The Synthesis of Some Analogs of the Hallucinogen 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM)

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The synthesis of a series of 4-substituted 1-(2,5-dimethoxyphenyl)-2-aminopropanes, in which the 4-substituent is Br, Cl, I, NO_2, NH_2, and NHAc, is described. These compounds are analogs of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), a known hallucinogen. A synthesis of *N*-(2,5-dimethoxy-4-methylphenethyl)hydroxylamine, the *N*-hydroxy homolog of DOM, is also reported. Brief reference is made to the preliminary pharmacology of these compounds.

La synthèse d'une série de (diméthoxy-2,5 phényl)-1 amino-2 propanes substituées en 4 par Br, Cl, I, NO_2, et NHAc, est décrite. Ces composés sont des analogues de la (diméthoxy-2,5 méthyl-4 phényl)-1 amino-2 propane (DOM), hallucinogène connu. Une synthèse de la *N*-(diméthoxy-2,5 méthyl-4 phénétyl) hydroxylamine, homologue *N*-hydroxyle de la DOM, a été aussi rapportée. Une référence brève a été faite sur la pharmacologie préliminaire de ces composés. [Traduit par le journal]

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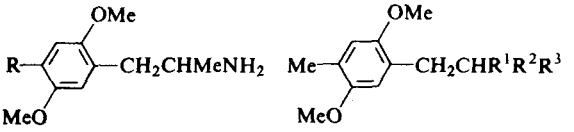
Structure-activity relationship studies of potential psychotomimetic phenethylamines have shown (1–3) that the most potent psychoactive drugs of this chemical class are ring-methoxylated phenylisopropylamines. The compounds possessing greatest psycho-activity are 1-(2,5-dimethoxy-4-substituted-phenyl)-2-aminopropanes (**1**). Five such compounds (**1***a–e*) have been prepared and pharmacologically evaluated (3–7). Of these, the 4-methyl analog (DOM) (**1***c*) has gained wide publicity as the potent major constituent of the 'street hallucinogen', STP. The related compound, 1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (**1***e*) has only recently been evaluated and has been found to induce in humans a mescaline-like action more profound than that of an equal amount of DOM (6). Five other bromo-isomers were also evaluated in this study but all were less active than **1***e*. Ho *et al.* (8) described some compounds which retained the 2,4,5-trisubstituted-phenyl moiety of DOM (*i.e.* **2**; R^1, R^2, and R^3 = H or CH_3) and found that psychoactivity (disruption of rat behavior) was also retained.

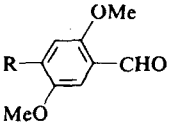
The studies just described suggest that a 2,5-dimethoxy-4-substituted-phenyl substituent might be important for psychotomimetic activity. For this reason, the preparation of additional compounds of general structure **1** was undertaken.

The synthetic approach most commonly employed to prepare 1-phenyl-2-aminopropanes involves the synthesis of the corresponding phenylnitropropenes which are then reduced by means of lithium aluminum hydride in ether or tetrahydrofuran (*e.g.* 5, 8) (Scheme 1). For the preparation of compounds **1***e–g* by this method, the aldehydes **3***a–c* were required but none of the various synthetic methods attempted proved satisfactory. Formylation of 1-bromo and 1-chloro-2,5-dimethoxybenzene using phosphorus oxychloride and *N*-methylformanilide (5) did produce the aldehydes **3***a* and *b* but yields were very low and purification proved impossible. The synthetic approach summarized in Scheme 1, therefore, could not be used.



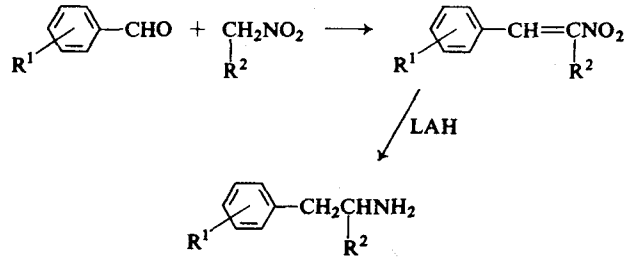
1 **2**

R		R	
a	OMe	*f*	Cl
b	OEt	*g*	I
c	Me	*h*	NO_2
d	Et	*i*	NH_2
e	Br	*j*	NHAc

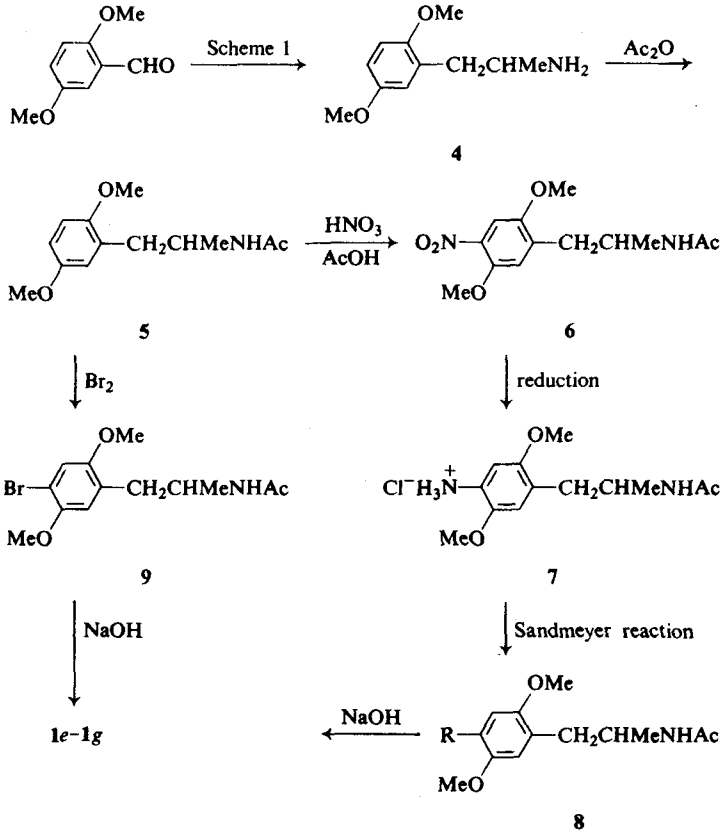


3

R	
a	Br
b	Cl
c	I

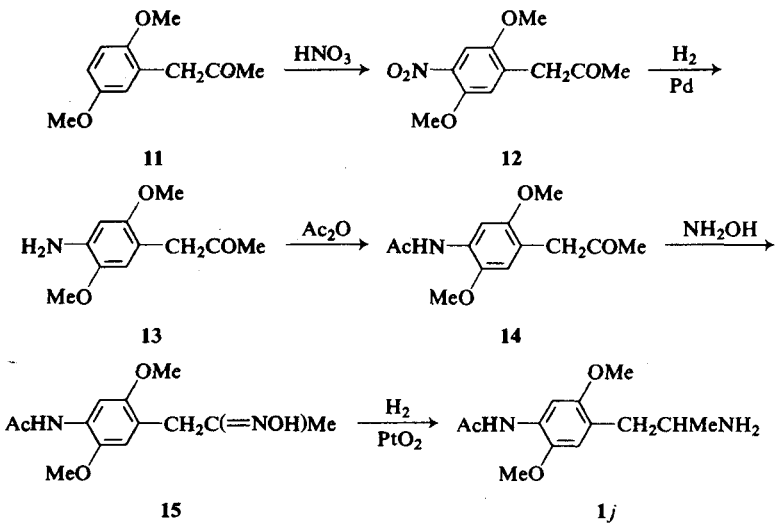


SCHEME 1



SCHEME 2

The halogenated compounds (**1***e–g*) were prepared successfully from 1-(2,5-dimethoxyphenyl)-2-aminopropane (**4**) which was readily synthesized from 2,5-dimethoxybenzaldehyde using Scheme 1. The reaction sequences employed are summarized in Scheme 2. Acetylation of **4** followed by nitration of the acetate (**5**) gave *N*-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (**6**) in excellent yield. Verification that nitration had occurred at the 4-position was obtained from n.m.r. spectral data. The two aromatic protons came to resonance at δ 6.97 and 7.41 and appeared as singlets, indicative of a para arrangement.



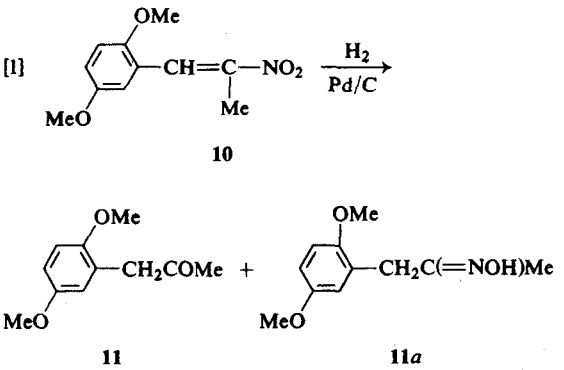
SCHEME 3

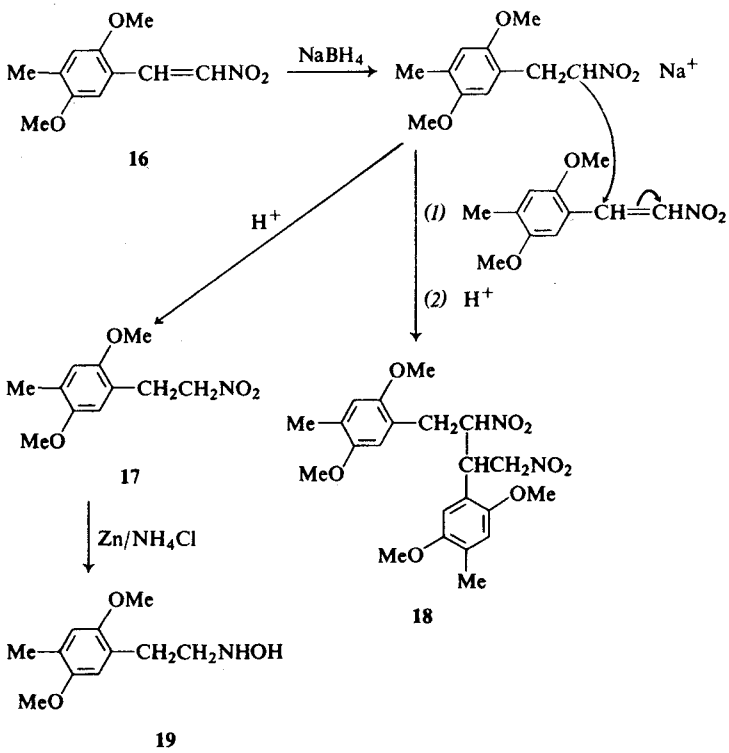
The nitro-compound (**6**) when subjected to catalytic hydrogenation readily incorporated hydrogen and *N*-acetyl-1-(4-amino-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (**7**) was isolated in good yield. *N*-Acetyl-1-(4-chloro-2,5-dimethoxyphenyl)-2-aminopropane (**8***a*) and the related 4-iodo-compound (**8***b*) were successfully prepared by subjecting the amine (**7**) to the Sandmeyer reaction, whereas the 4-bromo-compound (**9**) was obtained by the action of bromine water on *N*-acetyl-(2,5-dimethoxyphenyl)-2-aminopropane (**5**). The aromatic protons again appeared as singlets in the n.m.r. spectrum of **5**, which confirmed that the bromine atom occupied the 4-position in the ring.

A suitable means of hydrolyzing the amide group of compounds **9**, **8***a*, **8***b*, **6** and **7**, thereby completing the syntheses of **1***e–i* respectively, was sought. In most instances, these aliphatic amides proved resistant to hydrolysis by means of hydrochloric acid, sulfuric acid, or aqueous sodium hydroxide. Various reaction temperatures and times were tried and reagent concentrations were altered, but the amines were usually isolated in low yields, if at all. Eventually, a procedure employing ethylene glycol and sodium hydroxide (9) was used and reasonable yields of the 2-aminopropanes **1***e–h* were recovered.

The hydrolysis of *N*-acetyl-1-(4-amino-2,5-dimethoxyphenyl)-2-aminopropane (**7**) was also successful but the product (**1***i*) could not be purified by crystallization. An alternative procedure, in which 1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (**1***h*) was catalytically reduced, produced the pure amine (**1***i*).

After a preliminary pharmacological screening of compounds **1***e–i*, (see below), it became necessary to prepare and evaluate 1-(4-acetamido-2,5-dimethoxyphenyl)-2-aminopropane (**1***j*). The synthetic route summarized in Scheme 2 cannot be used for this compound in view of the severe hydrolytic conditions necessary to cleave the aliphatic amide group. The most obvious alternative synthetic route involved the preparation of 4-acetamido-2,5-dimethoxyphenylacetone oxime (**15**) which would be expected (10) to reduce catalytically to the desired compound. The series of reactions leading to the synthesis of **1***j* is shown in Scheme 3. The starting material, 2,5-dimethoxyphenylacetone (**11**), together with the related oxime (**11***a*) were the products recovered from a catalytic reduction of 1-(2,5-dimethoxyphenyl)-2-nitropropene-1 (**10**) (see eq. 1).





SCHEME 4

Nitration of 2,5-dimethoxyphenylacetone with nitric acid in glacial acetic acid gave the 4-nitro-derivative (**12**). The position at which nitration occurred was again confirmed by n.m.r. spectral data. Catalytic reduction of **12** followed by acetylation gave the intermediates **13** and **14** respectively in good yields. The preparation of the oxime (**15**) was somewhat difficult. Catalytic hydrogenation of this material yielded the desired amine (**1***j*). Each of the compounds illustrated in Scheme 3 was characterized by its elemental analysis and by i.r. spectral data.

One additional compound related to DOM was required in the present study, *i.e.* the *N*-hydroxy-derivative, *N*-(2,5-dimethoxy-4-methylphenethyl)-hydroxylamine (**19**). The method employed in its synthesis is outlined in Scheme 4. 1-(2,5-Dimethoxy-4-methylphenyl)-2-nitroethene (**16**), the starting material, was obtained from the interaction of 2,5-dimethoxy-4-methylbenzaldehyde and nitromethane (see Scheme 1). Reduction of this styrene with sodium borohydride gave two compounds which were easily separated because of differences in their solubilities in ethanol. The ethanol-soluble product, $C_{11}H_{15}NO_4$, gave i.r. and n.m.r. spectra which established its structure as 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethane (**17**).

Shechter *et al.* (11) found that the sodium borohydride reduction of nitroalkenes was accompanied by a concurrent reaction of the Michael-type in which the primary reduction product, the nitroalkane salt, added to the initial nitroalkene to yield a 1,3-dinitroalkane. The ethanol-insoluble product from the reduction of the nitrostyrene (**16**), therefore, was suspected to be 2,4-di-(2,5-dimethoxy-4-methylphenyl)-1,3-dinitrobutane (**18**). The elemental analysis of the compound and its i.r. spectrum were consistent with this deduction. The molecular ion in its mass spectrum was located at *m/e* 448 which corresponds to the molecular weight of the dinitroalkane (**18**).

An ethanolic solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethane (**17**) was heated with zinc and ammonium chloride and yielded the required *N*-(2,5-dimethoxy-4-methylphenethyl)-hydroxylamine (**19**).

Preliminary Pharmacology

The 2-aminopropanes prepared in this study were subjected to a simple preliminary pharmacological screening to provide some guidelines for the synthesis of other compounds and to select compounds for more detailed pharmacological testing. The effects of an oral dose of each compound on male rats (150–500 g) were compared with those caused by an oral dose of DOM (10 mg/kg) which reliably caused hypersalivation, papillary dilation, retraction of scrotum, loss of orientation reflexes, analgesia, hypomotility, and walking with a slinking gait. This crude test revealed that compounds **1***e*, *f*, and *h* (10 mg/kg) were equipotent with DOM but that compound **1***i* was devoid of activity. Compound **1***g* was not evaluated. The inactivity of **1***i* suggested it, or its active metabolite, was not reaching the brain so the acetamide (**1***j*) was prepared and evaluated. It, too, was devoid of activity. The nature of the substituent at C-4 in the phenyl ring undoubtedly has a profound effect on pharmacological activity.

A 60 mg/kg intraperitoneal dose of compound **19** in male rats caused hypersalivation, pupil dilation, loss of orientation reflex, and a reduction in motility, and caused the rat to crouch and walk backwards following a circular path when objects were placed in front of it.

Experimental

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. I.r. spectra were recorded on a Beckman IR-10 spectrophotometer as Nujol mulls and n.m.r. spectra were taken on a Varian A-60D spectrometer. Tetramethylsilane was used as the internal standard. Mass spectra were recorded by Dr. A. M. Hogg and his associates at the Department of Chemistry, University of Alberta, Edmonton, with an A.E.I. MS-9 or MS-12 mass spectrometer at an ionizing potential of 70 eV using the direct probe technique. Elemental analyses were determined at the Department of Chemistry, and at the Faculty of Pharmacy and Pharmaceutical Sciences (by Mr. W. Dylke), University of Alberta, Edmonton.

1-(2,5-Dimethoxyphenyl)-2-nitropropene-1

A solution of 2,5-dimethoxybenzaldehyde (10.0 g), ammonium acetate (4.0 g), and nitroethane (6.8 g) in glacial acetic acid (50 ml) was heated on a boiling water-bath for 3 h, then the solvent was evaporated. The residue which remained was suspended in water and extracted with chloroform. Evaporation of the chloroform left the title compound (11.2 g). Crystallization from ethanol gave m.p. 73–75°; no lit. (12) m.p. reported; i.r. ν_{max} 1300, 1502 (NO_2), 1645 (C=C) cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}NO_4$: C, 59.18; H, 5.87; N, 6.28. Found: C, 58.99; H, 5.88; N, 5.95.

1-(2,5-Dimethoxyphenyl)-2-aminopropane Hydrochloride (4)

A solution of 1-(2,5-dimethoxyphenyl)-2-nitropropene-1 (17.0 g) in dry ether (500 ml) was added slowly to a stirred suspension of lithium aluminum hydride (12.0 g) in the same solvent (150 ml). When the addition was complete, the mixture was refluxed for 20 h, cooled, and the excess lithium aluminum hydride was decomposed by the careful addition of water. The resulting suspension was filtered and the solid which was removed was washed with ether. The combined ether solutions were dried ($MgSO_4$), then saturated with dry hydrogen chloride. This precipitated the title compound (16.3 g), m.p. 114–116° (from ethanol); lit. (13) m.p. 111.5–112.5°; i.r. ν_{max} 1600; 2000–2550 (weak bands) ($\overset{+}{N}$—H) cm^{-1}.

N-Acetyl-1-(2,5-dimethoxyphenyl)-2-aminopropane (5)

Acetic anhydride (40 ml) was added to a solution of 1-(2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (5.0 g) and sodium acetate (25.0 g) in water (300 ml) and the mixture was shaken vigorously until the exothermic reaction ceased. The cooled solution was filtered and gave the title compound (4.2 g), m.p. 104–105.5° when crystallized from ethanol. The i.r. ν_{max} 1635 (C=O); 3100 (NH) cm^{-1}.

Anal. Calcd. for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.75; H, 8.13; N, 5.90.

N-Acetyl-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (6)

A solution of 70% nitric acid (50 ml) in water (400 ml) was added to a solution of *N*-acetyl-1-(2,5-dimethoxyphenyl)-2-aminopropane (40.0 g) and sodium nitrite (0.5 g) in glacial acetic acid (400 ml). The solution was stirred for 4 h, cooled, then diluted with water (400 ml). The title compound (42.1 g) precipitated and, when crystallized from ethanol, had m.p. 166–168°. The i.r. ν_{max} 1350, 1515 (NO_2); 1640 (C=O); 3310 (NH) cm^{-1}. The n.m.r. ($CDCl_3$) δ 1.16 (d, 3H, J = 7, α-CH_3); 1.88 (s, 3H, $COCH_3$); 2.85 (d, 2H, J = 7, CH_2); 3.85 (s, 3H, OCH_3); 3.90 (s, 3H, OCH_3); 4.0–4.5 (m, 1H, CH); 5.66–5.91 (m, 1H, NH); 6.97 (s, 1H) and 7.41 (s, 1H) (aromatic protons).

Anal. Calcd. for $C_{13}H_{18}N_2O_5$: C, 55.31; H, 6.43; N, 9.92. Found: C, 55.26; H, 6.63; N, 9.92.

N-Acetyl-1-(4-amino-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (7)

A solution of *N*-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (39.0 g) in ethanol was hydrogenated over 10% palladium–charcoal (1.0 g) until the theoretical amount of hydrogen was absorbed (3 days). The catalyst was removed and the filtrate evaporated. The residue was suspended in 5% sodium hydroxide solution (100 ml) and extracted with chloroform (3 × 100 ml). The combined chloroform solution was evaporated and the solid which remained was dissolved in dry ether. When dry hydrogen chloride was passed through this solution, the title compound (31.5 g) precipitated. It had m.p. 237–239° when crystallized from ethanol–ether. The i.r. ν_{max} 1635 (C=O); 2450–2600 (weak bands) ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{13}H_{21}ClN_2O_3$: C, 54.07; H, 7.33; N, 9.70. Found: C, 54.18; H, 7.40; N, 9.78.

N-Acetyl-1-(4-chloro-2,5-di aminopropane (8a)

A solution of *N*-ace phenyl)-2-aminopropane h chloric acid (15 ml) and w To this stirred solution, s (10 ml) was slowly added w of diazonium salt was ad solution of cuprous chlori (9 ml). The reaction mixt room temperature, then h title compound (2.8 g) pre 152° when crystallized fro (C=O); 3310 (NH) cm^{-1}; J = 7, α-CH_3); 1.85 (s, 3H CH_2), 3.79 (s, 3) and 3. groups); 4.20 (m, 1H, C 6.76 (s, 1H) and 6.90 (s, 1H

Anal. Calcd. for $C_{13}H_{1}$ 5.16. Found: C, 57.35; H,

N-Acetyl-1-(2,5-dimethox aminopropane (8b)

The diazonium salt o described immediately a solution was added grad iodide (8.0 g) in water (10 to warm to room tempera of nitrogen ceased. The which separated was diss the title material (1.97 g) s when crystallized from eth 3310 (NH) cm^{-1}.

Anal. Calcd. for $C_{13}H$ 3.86. Found: C, 43.00; H

N-Acetyl-1-(4-bromo-2,5- aminopropane (9)

A slight excess of bron tion of *N*-acetyl-1-(2,5 pane (3.0 g) in dioxane stirred for 6 h. The solve compound (3.0 g) which and had a m.p. 153–155°. (NH) cm^{-1}; n.m.r. (CD 1.90 (s, 3, $COCH_3$); 4.41 and 3.85 (s, 3) (OCH_3 g 5.91 (broad s, 1H, NH) (aromatic protons.) Ma $^{81}BrNO_3$); 315 (5) (C_1 abundance).

Anal. Calcd. for $C_{13}H$ 4.43. Found: C, 49.38; H

1-(4-Bromo-2,5-dimetho Hydrochloride (1e)

(*a*) A suspension of oxyphenyl)-2-aminoprop (60 ml) and water (60 ml) for 18 h during which tim dissolved. Unreacted sta the filtrate evaporated Crystallization from et pound as a colorless so m.p. 198–199°.

N-Acetyl-1-(4-chloro-2,5-dimethoxyphenyl)-2-aminopropane (8a)

A solution of *N*-acetyl-1-(4-amino-2,5-dimethoxyphenyl)-2-aminopropane hydrochloride (5.0 g) in hydrochloric acid (15 ml) and water (30 ml) was cooled to 0°. To this stirred solution, sodium nitrite (1.4 g) in water (10 ml) was slowly added with cooling. This cold solution of diazonium salt was added slowly with shaking to a solution of cuprous chloride (2.5 g) in hydrochloric acid (9 ml). The reaction mixture was allowed to come to room temperature, then heated to 70° and cooled. The title compound (2.8 g) precipitated. It gave a m.p. 150–152° when crystallized from ethanol. The i.r. ν_{max} 1630 (C=O); 3310 (NH) cm^{-1}; n.m.r. ($CDCl_3$) δ 1.11 (d, 3H, J = 7, α-CH_3); 1.85 (s, 3H, $COCH_3$); 4.60 (d, 2H, J = 7, CH_2), 3.79 (s, 3) and 3.81 (s, 3) (overlapping OCH_3 groups); 4.20 (m, 1H, CH); 5.96 (broad s, 1H, NH); 6.76 (s, 1H) and 6.90 (s, 1H) (aromatic protons).

Anal. Calcd. for $C_{13}H_{18}ClNO_3$: C, 57.46; H, 6.68; N, 5.16. Found: C, 57.35; H, 6.48; N, 5.33.

N-Acetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (8b)

The diazonium salt of **7** (5.0 g) was prepared as described immediately above and to the cooled (0°) solution was added gradually a solution of potassium iodide (8.0 g) in water (10 ml). The reaction was allowed to warm to room temperature and left until the evolution of nitrogen ceased. The dark brown viscous semi-solid which separated was dissolved in ethanol. On cooling, the title material (1.97 g) separated. It had a m.p. 167–168° when crystallized from ethanol. The i.r. ν_{max} 1645 (C=O); 3310 (NH) cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}INO_3$: C, 42.99; H, 4.99; N, 3.86. Found: C, 43.00; H, 5.01; N, 3.77.

N-Acetyl-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (9)

A slight excess of bromine water was added to a solution of *N*-acetyl-1-(2,5-dimethoxyphenyl)-2-aminopropane (3.0 g) in dioxane (30 ml), and the solution was stirred for 6 h. The solvent was removed, leaving the title compound (3.0 g) which was crystallized from ethanol and had a m.p. 153–155°. The i.r. ν_{max} 1630 (C=O); 3310 (NH) cm^{-1}; n.m.r. ($CDCl_3$) δ 1.16 (d, 3, J = 7, α-CH_3); 1.90 (s, 3, $COCH_3$); 4.41 (d, 2H, J = 7, CH_2); 3.81 (s, 3) and 3.85 (s, 3) (OCH_3 groups); 3.91–4.50 (m, 1H, CH); 5.91 (broad s, 1H, NH); 6.80 (s, 1H) and 7.07 (s, 1H) (aromatic protons.) Mass spectrum: 317 (5) ($C_{13}H_{18}{}^{81}BrNO_3$); 315 (5) ($C_{13}H_{18}{}^{79}BrNO_3$) *m/e* (% relative abundance).

Anal. Calcd. for $C_{13}H_{18}BrNO_3$: C, 49.38; H, 5.74; N, 4.43. Found: C, 49.38; H, 5.85; N, 4.29.

1-(4-Bromo-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (1e)

(*a*) A suspension of *N*-acetyl-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (2.5 g) in hydrochloric acid (60 ml) and water (60 ml) was heated at reflux temperature for 18 h during which time most of the *N*-acetyl compound dissolved. Unreacted starting material was removed and the filtrate evaporated to give a yellow solid (1.7 g). Crystallization from ethanol–ether gave the title compound as a colorless solid, m.p. 195–196°. Reported (7) m.p. 198–199°.

(*b*) *N*-Acetyl-1-(4-bromo-2,5-dimethoxyphenyl)-2-aminopropane (1.5 g) was added to a solution of sodium hydroxide (5.0 g) in water (25 ml) and ethylene glycol (50 ml) and the mixture was heated under reflux for 15 h then cooled. The solution was extracted with chloroform and the combined chloroform extracts evaporated. The resulting solid was dissolved in 5% hydrochloric acid (15 ml) and the solution filtered. The title compound (0.85 g) was the product obtained, m.p. 197–198° after crystallization from ethanol–ether. The i.r. ν_{max} 1610, 1980, 2010–2740 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{11}H_{17}BrClNO_2$: C, 42.53; H, 5.52; N, 4.51. Found: C, 42.86; H, 5.72; N, 4.29.

1-(4-Chloro-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (1f)

The title compound (0.46 g), m.p. *193–194.5°* (from ethanol–ether) was obtained when *N*-acetyl-1-(4-chloro-2,5-dimethoxyphenyl)-2-aminopropane (1.5 g) was treated as described for the synthesis of **1e**, method *b*. The i.r. ν_{max} 1610, 2010, 2500–2640 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{11}H_{17}Cl_2NO_2$: C, 49.63; H, 6.44; N, 5.44. Found: C, 49.79; H, 6.70; N, 5.44.

1-(2,5-Dimethoxy-4-iodophenyl)-2-aminopropane Hydrochloride (1g)

The title compound (0.75 g), m.p. 198–200° (from ethanol–ether) was prepared from *N*-acetyl-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (1.5 g) using method *b* procedure for the synthesis of compound **1e**. The i.r. ν_{max} 1605, 2000, 2500–2710 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{11}H_{17}ClINO_2$: C, 36.94; H, 4.79; N, 3.93. Found: C, 36.68; H, 4.75; N, 3.98.

1-(2,5-Dimethoxy-4-nitrophenyl)-2-aminopropane Hydrochloride (1h)

Hydrolysis of *N*-acetyl-1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane (2.0 g) using procedure *b* for the synthesis of compound **1e** gave the title compound (0.76 g), m.p. 203–204° when crystallized from ethanol–ether. The i.r. ν_{max} 1340, 1520 (NO_2); 1610, 2000, 2500–2690 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{11}H_{17}ClN_2O_4$: C, 47.74; H, 6.19; N, 10.13. Found: C, 47.98; H, 6.33; N, 10.01.

1-(4-Amino-2,5-dimethoxyphenyl)-2-aminopropane Dihydrochloride (1i)

A solution of 1-(2,5-dimethoxy-4-nitrophenyl)-2-aminopropane hydrochloride (1 g) in ethanol (25 ml) and hydrochloric acid (2 ml) was hydrogenated over 10% palladium–charcoal (0.1 g) until the theoretical amount of hydrogen was absorbed. The catalyst was removed and the filtrate evaporated to give a solid (0.92 g) which, when crystallized from ethanol–ether gave the title compound, m.p. 248–250°. The i.r. ν_{max} 1610, 2010, 2500–2610 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{11}H_{20}Cl_2N_2O_2$: C, 46.55; H, 7.12; N, 9.89. Found: C, 46.98; H, 7.36; N, 9.63.

Catalytic Reduction of 1-(2,5-Dimethoxyphenyl)-2-nitropropene-1

A solution of 1-(2,5-dimethoxyphenyl)-2-nitropropene-1 (7.0 g) in ethanol (150 ml) was hydrogenated at room temperature and pressure in the presence of palladium–

charcoal (0.7 g). After approximately 3 h, the uptake of hydrogen ceased. The mixture was filtered and the solution evaporated, leaving a light yellow oil. A solution of this oil in chloroform (100 ml) was extracted with 5% hydrochloric acid (3 × 50 ml) and the aqueous layer discarded. The oil which remained following evaporation of the chloroform was distilled under reduced pressure and yielded two fractions. The first (2.3 g), b.p. 100° (0.07 mm Hg) was 2,5-dimethoxyphenylacetone (reported (12) b.p. 95° (1.25 mm)). The i.r. ν_{max} 1710 (C=O) cm^{-1}; n.m.r. ($CDCl_3$) δ 1.95 (s, 3H, CH_3); 3.45 (s, 2H, CH_2); 4.25 (s, 6, $(OCH_3)_2$); 6.00–6.62 (m, 3, aromatic protons).

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 67.87; H, 7.25.

The second fraction (2.4 g), b.p. 150–170° (0.13–0.15 mm), was dissolved in ether and the solution saturated with dry hydrogen chloride. The resulting precipitate (1.2 g) was crystallized from acetone–ether to yield 2,5-dimethoxyphenylacetone oxime hydrochloride, m.p. 94–97°. The i.r. ν_{max} 2560 ($\overset{+}{N}$—H) cm^{-1}; mass spectrum: 209 (55), $C_{11}H_{15}NO_3$; 178 (100), $C_8H_{10}NO_2$ *m/e* (% relative abundance).

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: C, 53.55; H, 6.96; N, 5.68. Found: C, 53.87; H, 6.75; N, 5.98.

*2,5-Dimethoxy-4-nitrophenylacetone (**12**)*

To a solution of 2,5-dimethoxyphenylacetone (4.0 g) and sodium nitrite (0.03 g) in glacial acetic acid (25 ml), stirred and cooled to 5°, was slowly added a solution of 80% nitric acid (6 ml) in water (15 ml). Stirring for 2 h, then dilution with water (100 ml) caused the precipitation of the title compound (3.71 g) which, when crystallized from ethanol, had m.p. 77–79°. The i.r. ν_{max} 1350, 1515 (NO_2); 1730 (C=O) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.23 (s, 3H, CH_3); 3.80 (s, 2H, CH_2); 3.85 (s, 3H) and 3.92 (s, 3H) (OCH_3 groups); 6.98 (s, 1H) and 7.45 (s, 1H) (aromatic protons).

Anal. Calcd. for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.00; H, 5.42; N, 5.93.

*4-Amino-2,5-dimethoxyphenylacetone Hydrochloride (**13**)*

A solution of 2,5-dimethoxy-4-nitrophenylacetone (3.5 g) in ethanol (100 ml) and hydrochloric acid (5 ml) was hydrogenated at room temperature and normal pressure under 10% palladium–charcoal (1.0 g) until the theoretical amount of hydrogen was absorbed. The catalyst was removed and the filtrate evaporated *in vacuo* to give a colorless solid (3.1 g). Crystallization from ethanol–ether afforded the title compound, m.p. 195–198°. The i.r. ν_{max} 1711 (C=O); 1980, 2550 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.55; N, 5.70. Found: C, 53.85; H, 6.40; N, 6.03.

*4-Acetamido-2,5-dimethoxyphenylacetone (**14**)*

This compound (2.4 g) was prepared from the amine (**13**, 3.0 g) by the method described for the preparation of compound **5**. The title compound, when crystallized from ethanol, had m.p. 138–140°. The i.r. ν_{max} 1670 (amide C=O); 1710 (ketone C=O); 3390 (NH) cm^{-1}.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.58. Found: C, 61.81; H, 6.67; N, 5.92.

*4-Acetamido-2,5-dimethoxyphenylacetone Oxime (**15**)*

A solution of 4-acetamido-2,5-dimethoxyphenylacetone (2.0 g) and hydroxylamine hydrochloride (2.0 g) in ethanol (30 ml) and pyridine (5 ml) was heated at 75° for 7 h. The solvent was removed *in vacuo* and water (30 ml) was added to the residue. Extraction with chloroform (3 × 30 ml) followed by evaporation of the chloroform gave a pale yellow oil which solidified (1.4 g) on triturating with ether. Crystallization from ethanol yielded the title compound, m.p. 141–144°. The i.r. ν_{max} 1660 (C=O); 3250 broad peak (OH) cm^{-1}.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$: C, 58.63; H, 6.81; N, 10.52. Found: C, 58.63; H, 7.01; N, 10.29.

*1-(4-Acetamido-2,5-dimethoxyphenyl)-2-aminopropane Hydrochloride (**1j**)*

A solution of 4-acetamido-2,5-dimethoxyphenylacetone oxime (1.0 g) in ethanol (50 ml) and hydrochloric acid (1.0 ml) was hydrogenated at room temperature and 50 p.s.i. pressure in the presence of platinum dioxide (0.1 g) for 14 h (arbitrary). Evaporation of the filtrate gave a solid which, when crystallized from ethanol and ether gave the title compound (0.72 g), m.p. 249–250°. The i.r. ν_{max} 1600, 2500–2700 ($\overset{+}{N}$—H); 1660 (C=O); 3250 (NH) cm^{-1}.

Anal. Calcd. for $C_{13}H_{21}ClN_2O_3$: C, 54.07; H, 7.33; N, 9.70. Found: C, 54.35; H, 7.58; N, 9.64.

Sodium Borohydride Reduction of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethene

The title compound (8) (15.0 g, m.p. 116°), dissolved in dioxane, was added to a stirred solution of sodium borohydride (5.0 g) in water (25 ml) and dioxane (25 ml) at such a rate that decolorization occurred between additions. The final pale yellow solution was stirred for 1 h, cooled, and diluted with hydrochloric acid until effervescence ceased. The residue which remained after evaporation of the solvent was suspended in water (100 ml) and extracted with chloroform (100 ml). The chloroform extract was evaporated to give a dark brown oil which solidified (10.5 g) when triturated with cold ethanol. Crystallization from ethanol gave an insoluble product (2.8 g) and an ethanol-soluble compound (5.9 g), m.p. 67–70°. The latter was 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethane (**17**). The i.r. ν_{max} 1370, 1550 (NO_2) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.21 (s, 3H, CH_3); 4.91 (t, 2H, J = 8, CH_2); 4.58 (t, 2H, J = 8, CH_2); 6.63 (s, 1H) and 6.68 (s, 1H) (aromatic protons).

Anal. Calcd. for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.32; H, 7.06; N, 6.10.

The ethanol-insoluble product was recrystallized from dioxane to yield what was assumed to be 2,4-di(2,5-dimethoxy-4-methylphenyl)-1,3-dinitrobutane (**18**), m.p. 167.5–169°. The i.r. ν_{max} 1370, 1550 (NO_2) cm^{-1}; mass spectrum: 448 (27) ($C_{22}H_{28}N_2O_8$) *m/e* (% relative abundance).

Anal. Calcd. for $C_{22}H_{28}N_2O_8$: N, 6.24. Found: N, 6.18.

*N-(2,5-Dimethoxy-4-methylphenethyl)-hydroxylamine (**19**)*

A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitroethane (1.5 g) in ethanol (50 ml) and water (10 ml) was stirred with ammonium chloride (1.5 g) and zinc powder (1.5 g) for 30 min, then heated under reflux for 5 min. The suspension was cooled and filtered and the filtrate basified with 5% sodium bicarbonate solution

(50 ml) then extracted
The combined extract
chloride and evaporate
with water (100 ml) an
with ammonium hydr
chloroform (100 ml). T
with water, saturated
orated to give a solid
from ethanol–ether yi
hydrochloride, m.p. 13
2750 ($\overset{+}{N}$—H) cm^{-1}; m
NO_3) *m/e* (% relative a
Anal. Calcd. for C_1
N, 5.66. Found: C, 53.

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(50 ml) then extracted with chloroform (3 × 100 ml). The combined extract was saturated with dry hydrogen chloride and evaporated. The solid residue was treated with water (100 ml) and filtered. The filtrate was basified with ammonium hydroxide solution and extracted with chloroform (100 ml). The chloroform extract was washed with water, saturated with hydrogen chloride, and evaporated to give a solid (0.52 g) which when crystallized from ethanol–ether yielded the title compound as the hydrochloride, m.p. 137–138°. The i.r. ν_{max} 1610, 2510–2750 ($\overset{+}{N}$—H) cm^{-1}; mass spectrum: 211 (10) ($C_{10}H_{17}NO_3$) *m/e* (% relative abundance).

Anal. Calcd. for $C_{11}H_{18}ClNO_3$: C, 53.33; H, 7.32; N, 5.66. Found: C, 53.18; H, 7.57; N, 5.57.

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