The Synthesis of Four Possible *in vitro* Metabolites of the Hallucinogen 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM)

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The synthesis of four possible *in vitro* metabolites of the hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) is described. These compounds, 1-(2,5-dimethoxy-4-methylphenyl(-2-propanone, the corresponding oxime, 1-(2,5-dimethoxy-4-methylphenyl)-2-propanol, and 1-(2,5-dimethoxy)-4-methylphenyl-2-(hydroxylamino)propane, could be products of side chain metabolic oxidation of DOM.

On décrit la synthèse *in vitro* de quatres métabolites possibles de l'hallucinogène (diméthoxy-2,5 méthyl-4 phényl)-1 amino-2 propane sont décrites. Ces composés, la (diméthoxy-2,5 méthyl-4 phényl)-1 propanone-2, l'oxime correspondante, le (diméthoxy-2,5 méthyl-4 phényl)-1 propanol-2 et le (diméthoxy-2,5 méthyl-4 phényl)-1 hydroxylamino-2 propane, peuvent être des produits de l'oxydation métabolique de la chaîne latérale du DOM. [Traduit par le journal]

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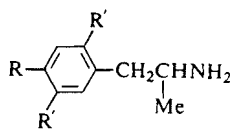
In 1955, Axelrod (1) reported that amphetamine (**1***a*) was metabolically oxidized by rat liver microsomes to phenylacetone (**2***a*). In view of this observation, it was of interest to us to determine whether the potent hallucinogen, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane(**1***b*, DOM), a ring-substituted amphetamine, was similarly metabolized to the related ketone (**2***b*). A preliminary *in vitro* metabolism of DOM by means of a rabbit microsomal preparation (10 000 *g* supernatant) indicated that, compared to amphetamine, very little metabolism took place although a g.l.c. examination of the products showed that very small quantities of some metabolites had formed. To confirm whether one of these products was the ketone (**2***b*), a synthesis of this compound was undertaken.

While this study was in progress, Ho and co-workers (2, 3) published their findings on the *in vivo* metabolism of DOM in rat and showed that the ketone **2***b* was not formed in that species. In the meantime, Hucker *et al.* (4) claimed that phenylacetone ketoxime (**3***a*) was the major *in vitro* metabolite of amphetamine using rabbit liver, and this ketoxime then hydrolyzed to yield the ketone (**2***a*). Subsequently, Beckett and Al-Sarraj (5) found that 2-hydroxylamino-1-phenylpropane (**4***a*) was, in fact, the primary *in vitro* metabolic product of amphetamine using microsomes from various species and these authors showed that the ketone **2***a*, the oxime **3***a*, and the alcohol **5***a* were chemical or metabolic breakdown products of the hydroxylamine **4***a*.



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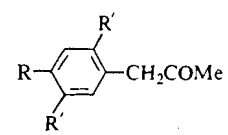

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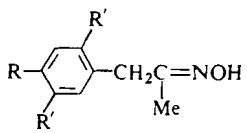

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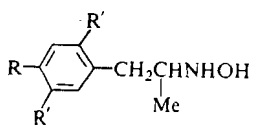

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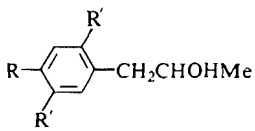

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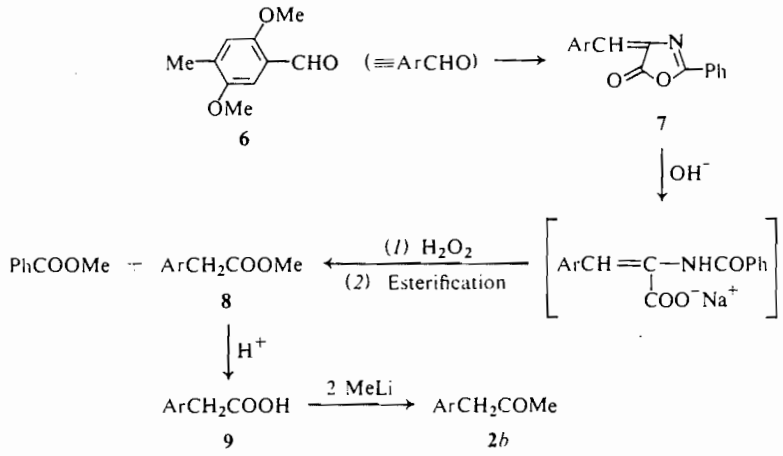
a R = R′ = H
b R = Me; R′ = OMe

These current findings prompted us to extend our studies to the synthesis of the ketone **2***b*, the oxime **3***b*, the hydroxylamine **4***b*, and the alcohol **5***b*, compounds which could be of assistance in the identification of rabbit *in vitro* metabolites and perhaps help identify the unknown minor *in vivo* metabolites of DOM, described by Ho and co-workers (2, 3).

The method selected for the preparation of 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone (**2***b*) required 2,5-dimethoxy-4-methylphenylacetic acid (**9**) as an intermediate. This acid

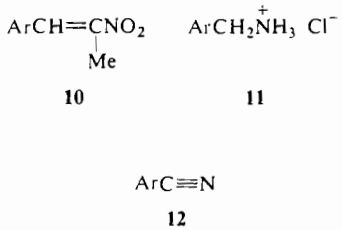


SCHEME 1

was prepared from 2,5-dimethoxy-4-methylbenzaldehyde (**6**) as outlined in Scheme 1. The azlactone, 4-(2,5-dimethoxy-4-methylbenzylidene)-2-phenyl-2-oxazolin-5-one (**7**), was obtained by reacting the aldehyde (**6**) with hippuric acid in the presence of a dehydrating agent (acetic anhydride). The azlactone was hydrolyzed in sodium hydroxide solution and oxidized with hydrogen peroxide (6) to yield a mixture of 2,5-dimethoxy-4-methylphenylacetic acid and benzoic acid. To separate this mixture, the acids were esterified and when a concentrated solution of the mixture of methyl esters was cooled, the less soluble component, methyl 2,5-dimethoxy-4-methylphenylacetate (**8**) precipitated. The acid **9** was regenerated from **8** and reacted with methyllithium to give the required 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone (**2***b*). Ho and Tansey (2) also prepared this ketone in modest yield by the action of iron and ferric chloride on 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene (**10**).

1-(2,5-Dimethoxy-4-methylphenyl)-2-propanone oxime (**3***b*) was obtained as an oil when the ketone **2***b* was reacted with hydroxylamine but was conveniently purified and characterized as its hydrochloride. When a synthesis of 1-(2,5-dimethoxy-4-methylphenyl)-2-propanol (**5***b*) was attempted by hydrogenating a solution of the ketone in the presence of palladium–charcoal, the compound failed to incorporate hydrogen. Reduction of the ketone **2***b* with sodium borohydride, however, proved successful.

For the preparation of 1-(2,5-dimethoxy-4-methylphenyl)-2-(hydroxylamino)propane (**4***b*), the feasibility of reducing 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene (**10**) was investi-



gated. This proved to be a complex reaction. When an ethanolic solution of **10** was hydrogenated catalytically, initial hydrogen incorporation was rapid, then the rate of uptake slowly decreased. When hydrogenation appeared to be complete, the reaction flask was removed from the hydrogenation apparatus and a strong odor of ammonia was discerned. The mixture was stirred at room temperature until the evolution of ammonia ceased and then hydrogenated further. More hydrogen was incorporated. The reaction mixture was separated into basic and neutral products. Fractional crystallization of the bases (as hydrochlorides) gave 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**1***b*) as the first and minor product. The second compound, $C_{12}H_{19}NO_3 . HCl$, was a reducing agent (ammoniacal silver nitrate test); a diagnostic ion, *m/e* 60, shown to be C_2H_6NO by accurate mass measurement, was present in its mass spectrum and is identified as $CH_3CH{=}\overset{+}{N}HOH$. This fragment is observed in the mass spectra of other *N*-hydroxyamphetamine derivatives (7). This basic reduction product, therefore, was concluded to be 1-(2,5-dimethoxy-4-methylphenyl)-2-(hydroxylamino)propane (**4***b*). The neutral products of the reduction of **10** were shown by comparison

with authentic samples to be 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone (**2***b*) and the corresponding oxime **3***b*.

The catalytic reduction of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene was repeated using ethanolic HCl as the solvent. This time, hydrogen uptake was rapid and the major product was the oxime (**3***b*); no hydroxylamine (**4***b*) was formed.

The 1-(2,5-dimethoxy-4-methylphenyl)-2-nitro–propene (**10**) employed in these reductions was prepared by reacting 2,5-dimethoxy-4-methyl-benzaldehyde with nitroethane in the presence of ammonium acetate and acetic acid (8). On one occasion, the crude reaction product (**10**) was hydrogenated as just described and an additional reduction product, $C_{10}H_{15}NO_2$.HCl, was isolated and identified by means of its i.r., n.m.r., and mass spectra as 2,5-dimethoxy-4-methylbenzylamine hydrochloride (**11**). It appeared likely that the crude sample of **10** was contaminated with 2,5-dimethoxy-4-methylbenzonitrile (**12**), which catalytically reduced to **11**. This assumption was confirmed when a pure sample of nitrile **12** was isolated from the crude nitropropene (**10**) by fractional crystallization. Other investigators have observed the formation of nitriles in this type of reaction (9, 10).

Nitrile by-product formation could have some significance in the preparation of illicit samples of DOM. If the intermediate (**10**) was not purified prior to reduction, the sample of DOM could contain 2,5-dimethoxy-4-methylbenzylamine as an impurity and this could alter the pharmacological properties of the product in view of the fact that 2,5-dimethoxybenzylamine and related compounds have been reported (11) to possess uterine-contracting properties.

Experimental

Melting points (capillary tube) are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian A-60D spectrometer, using tetramethylsilane as internal standard. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer as Nujol mulls. Dr. A. M. Hogg and his associates, Department of Chemistry, University of Alberta recorded the mass spectra on 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 Faculty of Pharmacy and Pharmaceutical Sciences by Mr. W. Dylke.

4-(2,5-Dimethoxy-4-methylbenzylidene)-2-phenyl-2-oxazolin-5-one (7)

A mixture of 2,5-dimethoxy-4-methylbenzaldehyde (15.0 g), hippuric acid (15.0 g), acetic anhydride (26.0 g), and anhydrous sodium acetate (7.0 g) was heated at 100° with stirring for 2 h, cooled, and diluted with ethanol (100 ml). An orange-red precipitate of the title compound formed (23.6 g), m.p. 208–210° (from benzene); i.r. ν_{max} 1645 (C=N), 1785 (C=O) cm^{-1}.

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.57; H, 5.30; N, 4.33. Found: C, 70.30; H, 5.52; N, 4.22.

Methyl 2,5-Dimethoxy-4-methylphenylacetate (8) and 2,5-Dimethoxy-4-methylphenylacetic Acid (9)

A solution of 4-(2,5-dimethoxy-4-methylbenzylidene)-2-phenyl-2-oxazolin-5-one (15.0 g) in 10% NaOH solution (100 ml) was heated under reflux for 12 h. The reaction mixture was cooled to 0° and diluted with ice-cold 40% NaOH solution (10 ml). To this solution was added with stirring, a 15% aqueous solution of H_2O_2 at such a rate as to maintain the temperature below 15°. After this addition was complete, the solution was left for 12 h at 25°, then acidified with concentrated HCl (50 ml) and extracted thoroughly with benzene (200 ml). The dried ($MgSO_4$) benzene extract was evaporated to give a solid (15.5 g) which was dissolved in methanol (100 ml) containing concentrated H_2SO_4 (2 ml). This solution was heated under reflux for 5 h, concentrated and cooled. The title ester (**8**, 9.2 g) precipitated, m.p. 66–67° (from ethanol); i.r. ν_{max} 1730 (C=O) cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 63.96; H, 7.29.

A suspension of this ester (8.0 g) in 10% NaOH solution (50 ml) was heated under reflux for 1 h, cooled and acidified with concentrated HCl. This gave a precipitate of 2,5-dimethoxy-4-methylphenylacetic acid (7.6 g), m.p. 128–129° (from ethanol); i.r. ν_{max} 1700 br (C=O), 2500–2700 (OH) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.20 (s, 3H, CH_3), 3.61 (s, 2H, CH_2), 3.73 (s, 6H, OCH_3 groups), 6.72 (s, 2H, aromatic protons), 10.80 (s, 1H, exchanges with D_2O, OH).

Anal. Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.60; H, 6.83.

1-(2,5-Dimethoxy-4-methylphenyl)-2-propanone (2b)

A solution of 2,5-dimethoxy-4-methylphenylacetic acid (9.0 g) in ether (100 ml) was added slowly to a solution of 2.1 *M* methyllithium (Alfa Inorganic, Inc.) (60 ml). The mixture was heated under reflux for 1 h then added to ice water (200 ml) saturated with ammonium chloride. The organic layer was collected and the aqueous portion was extracted with more ether (200 ml). Evaporation of the combined ether solution yielded the ketone (**2***b*, 4.7 g), m.p. 56–58° (from ethanol) (lit. (2) m.p. 49–51°); i.r. ν_{max} 1710 (C=O) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.13 (s, 3H, $COCH_3$), 2.23 (s, 3H, ring CH_3), 3.65 (s, 2H, CH_2), 3.78 (s, 6H, OCH_3 groups), 6.63 (s, 1H) and 6.72 (s, 1H, aromatic protons); mass spectrum *m/e* (% relative abundance) 208 (41) ($C_{12}H_{16}O_3$); 165 (100) ($C_{10}H_{13}O_2$).

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.75. Found: 69.53; H, 7.57.

Acidification of the aqueous solution remaining after the ether extraction caused the precipitation of starting material (**9**, 2.1 g).

1-(2,5-Dimethoxy-4-methylphenyl)-2-propanone Oxime (3b) Hydrochloride

A solution of the propanone (**2***b*, 1.0 g), hydroxylamine hydrochloride (1.0 g), and pyridine (5 ml) in ethanol (10 ml) was heated under reflux for 1 h, then evaporated. The

residue was suspended in 5% HCl solution (25 ml) and extracted with chloroform (2 × 25 ml). Evaporation of the chloroform gave a pale yellow oil (1.1 g), i.r. ν_{max} 3300 (OH) cm^{-1}. A solution of this oil in ether (50 ml) was saturated with gaseous HCl. A crystalline solid (0.64 g) slowly formed, m.p. 114–116°; i.r. ν_{max} 2500 ($\overset{+}{N}$—H) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.04 (s, 3H, aliphatic CH_3), 2.24 (s, 3H, aromatic CH_3), 3.66–3.95 (m, 8H, CH_2 and OCH_3 groups), 6.73 (s, 1H) and 6.80 (s, 1H, aromatic protons), 13.08 (s, br, 2H, $\overset{+}{N}HOH$); mass spectrum *m/e* (% relative abundance) 223 (100) ($C_{12}H_{17}NO_3$).

Anal. Calcd. for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.98; N, 5.39. Found: C, 55.46; H, 6.91; N, 5.59.

1-(2,5-Dimethoxy-4-methylphenyl)-2-propanol (5)

A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone (2.0 g) in methanol (30 ml) was slowly added to a stirred solution of sodium borohydride (2.0 g) in methanol (200 ml) and water (100 ml). Stirring was continued at room temperature for 1 h after the addition, then a slight excess of concentrated HCl was added to decompose the excess hydride. The solvent was removed under reduced pressure and the residue was suspended in water (100 ml) and extracted with chloroform (200 ml). Evaporation of the latter solution gave the title compound (1.2 g), m.p. 80.5–81.5° (from ethanol); n.m.r. (DMSO-d_6) δ 1.01 (d, 3H, J = 6, α-CH_3), 2.12 (s, 3H, ring CH_3), 2.65 (m, 1H (overlaps with DMSO), CH), 3.60–4.27 (m, 8H, overlapping CH_2 and OCH_3 signals), 4.27 (s, br, 1H, exchanges with D_2O, OH), 6.72 (s, 2H, aromatic protons).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.62; H, 8.73.

1-(2,5-Dimethoxy-4-methylphenyl)-2-nitropropene (10)

A solution of 2,5-dimethoxy-4-methylbenzaldehyde (15.0 g) and ammonium acetate (6.3 g) in acetic acid (75 ml) and nitroethane (9.9 g) was heated under gentle reflux for 3 h. The dark red solution was evaporated, leaving a red oil which was suspended in water (100 ml) and extracted with chloroform (100 ml). Evaporation of the latter gave an oil which solidified on standing. This crude product (14.4 g, m.p. 79–86°) crystallized from ethanol to give the yellow title compound, m.p. 85–87° (lit. (12) m.p. 85.5–87.5°); i.r. ν_{max} 1320, 1500 (NO_2), 1645 (C=C) cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37. Found: C, 61.04; H, 6.36.

Catalytic Hydrogenation of 1-(2,5-Dimethoxy-4-methylphenyl)-2-nitropropene

(*i*) A solution of the title compound (7.5 g) in ethanol (300 ml) containing 10% palladium–charcoal (1.0 g) was hydrogenated at room temperature and normal pressure until uptake of hydrogen apparently ceased. When the reaction flask was removed from the hydrogenation apparatus, a pungent ammonia-like odor was evident. The solution was stirred at room temperature for 3 h after which time the basic odor was no longer apparent, then hydrogenation was continued until uptake again ceased. Evaporation of the filtrate gave an oil which was dissolved in chloroform (100 ml) and extracted with 5% HCl solution (2 × 100 ml). The aqueous solution was basified (10% NaOH) and reextracted with chloroform (3 × 100 ml). The combined chloroform extract was dried ($MgSO_4$), saturated with gaseous HCl and evaporated to give a solid which was fractionally crystallized from ethanol–ether. The first product (0.24 g), m.p. 176–178° was 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane hydrochloride, confirmed by i.r. spectral comparison and mixture m.p. with authentic DOM. A second product (0.81 g), m.p. 121–123°, was 1-(2,5-dimethoxy-4-methylphenyl)-2-(hydroxylamino)propane hydrochloride; i.r. ν_{max} 2480–2750 ($\overset{+}{N}$—H, $\overset{+}{N}$—OH) cm^{-1}; mass spectrum *m/e* (% relative abundance) 225 (9) ($C_{12}H_{19}NO_3$); 193 (5) ($C_{12}H_{17}O_2$); 166 (100) ($C_{10}H_{14}O_2$); 60 (45) (C_2H_6NO); 44 (18) (C_2H_6N) (Formulae identified by accurate mass measurements).

Anal. Calcd. for $C_{12}H_{20}ClNO_3$: C, 55.06; H, 7.70; N, 5.35. Found; C, 55.06; H, 7.81; N, 5.51.

The chloroform solution remaining after extraction with 5% HCl (see above) was evaporated and the oil which resulted was dissolved in ether and saturated with gaseous HCl. A product separated as an oil from which the ether layer was decanted and treated as described later. Treatment of the oil with ethanol–ether gave a solid (1.1 g), m.p. 112–115°, which was identified by i.r. spectrum and mixture m.p. as the oxime (**3***b*) hydrochloride.

The ether solution referred to above was evaporated and the product obtained was distilled under reduced pressure. An oil, b.p. 130–160° (0.5–1.5 mm) was collected and triturated with ethanol. This gave 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone (**2***b*, 1.7 g), m.p. 55–57°, the i.r. spectrum of which was superimposable on that of the authentic ketone (**2***b*).

(*ii*) A solution of 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene (7.0 g) in ethanol (100 ml) and concentrated HCl (7 ml) was hydrogenated at room temperature and normal pressure in the presence of 10% palladium–charcoal (1.0 g). Hydrogen was rapidly incorporated, and when uptake ceased, the filtrate was evaporated to give an oil. This was dissolved in chloroform and separated into basic and neutral fractions as described in (*i*) above. Evaporation of the chloroform solution containing the basic material gave a solid (0.46 g) which was dissolved in ether, and the solution was saturated with gaseous HCl. This gave 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane hydrochloride (DOM), m.p. 176–178°, identified (i.r.; mixture m.p.) by comparison with an authentic sample.

The chloroform solution which remained after extracting basic material was evaporated to give a red oil (5.4 g) which was dissolved in ether and saturated with gaseous HCl. 1-(2,5-Dimethoxy-4-methylphenyl)-2-propanone oxime hydrochloride (3.3 g) slowly precipitated. It had an i.r. spectrum and m.p. identical to that of authentic **3***b* hydrochloride, and a mixture m.p. was undepressed.

(*iii*) Crude 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene (m.p. 79–86°; i.r. ν_{max} 1320, 1500 (NO_2), 2210 (C≡N) cm^{-1}; see preparation of **10**) (7.0 g) dissolved in ethanol (100 ml) and concentrated HCl (10 ml) was hydrogenated at room temperature and normal pressure with 10% palladium–charcoal (0.7 g) as catalyst. Hydrogen was incorporated rapidly for 2 h then more slowly for 12 h. The filtrate was evaporated to an oil which was dissolved in ethanol (10 ml), cooled, and diluted with

ether until cloudy. A solid precipitated (0.81 g), which was crystallized from ethanol–ether and gave 2,5-dimethoxy-4-methylbenzylamine hydrochloride (**11**), m.p. 244–246°; i.r. ν_{max} 1598, 2010, 2580–2720 ($\overset{+}{N}$—H) cm^{-1}; n.m.r. (DMSO-d_6) δ 2.16 (s, 3H, CH_3), 3.78 (s, 6H, OCH_3 groups), 3.96 (s, 2H, CH_2), 6.90 (s, 1H) and 7.23 (s, 1H, aromatic protons), 8.00–8.83 (s, br, 3H, exchanges with D_2O, $\overset{+}{N}H_3$).

Anal. Calcd. for $C_{10}H_{16}ClNO_2$: C, 55.17; H, 7.41; N, 6.44. Found; C, 55.41; H, 7.21; N, 6.60.

The filtrate was treated as described in method (*ii*) and 1-(2,5-dimethoxy-4-methylphenyl)-2-propanone oxime hydrochloride (2.8 g) was obtained.

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

Crude 1-(2,5-dimethoxy-4-methylphenyl)-2-nitropropene, m.p. 79–86° (see preparation of **10**), (5 g) was fractionally crystallized from ethanol. The initial precipitate was pure **10**; concentration of the mother liquors and repeated crystallization of the resulting precipitate from ethanol gave the title compound (0.6 g), m.p. 127–129°; i.r. ν_{max} 2210 (C≡N) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.33 (s, 3H, CH_3), 3.86 (s, 3H) and 3.93 (s, 3H, OCH_3 groups), 6.87 (s, 1H) and 6.96 (s, 1H, aromatic protons).

Anal. Calcd. for $C_{10}H_{11}NO$: C, 67.77; H, 6.26; N, 7.91. Found: C, 67.82; H, 6.36; N, 7.48.

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