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

RONALD T. COUTTS AND JERRY L. MALICKY
Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta
Received October 31, 1972

The synthesis of a series of 4-substituted 1-(2,5-dimethoxyphenyl)-2-aminopropanes, in which the 4-substituent is Br, Cl, I, NO₂, NH₂, 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.

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 (1a–e) have been prepared and pharmacologically evaluated (3–7). Of these, the 4-methyl analog (DOM) (1c) 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 (1e) 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 1e. Ho et al. (8) described some compounds which retained the 2,4,5-trisubstituted-phenyl moiety of DOM (i.e. 2; R¹, R², and R³ = H or CH₃) 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 phenyl-nitropropanes 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 1e–g by this method, the aldehydes 3a–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 3a and b but yields were very low and purification proved impossible. The synthetic approach summarized in Scheme 1, therefore, could not be used.
in which the analogs of 1-(2,5-dimethoxyphenyl)-2-aminopropane proved impossible. Briefly, the halogenated compounds (1e-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.
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) and the related 4-iodo-compound (8b) 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, 8a, 8b, 6 and 7, thereby completing the syntheses of 1e–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 1e–h were recovered.

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

After a preliminary pharmacological screening of compounds 1e–i, (see below), it became necessary to prepare and evaluate 1-(4-acetamido-2,5-dimethoxyphenyl)-2-aminopropane (1j). 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 1j is shown in Scheme 3. The starting material, 2,5-dimethoxyphenylacetone (11), together with the related oxime (11a) were the products recovered from a catalytic reduction of 1-(2,5-dimethoxyphenyl)-2-nitropropene-1 (10) (see eq. 1).

Nitration of 2,5-c nitric acid in glacial derivative (12). The occurred was again data. Catalytic reacetylation gave tl respectively in good the oxime (15) was hydrogenation of the required amine (1j). Illustrated in Scheme elemental analysis was.

One additional was required in thhydroxy-derivative, phenethyl)-hydroxy employed in its synt 1-(2,5-Dimethoxy-4 (16), the starting r interaction of aldehyde and nitro duction of this styrene gave two compounds because of different.
Nitrated analytically reduced, it became n-ate 1-(4-acetamido-propane (I)). The n Scheme 2 cannot of the severe ry to cleave the al-obvious alternative preparation of 4-enylacetone oxime ted (10) to reduce mpound. The series synthesis of 1j is nert material, 2,5-t, together with the products recovered f 1-(2,5-dimethoxy-)

COUTTS AND MALICKY: ANALOGS OF THE HALLUCINOGEN DOM

Nitratation 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 de-sired amine (lj). 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, C11H15NO8, 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 hyper-salivation, papillary dilation, retraction of scrotum, loss of orientation reflexes, analgesia, hypotomility, and walking with a slinking gait. This crude test revealed that compounds 1e, f, and h (10 mg/kg) were equipotent with DOM but that compound i was devoid of activity. Compound 1g was not evaluated. The inactivity of 1i suggested it, or its active metabolite, was not reaching the brain so the acetamide (1j) was prepared and evaluated. It, too, was devoid of activity. The nature of the constituent 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 reflexes, 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. Dykke), University of Alberta, Edmonton.

1-(2,5-Dimethoxyphenyl)-2-nitropropane (4)

A solution of 1-(2,5-dimethoxyphenyl)-2-nitropropane (17.0 g) in dry ether (500 ml) was added slowly to a stirred suspension of lithium aluminium 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 aluminium 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 (MgSO₄), then saturated with dry hydrogen chloride. This precipitated the title compound (16.3 g), m.p. 114-116° (from ethanol); i.r. 1635 (C=O); 3100 (NH) cm⁻¹.


1-(2,5-Dimethoxy-4-nitrophenyl)-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. I.r. 3100 (C=O); 3000 (NH) cm⁻¹.


1-(2,5-Dimethoxy-4-nitrophenyl)-2-aminopropane Hydrochloride (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. 1635, 1515 (NO₂); 1640 (C=O); 3100 (NH) cm⁻¹. The n.m.r. (CDCl₃) δ 1.16 (3H, J = 7, α-CH₃); 1.88 (3H, CH₃); 2.85 (2H, J = 7, CH₂); 3.83 (3H, OCH₃); 3.90 (3H, OCH₂); 4.0-4.5 (m, 1H, CH); 5.66-5.91 (m, 1H, NH); 6.37 (6H) and 7.41 (6H) (aromatic protons).


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 suspended in 5% sodium hydroxide solution (100 ml) and extracted with chloroform (3 x 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. 1635 (C=O); 2450-2600 (weak bands) (N-H) cm⁻¹.

N-acetyl-1-(4-bromo-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°C. 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°C. The title compound (2.8 g) precipitated. It gave a m.p. 159-162°C when crystallized from ethanol. The i.r. νmax 1630 (C=O); 3310 (NH) cm⁻¹; n.m.r. (CDCl₃) δ 1.11 (d, 3H, J = 7, α-CH₃); 1.85 (s, 3H, COCH₃); 4.60 (2H, J = 7, CH₂); 3.79 (s, 3) and 3.81 (s, 3) (overlapping OCH₃ 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 C₁₃H₁₈ClNO₃: C, 49.63; H, 6.44; N, 5.44. Found: C, 49.79; H, 6.70; N, 5.44.

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

The title compound (0.46 g), m.p. 193–194°C (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 Ie, method b. The i.r. νmax 1610, 2050–2640 (N–H) cm⁻¹. Anal. Calcd. for C₁₁H₁₇ClNO₂: C, 55.79; H, 6.33; N, 3.98. Found: C, 55.68; H, 6.43; N, 3.77.

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

The title compound (0.76 g), m.p. 198–200°C (from ethanol–ether) was treated with sodium nitrite (1.4 g) 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°C after crystallization from ethanol–ether. The i.r. νmax 1610, 2010–2740 (N–H) cm⁻¹. Anal. Calcd. for C₁₁H₁₇I₂NO₂: C, 42.53; H, 5.52; N, 4.51. Found: C, 42.86; H, 5.72; N, 4.29.

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

Hydrolysis of N-acetyl-1-(2,5-dimethoxy-4-nitrophophyl)-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°C when crystallized from ethanol–ether. The i.r. νmax 1340, 1520 (NO₂); 1610, 2500–2690 (N–H) cm⁻¹. Anal. Calcd. for C₁₁H₁₇NO₃: 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-nitrophophyl)-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°C. The i.r. νmax 1610, 2010, 2500–2610 (N–H) cm⁻¹.


Catalytic Reduction of I-(2,5-Dimethoxyphenyl)-2-nitropropane

A solution of 1-(2,5-dimethoxyphenyl)-2-nitropropane (0.7 g) in ethanol (150 ml) was hydrogenated at room temperature and pressure in the presence of palladium-
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 (10 ml) was added to the residue. Extraction with chloroform (3 x 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. v_max 1660 (C=O); 3250 broad peak (OH) cm⁻¹. Anal. Calcd. for C₁₃H₁₅NO₄: 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-nitroethene (17). The i.r. v_max 1370, 1550 (NO₂) cm⁻¹; n.m.r. (CDCl₃) δ 2.21 (s, 3H, CH₃) ; 3.82 (s, 2H, CH₂); 3.85 (s, 3H) and 3.92 (s, 3H) (OCH₃ groups); 6.98 (s, 1H) and 7.45 (s, 1H) (aromatic protons).

Anal. Calcd. for C₁₃H₁₅NO₄: 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 to give a colorless solid (3.1 g). Crystallization from ethanol–ether afforded the title compound, m.p. 195-198°. The i.r. v_max 1711 (C=O); 1980, 2550 (N–H) cm⁻¹. Anal. Calcd. for C₁₃H₁₅NO₄: C, 55.77; 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 8. The title compound, when crystallized from ethanol, had m.p. 138-140°. The i.r. v_max 1670 (amide C=O); 1110 (amide C–O); 3390 (NH) cm⁻¹. Anal. Calcd. for C₁₃H₁₅NO₄: 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 (10 ml) was added to the residue. Extraction with chloroform (3 x 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. v_max 1660 (C=O); 3250 broad peak (OH) cm⁻¹. Anal. Calcd. for C₁₃H₁₅NO₄: C, 54.07; H, 7.33; N, 9.70. Found: C, 54.35; H, 7.58; N, 9.64.

The authors thank t Canada for the award, J. R. SMYTHIES, R BENINGTON, R. Psychopharmacol.

2. J. R. SMYTHIES, V...
chloride (2.0 g) in 2 ml) was heated at 75° in vacuo and water extraction with chloroform (100 ml). 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. v, C=O 1610, 2510 cm⁻¹; m/e 211 (10) (C₁₀H₁₇NO₃) (% relative abundance).


The authors thank the Medical Research Council of Canada for the award of a studentship (to J. L. M.) and an operating grant, MA-2993 (to R. T. C.). Helpful discussions with Dr. D. F. Biggs are also acknowledged.