55      | C₁₀H₁₂N₂O₂.HCl | 56.62 | 56.70 | 7.04  | 7.77  | 5.98  | 5.28  |        |
| 3  | H  | HO | HO | HO | H     | Br      | 192-196° | 65      | C₁₂H₁₄N₂O₂.HBr | 38.30 | 38.57 | 5.14  | 5.07  | 5.58  | 5.45  |        |
| 4  | H  | MeO| MeO| MeO| H     | Cl     | 184-185° | 90      | C₁₀H₁₂N₂O₂.HCl | 53.33 | 53.45 | 7.32  | 7.56  | 5.96  | 5.65  |        |
| 5  | HO | MeO| H  | H  | H     | Cl     | 172-175° | 72      | C₁₀H₁₂N₂O₂.HCl | 53.07 | 52.90 | 6.93  | 7.08  | 6.88  | 6.93  |        |
| 6  | HO | HO | H  | H  | Br    | Br     | 145-148° | 35      | C₁₂H₁₄N₂O₂.HBr | 40.91 | 40.81 | 5.49  | 5.36  | 5.96  | 5.95  |        |
| 7  | H  | HO | HO | HO | H     | Cl     | 212-214° | 76      | C₁₀H₁₂N₂O₂.HCl | 53.07 | 53.12 | 6.93  | 7.18  | 6.89  | 6.63  |        |
| 8  | H  | HO | H  | HO | H     | Cl     | 215-218° | 43      | C₁₂H₁₄N₂O₂.HCl | 40.91 | 40.81 | 5.49  | 5.28  | 5.96  | 5.81  |        |
| 9  | MeO| H  | MeO| MeO| H     | Cl     | 193-195° | 51      | C₁₀H₁₂N₂O₂.HCl | 53.33 | 53.28 | 7.32  | 7.50  | 5.69  | 5.46  |        |
| 10 | HO | H  | HO | HO | H     | Cl     | 218-220° | 56      | C₁₂H₁₄N₂O₂.HBr | 33.42 | 38.16 | 4.84  | 5.00  | 6.60  | 5.46  |        |


Spectral data Table 2a

<table>
<thead>
<tr>
<th>Cmpd. No.</th>
<th>IR (KBr) NH and OH Stretch (cm⁻¹)*</th>
<th>NMR (Solvent) Chemical Shifts (δ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3650-2500 639 (2H, s, aromatic-H); 3-83 (6H, s, OCH₃); 2-47-3.25 (4H, s, CH₂CH₂N and 2H, m, OH and NH₂); [CDCl₃]</td>
<td>6-39 (2H, s, aromatic-H); 3-83 (6H, s, OCH₃); 2-47-3.25 (4H, s, CH₂CH₂N and 2H, m, OH and NH₂); [CDCl₃]</td>
</tr>
<tr>
<td>2</td>
<td>3650-2300 6-39 (2H, s, aromatic-H); 3-80 (6H, s, OCH₃ × 2); 3-10-3.43 (2H, br s, NH and OH); 2-67-2.80 (5H, m, CH₂CH₂NCH₃); 1-00 (3H, s, CH₃); 1-08 (3H, s, CH₃); [CDCl₃]</td>
<td>6-39 (2H, s, aromatic-H); 3-80 (6H, s, OCH₃ × 2); 3-10-3.43 (2H, br s, NH and OH); 2-67-2.80 (5H, m, CH₂CH₂NCH₃); 1-00 (3H, s, CH₃); 1-08 (3H, s, CH₃); [CDCl₃]</td>
</tr>
<tr>
<td>3</td>
<td>3650-1900 6.46 (2H, s, aromatic-H); 2-67-3.23 (4H, m, CH₂CH₂) [D₂O]</td>
<td>6.26 (2H, s, aromatic-H); 2-67-3.23 (4H, m, CH₂CH₂) [D₂O]</td>
</tr>
<tr>
<td>4</td>
<td>3250-1900 6.90 (2H, s, aromatic-H); 3.68 (6H, s, OCH₃ × 2); 3.90 (3H, s, OCH₃); 2-90-3.63 (4H, m, CH₂CH₂) [D₂O]</td>
<td>6.90 (2H, s, aromatic-H); 3.68 (6H, s, OCH₃ × 2); 3.90 (3H, s, OCH₃); 2-90-3.63 (4H, m, CH₂CH₂) [D₂O]</td>
</tr>
<tr>
<td>5</td>
<td>3650-2300 6-97-7.22 (3H, m, aromatic-H); 4-00 (3H, s, OCH₃); 2-38-3.63 (4H, m, CH₂CH₂) [D₂O]</td>
<td>6-97-7.22 (3H, m, aromatic-H); 4-00 (3H, s, OCH₃); 2-38-3.63 (4H, m, CH₂CH₂) [D₂O]</td>
</tr>
<tr>
<td>6</td>
<td>3650-1800 6.80-7.00 (3H, m, aromatic-H); 2-87-3.47 (4H, m, CH₂CH₂) [D₂O]</td>
<td>6.80-7.00 (3H, m, aromatic-H); 2-87-3.47 (4H, m, CH₂CH₂) [D₂O]</td>
</tr>
<tr>
<td>7</td>
<td>3650-1800 9.00 (H, br s, OH); 8.33 (3H, br s, &quot;NH₃&quot;; 6.67-6.77 (3H, m, aromatic-H); 3.83 (3H, s, OCH₃); 2-83-3.13 (4H, br s, CH₂CH₂) [dDMSO]</td>
<td>9.00 (H, br s, OH); 8.33 (3H, br s, &quot;NH₃&quot;; 6.67-6.77 (3H, m, aromatic-H); 3.83 (3H, s, OCH₃); 2-83-3.13 (4H, br s, CH₂CH₂) [dDMSO]</td>
</tr>
<tr>
<td>8</td>
<td>3650-1800 8-17 (5H, br s, OH) × 2 and &quot;NH₃&quot;; 6-40-6.87 (3H, m, aromatic-H); 2-60-3.10 (4H, m, CH₂CH₂) [dDMSO]</td>
<td>8-17 (5H, br s, OH) × 2 and &quot;NH₃&quot;; 6-40-6.87 (3H, m, aromatic-H); 2-60-3.10 (4H, m, CH₂CH₂) [dDMSO]</td>
</tr>
<tr>
<td>9</td>
<td>3650-1900 6-92 (H, s, aromatic-H); 6.72 (H, s, aromatic-H); 3-90 (9H, s, OCH₃ × 3); 2-73-3.50 (4H, m, CH₂CH₂) [D₂O]</td>
<td>6.92 (H, s, aromatic-H); 6.72 (H, s, aromatic-H); 3-90 (9H, s, OCH₃ × 3); 2-73-3.50 (4H, m, CH₂CH₂) [D₂O]</td>
</tr>
<tr>
<td>10</td>
<td>3650-1900 6.83 (H, s, aromatic-H); 6.63 (H, s, aromatic-H); 2.70-3.47 (4H, m, CH₂CH₂) [D₂O]</td>
<td>6.83 (H, s, aromatic-H); 6.63 (H, s, aromatic-H); 2.70-3.47 (4H, m, CH₂CH₂) [D₂O]</td>
</tr>
</tbody>
</table>

*Strong broad complex absorption due to superimposing OH stretching and NH stretching of the phenolic hydroxyls and the ammonium
N-(3,5-Dimethoxy-4-hydroxyphenethyl)-3,5-dimethoxy-4-hydroxyphenylacemamide (8). A mixture of homosyringic acid (21.1 g; 0.1 mole) and 3,5-dimethoxy-4-hydroxyphenethylamine (19.7 g; 0.1 mole) was allowed to react in the manner described by Teitel and Brossi,\textsuperscript{13} for the preparation of N-(4-hydroxy-3-methoxyphenethyl)-4-hydroxyphenylacemamide, except that the crude product was taken up in chloroform. Recrystallization from EtOAc and then from EtOH gave 27.0 g (69%) of tan solid, m.p. 150-2°C; IR (Nujol): 3500-3050 (OH), 3380 (NH) and 1650 cm\textsuperscript{-1} (amide CO); \(\varepsilon\) (CDCl\textsubscript{3}) 6.40-20 (2H, s, aromatic-H), 6.33 (2H, s, aromatic-H), 5.77-5.37 (3H, br s, NH and OH \times 2), 3.75 (12 H, s, OMe \times 4), 3.67-3.27 (4H, m, NCH\textsubscript{2} and CH\textsubscript{2}CO), and 2.83-2.47 (2H, m, CH\textsubscript{2}). (Found: C, 61.54; H, 6.38; N, 3.53. Calc. for C\textsubscript{29}H\textsubscript{37}NO\textsubscript{4}; C, 61.37; H, 6.44; N, 3.58%).

3,4-Dihydro-6,8-dimethoxy-1(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxyisoquinoline (9). Cyclization of N-(3,5-dimethoxy-4-hydroxyphenethyl)-3,5-dimethoxy-4-hydroxyphenylacemamide (20.5 g; 0.05 mole) was effected in the manner described by Teitel and Brossi\textsuperscript{13} for the preparation of 7-hydroxy-6-methoxy-1-(4-hydroxybenzyl)-3,4-dihydroisoquinoline. The crude product precipitated from the mixture. It was collected on a filter, washed with acetonitrile and then with ether. The crude product (as the hydrochloride) weighed 19.5 g and melted at 194-197°C.\textsuperscript{*}

A portion was converted to the free base by addition of Na\textsubscript{2}CO\textsubscript{3} aq. and crystallized from MeOH, m.p. 192-193°C, IR (Nujol): 3440 (bonded OH), 1565 cm\textsuperscript{-1} (C=N); \(\varepsilon\) (DMSO): 7.77 (H, s, aromatic-H). 6.77 (2H, s, aromatic-H) 5.00 (2H, br s, aromatic-H); 5.00 (2H, br s, aromatic-H); 4.75 (2H, m, CH\textsubscript{2}), 4.17 (2H, d, J=3, NCH\textsubscript{2}) 3.74 (3H, s, OMe). (Found: C, 64.33; H, 6.21; N, 3.75. Calc. for C\textsubscript{34}H\textsubscript{42}NO\textsubscript{4}; C, 64.57; H, 6.26; N, 3.43%).

6,8-Dimethoxy-1(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (11). To a solution of crude 3,4-dihydro-6,8-dimethoxy-1(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxyisoquinoline in 120 ml MeOH was added a suspension of PtC (2.4 g) in 30 ml EtOH. Hydrogenation was carried out at low pressure. The catalyst and solvent were removed and the solid residue was washed with acetone and then with ether. The crude product (as the hydrochloride) weighed 19.5 g and melted at 194-197°C.\textsuperscript{*}

A portion was converted to the free base by addition of Na\textsubscript{2}CO\textsubscript{3} aq. and crystallized from MeOH, m.p. 192-193°C, IR (Nujol): 3440 (bonded OH), 1565 cm\textsuperscript{-1} (C=N); \(\varepsilon\) (DMSO): 7.77 (H, s, aromatic-H). 6.77 (2H, s, aromatic-H) 5.00 (2H, br s, aromatic-H); 5.00 (2H, br s, aromatic-H); 4.75 (2H, m, CH\textsubscript{2}), 4.17 (2H, d, J=3, NCH\textsubscript{2}) 3.74 (3H, s, OMe). (Found: C, 64.33; H, 6.21; N, 3.75. Calc. for C\textsubscript{34}H\textsubscript{42}NO\textsubscript{4}; C, 64.57; H, 6.26; N, 3.43%).

6,8-Dimethoxy-1(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxyisoquinoline hydrochloride (14). The cyclization of 12 (16.9 g; 0.028 mole) was effected as described above. An oil (13) was obtained which was not purified further. The same oil was obtained from benzyl bromide and 9. The yield was 2.0 g (10%); IR (KBr): 3650-2230 (Strong broad complex absorption due to superimposing OH and NH stretching vibrations); \(\varepsilon\) (DMSO): 7.77 (H, s, aromatic-H), 6.77 (2H, s, aromatic-H) 5.00 (2H, br s, CH\textsubscript{2}), 4.17 (2H, s, OMe), 3.97 (3H, s, OMe), 3.75 (3H, s, OMe), 3.75-3.27 (4H, m, CH\textsubscript{2}). (Found: C, 58.90; H, 5.44; N, 3.43%).

Acknowledgments — The authors wish to thank Mr. Victor Rauschel and his associates for analytical data. The IR spectra were determined by Mr. William Washburn. The NMR spectra were provided by Dr. Richard Egan and Mrs. Ruth Stanaszew. Mr. James Holland assisted with the pressure reactions.

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*Elemental analyses indicated that the POCl\textsubscript{3} had reacted with the OH groups to a considerable extent. The free OH groups were readily regenerated by treatment with dilute base.
Synthesis of phenethylamines from phenylacetonitriles