

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

J. H. SHORT, D. A. DUNNIGAN and C. W. OURS†

Department of Organic Chemistry, Division of Experimental Therapy, Abbott Laboratories, North Chicago, Illinois 60064, U.S.A.

(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-methoxyphenylacetone nitrile 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-methoxyphenylacetone nitrile 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. Patel<sup>1</sup> 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 aluminum hydride is troublesome, and catalytic reduction usually is unsatisfactory. Reduction of phenylacetone nitriles, 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 alkylate cyanide ion. The amines are easy to make and are stable, and it is not necessary to protect OH groups.

\*Part of this paper was presented before the joint American Chemical Society—Canadian Institute of Chemistry Meeting, Toronto, May, 1970.

†Author to whom requests for reprints should be addressed.

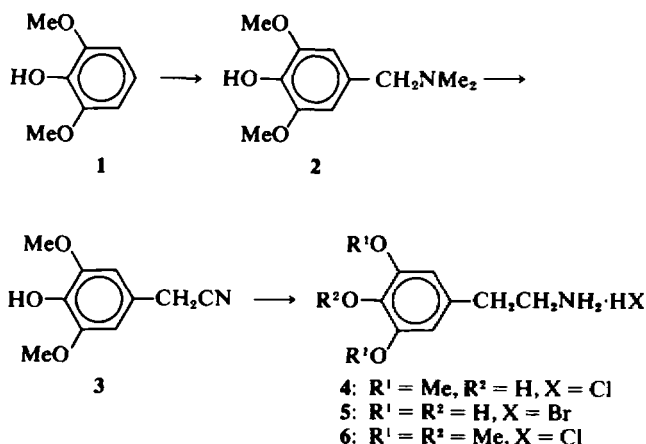
‡Esters prepared by this method must be treated with a weak base such as ammonia or sodium bicarbonate to regenerate the OH group since the latter does react with PCls.

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-hydroxyphenylacetone nitrile (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.<sup>2</sup>

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)<sup>3</sup>.

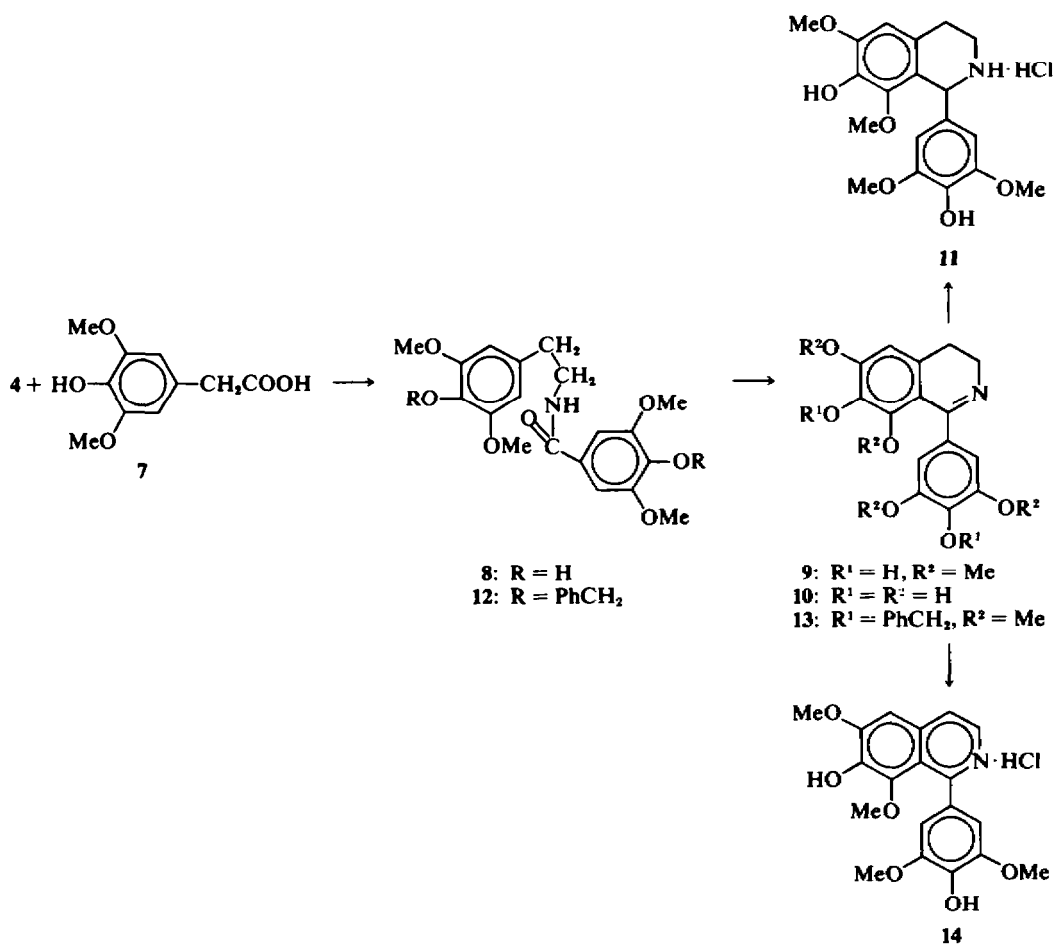
The nitrile, 3, was hydrolysed to 4-hydroxy-3,5-dimethoxyphenylacetic (homosyringic) acid (7), and the acid could be converted to the acid chloride by the action of phosphorus pentachloride. The latter yielded the corresponding amide upon treatment with ammonia. This method is worth noting, since the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

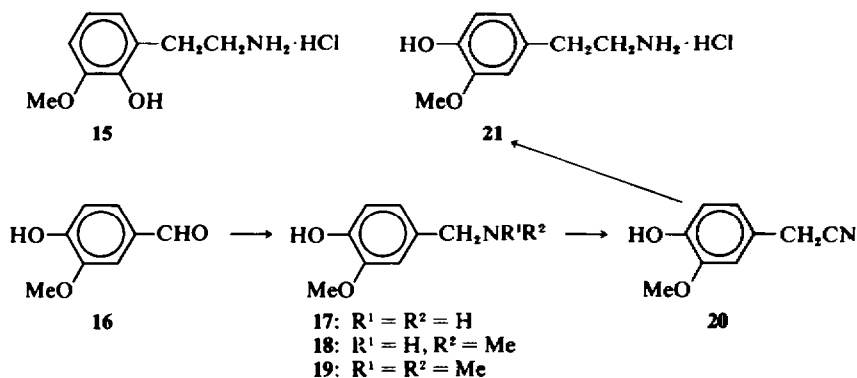
The amide, 8, was obtained from the acid, 7 and the amine 4. Cyclization of 8 by the Bischler-Napieralski method gave 3,4-dihydro-6,8-dimethoxy-1-(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxyisoquinoline (9). Hydrolysis of 9 with hydrobromic acid gave 3,4-dihydro-6,7,8-trihydroxy-1-(3,4,5-trihydroxybenzyl)isoquinoline (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 debenzyla-

tion and oxidation of **13**, which in turn was obtained by benzoylation 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**.





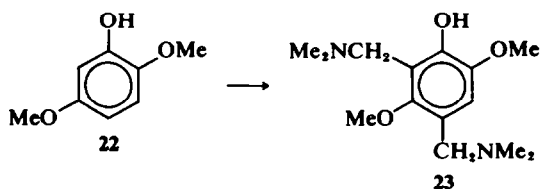
The ultimate product of this scheme depended, of course, upon the orientation of the Mannich side chain. For example, starting with 2-methoxyphenol, we obtained 2-hydroxy-3-methoxyphenethylamine hydrochloride (15), and not 4-hydroxy-3-methoxyphenethylamine hydrochloride (21). The latter compound, however, 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.

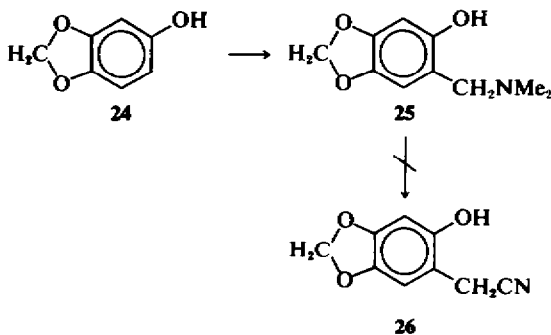
Hydrolysis of 20 gave 4-hydroxy-3-methoxyphenylacetic acid (homovanillic acid), a naturally occurring metabolite of dopamine. This method of synthesis of homovanillic acid was superior to the reported oxidation of eugenol,<sup>4-6</sup> or from vanillin through the rhodanine derivative,<sup>7</sup> or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

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.

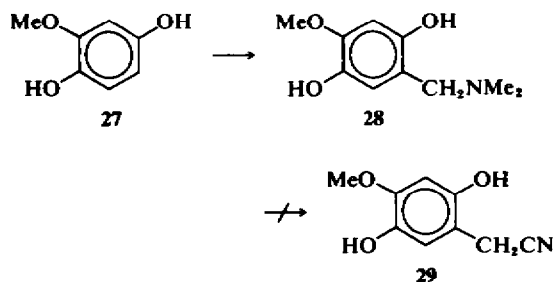


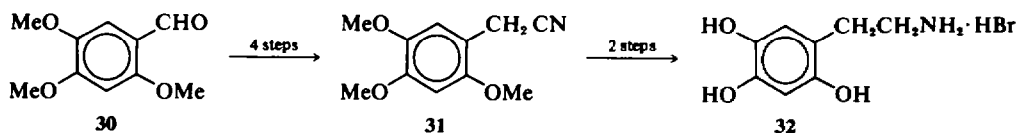
The Mannich reaction was carried out successfully on sesamol (24) to give 2-dimethylaminomethyl-4,5-methylenedioxyphenol (25). The latter compound, however, inexplicably failed to give the desired nitrile, 26.



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-



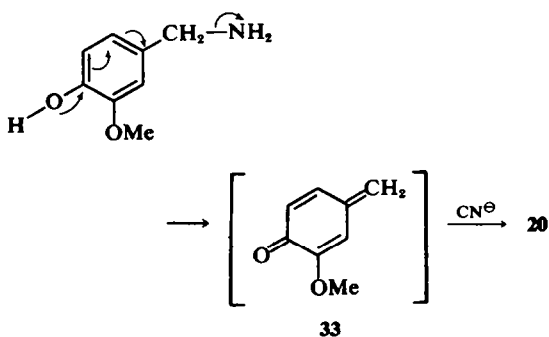


acetonitrile (31). Reduction of the nitrile group followed by hydrolysis with hydrobromic acid gave 6-hydroxydopamine hydrobromide (32) in 22% yield overall.

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 *para* or *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 *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 transamidation product, N-(3-hydroxy-4-methoxybenzyl)formamide.

It seemed reasonable, then, to postulate that the quaternary salts reacted in the typical  $SN_2$  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<sup>9-11</sup> and others<sup>12,13</sup> for related reactions. Gardner *et al.*<sup>14</sup> have discussed the reaction of phenolic Mannich bases (but as the methiodides) with various nucleophiles. Andrisano *et al.*<sup>15</sup> invoke this type of elimination-addition reaction for the preparation of thioethers from aminomethylnaphthols (as the hydrochlorides) and benzenethiols.



## EXPERIMENTAL

M.p.s 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.

**2,6-Dimethoxy-4-dimethylaminomethylphenol (2).** A soln of 2,6-dimethoxyphenol (154.2 g; 1.0 mole) in 225 ml (2.0 mole) 40% aqueous dimethylamine was stirred as 100 ml (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 84–85.5°; IR (CHCl<sub>3</sub>): 3570 (OH), 2890–2850 (Me), 2800 (N–Me);  $\delta$ (CDCl<sub>3</sub>): 6.58 (2H, s, aromatic-H), 6.22 (H, br s, OH), 3.86 (6H, s, OMe  $\times$  2), 3.36 (2H, s, NCH<sub>2</sub>), 2.25 (6H, s, NMe  $\times$  2); (Found: C, 62.27; H, 8.29; N, 6.45. Calc. for C<sub>11</sub>H<sub>17</sub>NO<sub>3</sub>: C, 62.56; H, 8.11; N, 6.63%).

**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),  $n_D^{25}$  1.5342; m.p. 47–48°, utilizing the procedure of Décombe<sup>16</sup> who reported m.p. 46–47°.

**2-Dimethylaminomethyl-4,5-methylenedioxyphenol (25).** A soln of 3,4-methylenedioxyphenol (27.6 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<sub>3</sub>): 3300–2400 cm<sup>-1</sup> (superimposed OCH<sub>2</sub>O, NMe and bonded OH stretching);  $\delta$ (CDCl<sub>3</sub>): 10.47 (H, s, OH), 6.47 (H, s, aromatic-H), 6.43 (H, s, aromatic-H), 5.80 (2H, s, OCH<sub>2</sub>O), 3.55 (2H, s, NCH<sub>2</sub>), 2.31 (6H, s, NMe  $\times$  2); (Found: C, 61.52; H, 6.84; N, 6.98. Calc. for C<sub>16</sub>H<sub>13</sub>NO<sub>3</sub>: C, 61.52; H, 6.71; N, 7.18%).

**Mannich reaction of 2,5-dimethoxyphenol.** A soln of 2,5-dimethoxyphenol<sup>17</sup> (8.3 g; 0.054 mole), formalin, (5 ml; 0.06 mole) and dimethylamine (10.7 ml; 0.1 mole) in 50 ml EtOH was left overnight at room temp. The solvent was evaporated leaving an 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<sup>-1</sup> (aromatic ring vibration);  $\delta$ (DMSO): 8.57 (2H, br s, OH  $\times$  2), 6.40 (2H, s, aromatic-H), 6.30 (2H, s, aromatic-H); (3.37 (6H, s, OMe  $\times$  2), 3.31 (8H, s, OMe  $\times$  2 and CH<sub>2</sub>). (Found: C, 64.01; H, 6.03. Calc. for C<sub>17</sub>H<sub>20</sub>O<sub>6</sub>: C, 63.74; H, 6.29%).

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 (KBr): Strong absorption between 3650–2300 cm<sup>-1</sup> due to OH, NH, NMe stretch;  $\delta$ (D<sub>2</sub>O): 7.35 (H, s, aromatic-H); 4.48 (2H, s, CH<sub>2</sub>N), 4.39 (2H, s, CH<sub>2</sub>N), 4.00 (3H, s, OMe), 3.89 (3H, s, OMe), 2.98 (6H, s, NMe  $\times$  2) 2.95 (6H, s, NMe  $\times$  2). (Found: C, 49.54; H,

7.96; N, 8.19. Calc. for  $C_{14}H_{25}ClN_2O_2$ : C, 49.27; H, 7.68; N, 8.21%.

**2-Methylaminomethyl-5-methoxyhydroquinone (28).** A soln of 2-methoxyhydroquinone<sup>18</sup>, (22 g; 0.16 mole) paraformaldehyde (4.8 g; 0.16 mole) and 36 ml of 40% aqueous dimethylamine in 100 ml EtOH was left overnight at room temp. The soln was evaporated leaving an oil which was dissolved in 50 ml of benzene and concentrated until a brown solid precipitated. The solid was recrystallized from benzene to give 23.6 g (76%) of the amine, m.p. 118–120°. The hydrochloride was prepared and melted at 161–163° after crystallization from EtOH-ether; IR (KBr of HCl salt): Strong absorption between 3650–2300  $cm^{-1}$  due to OH, NH and NMe stretching;  $\delta$ (free base in  $CDCl_3$ ): 7.95 (2H, s, OH  $\times 2$ ) 6.58 (H, s, aromatic-H) 6.45 (H, s, aromatic-H), 3.82 (3H, s, OMe), 3.54 (2H, s,  $NCH_2$ ), 2.30 (6H, s, NMe  $\times 2$ ). (Found: C, 51.69; H, 7.20; N, 5.96. Calc. for  $C_{10}H_{16}ClNO_2$ : C, 51.40; H, 6.90; N, 5.99%.)

**N-Methylvanillylamine (18).** A soln of vanillin (152 g; 1.0 mole) and 200 ml liquid methylamine in 900 ml abs EtOH was allowed to stand at room temp for 1 hr before 4.0 g  $PtO_2$  was added with 100 ml EtOH. Reduction was effected with  $H_2$  at an initial pressure of 42 psi. The catalyst and solvent were removed leaving 160 g (96%) of amine, m.p. 111–114°. Crystallization from benzene did not raise the m.p.; IR ( $CHCl_3$ ): 3565 (free OH), 3350 (NH), 2870 (—OMe), 1620 and 1530  $cm^{-1}$  (aromatic ring);  $\delta$ ( $CDCl_3$ ): 7.03 (3H, m, aromatic-H), 4.86 (2H, s, NH and OH), 3.92 (3H, s, OMe), 3.79 (2H, s,  $NCH_2$ ) 2.55 (6H, s, NMe  $\times 2$ ). (Found: C, 64.42; H, 8.08; N, 8.19. Calc. for  $C_9H_{13}NO_2$ : C, 64.65; H, 7.84; N, 8.38%.)

**N,N-Dimethylvanillylamine (19).** A soln of vanillin (76 g; 0.5 mole) and 75 ml dimethylamine in 500 ml EtOH was hydrogenated over 1.5 g of  $PtO_2$  at low pressure. The catalyst was removed and the soln was evaporated. The oil was taken up in chloroform and extracted with 500 ml of 2N HCl. The aqueous layer was extracted 3 times with 100 ml portions of chloroform and then made basic with aqueous ammonia. The amine was taken up in chloroform, dried and evaporated to give 90 g (77%) of light brown oil. A portion was converted to the hydrochloride and crystallized from dry EtOH to give white plates, m.p. 203–205°; IR (KBr). Strong absorption between 3650–2300  $cm^{-1}$  due to OH, OMe, NMe stretching;  $\delta$  ( $D_2O$ ): 7.10 (3H, m, aromatic-H), 4.28 (2H, s,  $NCH_2$ ), 3.97 (3H, s, OMe), 2.95 (6H, s, NMe  $\times 2$ ). (Found: C, 55.19; H, 7.57; N, 6.38. Calc. for  $C_{10}H_{16}ClNO_2$ : C, 55.17; H, 7.41; N, 6.43%.)

**3,4,5-Trimethoxyphenylacetonitrile.** A soln of 3,5-dimethoxy-4-hydroxyphenylacetonitrile (43.4 g; 0.22 mole) and dimethyl sulfate (37.8 g; 0.3 mole) in 500 ml acetone containing  $K_2CO_3$  (55.2 g; 0.4 mole) was stirred and heated under reflux for 18 hr. The inorganic salts were collected on a filter and washed with acetone. The filtrate was evaporated and the residue was distilled. The product is described in Table 1.

**Preparation of phenylacetonitriles from benzylamines.** The amine (1.0 mole) was dissolved in 1.0 liter dimethylformamide and KCN (1.1 mole) was added. The mixture was stirred under  $N_2$  and heated for 6 hr at 110–130°. The mixture was acidified with 50 ml AcOH in 200 ml water. The soln was evaporated, and the residue was treated with 500 ml water and extracted with three 150 ml portions chloroform. The chloroform soln was dried and evaporated leaving an oil which was subjected to vacuum distillation. The nitriles are described in Table 1.

**2,4,5-Trimethoxyphenylacetonitrile (31).** A soln of 2,4,5-trimethoxybenzaldehyde (19.6 g; 0.1 mole) and 20 ml liquid methylamine in 200 ml EtOH was reduced with  $H_2$  at low pressure over  $PtO_2$ . The excess methylamine was removed under reduced pressure. Then 18 ml of formalin was added and the catalytic reduction step was repeated without adding fresh catalyst. The catalyst and solvent were removed and the residual oil was dissolved in 300 ml dimethylformamide and MeI (16.9 g; 0.12 mole) was added. The soln was stirred and heated for 1 hr at 110°. A slight excess of KCN was added and heating was continued at 110–130° for 18 hr. The reaction was worked up as described, and the product is described in Table 1.

#### Preparation of phenethylamines 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.

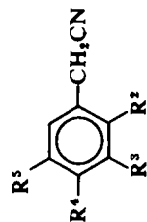
**Method B.** The dihydroxy and trihydroxyphenethylamines were prepared from the appropriate methyl ethers by allowing them to reflux for 4 hr in HBr and AcOH in the manner described by Senoh and Witkop.<sup>19</sup> The amines are described in Table 2.

**N-Isopropyl-2-(3,5-dimethoxy-4-hydroxy)phenethylamine hydrochloride.** A Parr bottle was charged with 3,5-dihydroxy-4-methoxyphenethylamine (27 g; 0.14 mole) 12 ml acetone, and 240 ml dry EtOH. Reductive alkylation was effected at low hydrogen pressure over 8 g of 5% Pd C at 45° for 5 days. The catalyst and solvent were removed. The residue was recrystallized from benzene to give 26 g (79%) of the desired amine, m.p. 111–113.5°, which was converted to the hydrochloride salt and is described in Table 2.

**Homovanillic acid.** To 250 ml of 50% NaOH was added a soln of 4-hydroxy-3-methoxyphenylacetonitrile (85 g; 0.52 mole) in 200 ml 2-methoxyethanol. The soln was heated under reflux under  $N_2$  for 3 hr. The soln was evaporated to half its initial volume; chilled, and neutralized carefully with conc HCl. The 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°. The recorded m.p. is 143°.<sup>4</sup>

**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°. <sup>20</sup>

**3,5-Dimethoxy-4-hydroxyphenylacetamide.** A soln of homosyringic acid (11.8 g; 0.056 mole) in 200 ml anhyd ether was stirred in an ice bath as  $PCl_5$  (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);  $\delta$ ( $CDCl_3$ ): 6.50 (2H, s, aromatic-H), 5.43–5.20 (2H, br s,  $NH_2$ ) 3.87 (6H, s, OMe  $\times 2$ ), 3.47 (2H, s,  $CH_2$ ). (Found: C, 57.13; H, 6.26; N, 6.54. Calc. for  $C_{11}H_{13}NO_4$ : C, 56.86; H, 6.20; N, 6.63%.)

Table 1. Phenylacetone nitriles<sup>a</sup>

R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	B.p., °C	n <sub>D</sub> <sup>25</sup>	M.p., °C	Yield, %	Formula	C, %		H, %		N, %	
									Calc.	Found	Calc.	Found	Calc.	Found
1	H	MeO	MeO	144-145 (0.03)	1.5532		76	C <sub>10</sub> H <sub>11</sub> NO <sub>3</sub>	62.16	62.12	5.57	5.71	7.25	7.32
2 <sup>b</sup>	H	MeO	MeO	140-155 (0.1)		77-78 <sup>c</sup>	88	C <sub>11</sub> H <sub>13</sub> NO <sub>3</sub>	63.75	63.89	6.32	6.55	6.76	6.83
3	HO	MeO	H	140-145 (0.3)		102-104 <sup>d</sup>	23	C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub>	66.24	66.50	5.56	5.76	8.58	8.64
4	H	MeO	HO	140-144 (0.1)	1.5484		e	C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub>	66.24	66.11	5.56	5.62	8.58	8.56
5 <sup>b</sup>	MeO	H	MeO	160-165 (1.0)		83-86 <sup>f</sup>	43	C <sub>11</sub> H <sub>13</sub> NO <sub>3</sub>	63.75	63.53	6.32	6.34	6.76	6.71

<sup>a</sup>The nitriles were prepared by the procedure described in the Experimental section for 3,5-dimethoxy-4-hydroxyphenylacetone nitrile. Preparation of the required amines is described in the Experimental section. <sup>b</sup>The recorded m.p. is 77°, W. Baker and R. Robinson, *J. Chem. Soc.* 132, 147 (1929). <sup>c</sup>Recrystallized from benzene. <sup>d</sup>The yield from vanillylamine was 64%, from N-methylvanillylamine, 58%, from N,N-dimethylvanillylamine, 56%, and from the quat salt, 41%. The recorded b.p. is 135-145° (2.0 mm), K. Kraetzl and E. Meiser, *Monatsh. Chem.* 88, 1056 (1957). <sup>e</sup>Recrystallized from methanol. The recorded m.p. is 84°, J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.* 1165 (1954).

Spectral data table 1a

IR (cm <sup>-1</sup> ) in CHCl <sub>3</sub>	NMR CDCl <sub>3</sub>	
	—OH	—CN
1	3525	2250
2	—	2250
3	3550	2255
4	3656	2275
5	—	2265

Chemical shifts (δ)	
1	6.50 (2H, s, aromatic-H); 5.63 (H, s, OH); 3.86 (6H, s, OCH <sub>3</sub> × 2); 3.67 (2H, s, CH <sub>2</sub> ); 6.68 (2H, s, aromatic-H); 3.93 (9H, s, OCH <sub>3</sub> × 3); 3.77 (2H, s, CH <sub>2</sub> ); 6.80-7.00 (3H, m, aromatic-H); 5.84 (H, s, OH); 3.90 (3H, s, OCH <sub>3</sub> ); 3.73 (2H, s, CH <sub>2</sub> ); 7.00-7.01 (3H, m, aromatic-H); 5.95 (H, s, OH); 3.97 (3H, s, OCH <sub>3</sub> ); 3.78 (2H, s, CH <sub>2</sub> ); 6.90 (H, s, aromatic-H); 6.57 (H, s, aromatic-H); 3.93 (3H, s, OCH <sub>3</sub> ); 3.90 (6H, s, OCH <sub>3</sub> × 2); 3.68 (2H, s, CH <sub>2</sub> )

Table 2. Phenethylamines

R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>1</sup>	X	Method <sup>a</sup>	M.p., °C	Yield, %	Formula	C, %		H, %		N, %	
										Calc.	Found	Calc.	Found	Calc.	Found
1	H	MeO	HO	HO	Cl	A	256-258 <sup>b</sup>	95	C <sub>10</sub> H <sub>13</sub> NO <sub>3</sub> ·HCl	51.40	51.66	6.90	6.77	5.99	6.11
2	H	MeO	HO	Me <sub>2</sub> CH	Cl	c	216-218-6	55	C <sub>13</sub> H <sub>17</sub> NO <sub>3</sub> ·HCl	56.62	56.70	8.04	7.77	5.08	5.28
3	H	HO	HO	H	Br	B <sup>d</sup>	192-196	65	C <sub>8</sub> H <sub>11</sub> NO <sub>3</sub> ·HBr	38.30	38.57	5.14	5.07	5.58	5.45
4	H	MeO	MeO	H	Cl	A	184-185.5 <sup>e</sup>	90	C <sub>11</sub> H <sub>17</sub> NO <sub>3</sub> ·HCl	53.33	53.45	7.32	7.56	5.66	5.65
5	HO	HO	H	H	Cl	A	172-175 <sup>f</sup>	72	C <sub>8</sub> H <sub>13</sub> NO <sub>2</sub> ·HCl	53.07	52.90	6.93	7.08	6.88	6.93
6	HO	HO	H	H	Br	B <sup>g</sup>	145-148	35	C <sub>8</sub> H <sub>11</sub> NO <sub>3</sub> ·HBr	40.91	40.81	5.49	5.36	5.96	5.95
7	H	MeO	HO	H	Cl	A	212-214 <sup>h</sup>	76	C <sub>8</sub> H <sub>13</sub> NO <sub>2</sub> ·HCl	53.07	53.12	6.93	7.18	6.88	6.93
8	H	HO	HO	H	Br	B <sup>i</sup>	215-218 <sup>j</sup>	43	C <sub>8</sub> H <sub>11</sub> NO <sub>2</sub> ·HBr	40.91	41.05	5.49	5.28	5.96	5.81
9	MeO	H	MeO	H	Cl	A	193-195 <sup>k</sup>	51	C <sub>11</sub> H <sub>17</sub> NO <sub>3</sub> ·HCl	53.33	53.28	7.32	7.50	5.66	5.46
10	HO	H	HO	H	Br	B	218-220 <sup>l</sup>	56	C <sub>8</sub> H <sub>11</sub> NO <sub>3</sub> ·HBr	38.42	38.16	4.84	5.00	5.60	5.46

<sup>a</sup>Methods A and B are described in the Experimental section. <sup>b</sup>The recorded m.p. is 258-259°, reference. <sup>c</sup>Preparation is described in the Experimental section. <sup>d</sup>Prepared from compound no. 1 in this Table. <sup>e</sup>The recorded m.p. is 182°, reference. <sup>f</sup>The recorded m.p. is 164-165.3°, V. G. Voronin, G. D. Kulikovskaya, L. D. Magda, *Zh. Organ. Khim.*, **1**, 719-21 (1965); *Chem. Abstr.*, **63**, 5546 (1965). <sup>g</sup>Prepared from compound no. 5. <sup>h</sup>The recorded m.p. is 213-214°, F. A. Ramirez and A. Burger, *J. Am. Chem. Soc.*, **72**, 2781 (1950). <sup>i</sup>Prepared from compound no. 7. The recorded m.p. is 212°, G. Burger and A. J. Ewins, *J. Chem. Soc.*, **97**, 2253 (1910). <sup>j</sup>The recorded m.p. is 193.5-194.5°, reference. <sup>k</sup>The recorded m.p. is 218-219°, reference. <sup>l</sup>

Spectral data Table 2a

Cmpd. No.	IR (KBr) NH and OH Stretch (cm <sup>-1</sup> ) <sup>a</sup>	NMR (Solvent) Chemical Shifts (δ)	
		IR (KBr)	Chemical Shifts (δ)
1	3650-2500	6.39 (2H, s, aromatic-H); 3.83 (6H, s, OCH <sub>3</sub> ); 2.47-3.25 (4H, s, CH <sub>2</sub> CH <sub>2</sub> N and 2H, m, OH and NH <sub>2</sub> ), [CDCl <sub>3</sub> ]	
2	3650-2300	6.39 (2H, s, aromatic-H); 3.80 (6H, s, OCH <sub>3</sub> × 2); 3.10-3.43 (2H, br s, NH and OH); 2.67-2.80 (5H, m, CH <sub>2</sub> CH <sub>2</sub> NCH); 1.00 (3H, s, CHCH <sub>3</sub> ); 1.08 (3H, s, CHCH <sub>3</sub> ), [CDCl <sub>3</sub> ]	
3	3650-1900	6.46 (2H, s, aromatic-H); 2.67-3.23 (4H, m, CH <sub>2</sub> CH <sub>2</sub> ), [D <sub>2</sub> O]	
4	3250-1900	6.90 (2H, s, aromatic-H); 3.68 (6H, s, OCH <sub>3</sub> × 2); 3.90 (3H, s, OCH <sub>3</sub> ); 2.90-3.63 (4H, m, CH <sub>2</sub> CH <sub>2</sub> ), [D <sub>2</sub> O]	
5	3650-2300	6.97-7.22 (3H, m, aromatic-H); 4.00 (3H, s, OCH <sub>3</sub> ); 2.38-3.63 (4H, m, CH <sub>2</sub> CH <sub>2</sub> ); [D <sub>2</sub> O]	
6	3650-1800	6.80-7.00 (3H, m, aromatic-H); 2.87-3.47 (4H, m, CH <sub>2</sub> CH <sub>2</sub> ), [D <sub>2</sub> O]	
7	3650-1800	9.00 (H, br s, OH); 8.33 (3H, br s, +NH <sub>3</sub> ); 6.67-6.77 (3H, m, aromatic-H); 3.83 (3H, s, OCH <sub>3</sub> ); 2.83-3.13 (4H, br s, CH <sub>2</sub> CH <sub>2</sub> ), [dDMSO]	
8	3650-1800	8.17 (5H, br s, OH × 2 and +NH <sub>3</sub> ); 6.40-6.87 (3H, m, aromatic-H); 2.60-3.10 (4H, m, CH <sub>2</sub> CH <sub>2</sub> ), [dDMSO]	
9	3650-1900	6.92 (H, s, aromatic-H); 6.72 (H, s, aromatic-H); 3.90 (9H, s, OCH <sub>3</sub> × 3); 2.73-3.50 (4H, m, CH <sub>2</sub> CH <sub>2</sub> ), [D <sub>2</sub> O]	
10	3650-1900	6.83 (H, s, aromatic-H); 6.63 (H, s, aromatic-H); 2.70-3.47 (4H, m, CH <sub>2</sub> CH <sub>2</sub> ), [D <sub>2</sub> O]	

<sup>a</sup>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-hydroxyphenylacetamide (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 Bossi,<sup>21</sup> for the preparation of N-(4-hydroxy-3-methoxy-phenethyl)-4-hydroxyphenylacetamide, except that the crude product was taken up in chloroform. Recrystallization from EtOAc and then from EtOH gave 27 g (69%) of tan solid, m.p. 150–2°; IR (Nujol): 3500–3050 (OH), 3380 (NH) and 1650 cm<sup>-1</sup> (amide CO);  $\delta$ (CDCl<sub>3</sub>): 6.40 (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<sub>2</sub> and CH<sub>2</sub>CO), and 2.83–2.47 (2H, m, CH<sub>2</sub>). (Found: C, 61.54; H, 6.38; N, 3.53. Calc. for C<sub>20</sub>H<sub>23</sub>NO<sub>7</sub>: 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-hydroxyphenylacetamide (20.5 g; 0.05 mole) was effected in the manner described by Teitel and Bossi<sup>21</sup> 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°. A portion was converted to the free base with NaHCO<sub>3</sub> aq, and crystallized from MeOH, m.p. 192–193°, IR (Nujol): 3440 (bonded OH), 1565 cm<sup>-1</sup> (C=N); (dDMSO): 7.07 (H, s, aromatic-H), 6.48 (2H, s, aromatic-H), 4.07 (2H, br s, CH<sub>2</sub>C=N), 3.83 (3H, s, OMe), 3.72 (3H, s, OMe), 3.70 (6H, s, OMe  $\times$  2), 3.75–3.21 (2H, m, CH<sub>2</sub>N), 2.43–2.08 (2H, m, CH<sub>2</sub>). (Found: C, 64.33; H, 6.21; N, 3.75. Calc. for C<sub>20</sub>H<sub>23</sub>NO<sub>6</sub>: C, 64.57; H, 6.26; N, 3.68%).

6,8-Dimethoxy-1-(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (11). To a soln of crude 3,5-dihydro-6,8-dimethoxy-1-(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxyisoquinoline hydrochloride (12 g; 0.02 mole) in 220 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 ether. The product weighed 8.6 g (71%), m.p. 234–236°; IR (Nujol): 3650–2400 cm<sup>-1</sup> (complex absorption due to OH and NH stretch); (D<sub>2</sub>O): 8.00 (H, s, aromatic-H), 6.53 (2H, s, aromatic-H), 3.92 (6H, s, OMe  $\times$  2) 3.68 (6H, s, OMe  $\times$  2), 3.50–3.33 (3H, m, CH and CH<sub>2</sub>N), 3.23–2.83 (4H, m, ar-CH<sub>2</sub>  $\times$  2). (Found: C, 58.32; H, 6.36; N, 3.40. Calc. for C<sub>20</sub>H<sub>26</sub>ClNO<sub>6</sub>: C, 58.07; H, 6.55; N, 3.29%).

3,4-Dihydro-6,7,8-trihydroxy-1-(3,4,5-trihydroxybenzyl)-isoquinoline (10). 3,4-Dihydro-6,8-dimethoxy-1-(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxyisoquinoline (10 g; 0.027 mole) in 150 ml 48% HBr was heated under reflux for 3 hr. The product was collected on a filter after chilling. The yield, after recrystallization from water, was 6.7 g (78%), m.p. 320°. The sample for analysis was also recrystallized from glacial AcOH; IR (KBr): 3675–2100 (bonded OH), 1590 and 1510 cm<sup>-1</sup> (aromatic);  $\delta$ (TFA): 6.80 (2H, s, aromatic-H), 6.73 (H, s, aromatic-H), 4.37 (2H, br s, CH<sub>2</sub>–C=N), 4.07–3.63 (2H, m, CH<sub>2</sub>N), 3.30–

2.77 (2H, m, CH<sub>2</sub>). (Found: C, 60.56; H, 4.77; N, 4.41. Calc. for C<sub>16</sub>H<sub>13</sub>NO<sub>6</sub>: C, 60.25; H, 4.73; N, 4.41%).

N-(4-Benzoyloxy-3,5-dimethoxyphenethyl)-4-benzoyloxy-3,5-dimethoxyphenylacetamide (12). A soln of 8 (17 g; 0.045 mole) and of benzyl bromide (25.7 g; 0.15 mole) in 300 ml MeOH containing anhyd K<sub>2</sub>CO<sub>3</sub> (27.6 g; 0.20 mole) was stirred and heated under reflux for 3 hr. The solvent was removed and the residue was treated with water. The insoluble material was collected on a filter, and recrystallized once from EtOAc and once from MeOH to give 16.0 g (62%) of the desired product, m.p. 160–162.5°.  $\delta$ (CDCl<sub>3</sub>): 7.73–7.30 (10H, m, phenyl-H  $\times$  2) 6.53 (2H, s, aromatic-H) 6.47 (2H, s, aromatic-H), 5.33 (H, br s, NH); 5.07 (4H, s, OCH<sub>2</sub>  $\times$  2) 3.83 (12H, s, OMe  $\times$  4), 3.67–3.40 (4H, m, CH<sub>2</sub>  $\times$  2) 2.93–2.57 (2H, m, CH<sub>2</sub>N).

6,8-Dimethoxy-1-(3,5-dimethoxy-4-hydroxybenzyl)-7-hydroxyisoquinoline hydrochloride (14). The cyclization of 12 (16.0 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 oil, (15 g; 0.027 mole), in 200 ml tetralin containing 5% Pd–C (3 g) was heated at 180–185° for 6 hr under N<sub>2</sub>. The catalyst was collected on a filter and washed with benzene. The filtrate was chilled. The solid which precipitated was collected on a filter, washed with acetone, and crystallized from EtOH to give the base, m.p. 145–148°, which was converted to the hydrochloride, m.p. 200–202°. The yield was 1.5 g (10%); IR (KBr): 3650–2230 (Strong broad complex absorption due to superimposing OH and NH stretching vibrations);  $\delta$ (dDMSO): 7.77 (H, s, aromatic-H), 6.77 (2H, s, aromatic-H) 5.00 (2H, br s, CH<sub>2</sub>), 4.17 (3H, s, OMe), 3.97 (3H, s, OMe), 3.75 (6H, s, OMe  $\times$  2). (Found: C, 58.72; H, 5.55; N, 3.51. Calc. for C<sub>20</sub>H<sub>22</sub>ClNO<sub>6</sub>: C, 58.90; H, 5.44; N, 3.43%).

Reaction of 3-hydroxy-4-methoxybenzylamine with cyanide ion in dimethylformamide. The amine,<sup>22</sup> (10 g; 0.065 mole), and KCN (6.5 g; 0.1 mole) in 100 ml dimethylformamide was allowed to react in the manner described. The product proved to be N-(3-hydroxy-4-methoxybenzyl)-formamide, and the yield was 5.0 g (42%), m.p. 149–152°; IR (Nujol): 3500–3100 (bonded OH) superimposed with a sharp band at 3320 (amide NH), 1660 cm<sup>-1</sup> (amide CO);  $\delta$ (dDMSO): 8.93 (H, s, OH), 8.52–8.17 (H, br s, NH), 8.18 (H, s, O=CH), 7.00–6.53 (3H, m, aromatic-H), 4.17 (2H, d, J=3, NCH<sub>2</sub>) 3.74 (3H, s, OMe). (Found: C, 59.51; H, 6.26; N, 7.83. Calc. for C<sub>9</sub>H<sub>11</sub>NO<sub>3</sub>: C, 59.66; H, 6.12; N, 7.73%).

**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 Stanaszek. Mr. James Holland assisted with the pressure reactions.

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