The Synthesis of Analogs of the Hallucinogen 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane (DOM). II.[1] Some Ring-methoxylated 1-Amino- and 2-Aminoindanes

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The synthesis of 2-amino-4,7-dimethoxy-5-methylindane (**12***a*), the cyclic analog of the known hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM), is described. The key intermediate was *trans*-2-amino-4,7-dimethoxy-6-methyl-1-indanol (*trans*-**10***a*) which was converted to **12***a* in two ways. The prolonged action of hydrochloric acid on *trans*-**10***a* gave 4,7-dimethoxy-5-methyl-2-indanone (**11***d*), the oxime of which, on catalytic reduction, was converted to **12***a* in low yield. A direct catalytic reduction of *trans*-**10***a* in the presence of hydrochloric acid also gave **12***a*, together with *cis*-2-amino-4,7-dimethoxy-6-methyl-1-indanol (*cis*-**10***a*).

The synthesis and properties of other derivatives of 2-aminoindane, and some derivatives of 1-aminoindane are also described.

On décrit la synthèse de l'amino-2 diméthoxy-4,7 méthyl-5 indane (**12***a*), un analogue cyclique de l'hallucinogène connu (diméthoxy-2,5 méthyl-4 phényl)-1 amino-2 propane (DOM). L'intermédiaire-clef de la synthèse est la *trans*-amino-2 diméthoxy-4,7 méthyl-6 indanol-1 (*trans*-**10***a*) qui peut être transformé en **12***a* selon deux procédés. L'action prolongée de l'acide chlorhydrique sur le *trans*-**10***a* conduit au diméthoxy-4,7 méthyl-5 indanone-2 (**11***d*) dont l'oxime, par réduction catalytique, conduit au produit **12***a* avec des rendements faibles. La réduction catalytique directe du *trans*-**10***a* en présence d'acide chlorhydrique conduit également au produit **12***a* mais aussi au *cis*-amino-2 diméthoxy-4,7 méthyl-6 indanol-1 (*cis*-**10***a*).

On décrit aussi la synthèse et les propriétés de certains autres dérivés de l'amino-2 indane ainsi que de l'amino-1 indane.

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Many ring-methoxylated phenethylamines (**1**) have been shown to possess psychotomimetic activity (1,2) and two conflicting theories have been propounded by Snyder *et al.* (3, 4) and Kang and Green (5) in an attempt to explain why these compounds are active. Both theories related the phenethylamine structures to that of lysergic acid diethylamine (LSD; **2**). In each case, the aromatic ring of the phenethylamines is equated with ring A of LSD but, whereas Snyder *et al.* consider the nitrogen atom of structure **1** to correspond to the N-1 of LSD, or to contribute to the formation of a pseudo-ring C, Kang and Green are of the opinion that the nitrogen atom of the phenethylamines is equivalent to N-6 of LSD at the receptor site in the brain.

In view of this conflict, it seemed desirable to synthesize and evaluate pharmacologically rigid molecules which were structurally related to known psychotomimetic compounds. The initial compounds selected (**12***a* and *b*) possessed an aromatic ring which corresponded to ring A of LSD, and a nitrogen atom in a rigid position comparable to that of N-6 in LSD; the former compound (**12***a*) is the cyclic analog of 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**3**; DOM), a known potent hallucinogen (6). The synthesis of these two aminoindanes (**12***a* and *b*) and some related compounds is now described. While this work was in progress, Horn and Snyder (7) reported their studies on the steric requirements for catecholamine uptake by rat brain, in which they compared the preferred conformation of amphetamine with 1- and 2-aminoindane.

The starting material for the synthesis of 2-amino-4,7-dimethoxy-5-methylindane (**12***a*) was 2,5-dimethoxy-4-methylbenzaldehyde (**4***a*). This was reacted with malonic acid to give a cinnamic acid derivative (**5***a*) which on catalytic reduction gave 3-(2,5-dimethoxy-4-methyl)propionic acid (**6***a*). Attempts to cyclize the latter to the 1-indanone (**7***a*) using phosphorous oxychloride as the dehydrating agent (8) gave a low yield of an

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[1]Reference 18 is considered Part I.

[2]Revision received October 1, 1973.

impure product. Polyphosphoric acid (*cf.* ref. 9) proved to be a much superior reagent for this purpose.

4,7-Dimethoxy-2-isonitroso-6-methyl-1-indanone (**8***a*) was formed when a solution of the indanone (**7***a*) in ethanolic HCl was treated with freshly prepared ethyl nitrite. Because of its low solubility in ethanol, the pure product crystallized from the solution as it was formed. Numerous attempts, in different solvents and employing different catalysts, were made to reduce the oxime (**8***a*) directly to the amine (**12***a*), but generally a dark red oil, which could not be purified, was obtained. Eventually, catalytic reduction of a suspension of **8***a* in ethanolic HCl containing palladium–charcoal was attempted and a white water-soluble solid was recovered. When an aqueous solution of this solid was basified, the solution turned dark red in color. An ethanolic solution of the same material slowly turned red during a recrystallization process but this color formation could be prevented by the addition of HCl to the ethanol. This behavior was consistent (10) with the product being 2-amino-4,7-dimethoxy-6-methyl-1-indanone (**9***a*) hydrochloride and its i.r. spectrum (ν_{max} 1720 cm^{-1}) and n.m.r. spectrum supported this conclusion, although the compound analyzed indifferently for $C_{12}H_{16}ClNO_3$.

The reduction of 2-amino-1-indanone with sodium borohydride is reported (11) to yield *trans*-2-amino-1-indanol. When the impure **9***a* was so reduced, an amino alcohol, $C_{12}H_{18}ClNO_3$, was isolated (ν_{max} 3350 cm^{-1}; m.p. 193–195°) and concluded to be *trans*-2-amino-4,7-dimethoxy-6-methyl-1-indanol (**10***a*) hydrochloride. The stereochemistry of this product is discussed below.

In view of the doubtful purity of the indanone (**9***a*), an alternative method of preparing the indanol (**10***a*) was sought. Hydrogenation of 2-isonitroso-1-indanones in ethanolic NaOH containing Raney nickel is known to produce 2-amino-1-indanols (12). 4,7-Dimethoxy-2-isonitroso-6-methyl-1-indanone (**8***a*) was reduced under conditions similar to those reported, except that palladium–charcoal was the catalyst employed, and the product isolated was the *trans*-indanol (**10***a*). Prolonged heating of this alcohol in concentrated HCl (11) caused dehydration and deamination, and the product isolated was deduced to be 4,7-dimethoxy-5-methyl-2-indanone (**11***d*); the i.r., n.m.r., and mass spectra were all consistent with this conclusion. The oxime (**11***e*) was readily prepared from compound **11***d* but its reduction to the required 2-aminoindane (**12***a*) proved more difficult than anticipated. Attempted catalytic hydrogenations (10% Pd–C or Pt_2O) in ethanol were unsuccessful and a lithium aluminum hydride reduction gave a very poor yield of the amine, largely because of the insolubility of the oxime in ether or tetrahydrofuran. Catalytic (10% Pd–C) reduction of the oxime in ethanolic HCl, however, gave a 35% yield of 2-amino-4,7-dimethoxy-5-methylindane; a better yield resulted when acetic acid – sulfuric acid was the solvent (10).

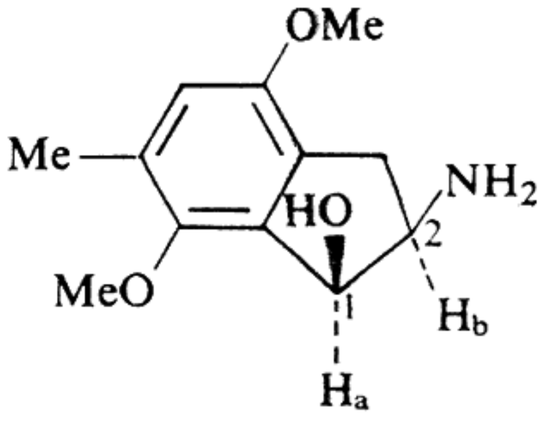
The possibility of reducing the amino alcohol (**10***a*) directly to the required amine (**12***a*) was then investigated. As indicated previously, the action of HCl on **10***a* yielded the ketone (**11***d*). It was reasoned that if this **10***a* → **11***d* transition proceeded via the chloro amine (**13**) and possibly the enamine (**14**), these intermediates might be expected to reduce catalytically and give the 2-aminoindane (**12***a*). This, in fact, did occur. When the amino alcohol (*trans*-**10***a*, m.p. 193–195°), dissolved in a dioxane – concentrated HCl solvent, was catalytically reduced (10% Pd–C), two compounds were isolated. The acetone-insoluble product was 2-amino-4,7-dimethoxy-5-methylindane (**12***a*) hydrochloride. The acetone-soluble compound, $C_{12}H_{18}ClNO_3$, was isomeric with the amino alcohol employed in the reduction but differed in melting point (206–208°) and in position of the O—H stretching frequency (ν_{max} 3150 cm^{-1}). This product is concluded to be *cis*-2-amino-4,7-dimethoxy-6-methyl-1-indanol (*cis*-**10***a*) hydrochloride since it can hydrogen bond intramolecularly (**15**) which explains the lower O—H stretching frequency.

To verify that the second product was *cis*-**10***a*, a stereospecific reduction (13, 14) of 2-amino-4,7-dimethoxy-6-methyl-1-indanone (**9***a*) was performed which involved hydrogenation in the presence of Pd–C and $PdCl_2$. The product isolated was identical to *cis*-**10***a*. Further support for the stereochemical assignments given to compounds *cis*-**10***a* and *trans*-**10***a* was obtained from an n.m.r. study of their hydrochlorides in D_2O. Proton H_a in the spectrum of *cis*-**10***a* was a doublet, δ 5.47, $J_{H_aH_b}$ = 5.7 Hz. Proton H_a in the spectrum of *trans*-10*a* was also a doublet, δ 5.52, $J_{H_aH_b}$ = 3.2 Hz. Assuming that the five-

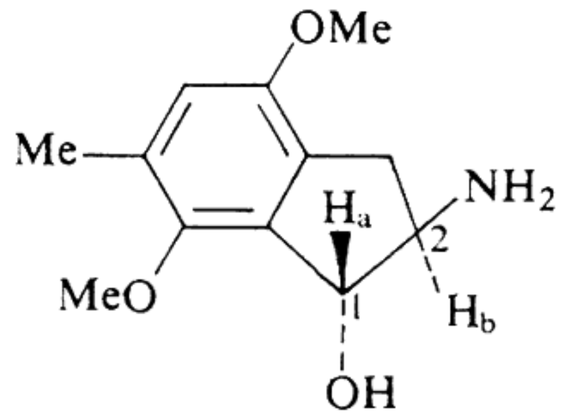
membered ring in *cis*- and *trans*-**10***a* is little distorted from the Dreiding model representation which indicated virtual planarity, it can be predicted from the Karplus equation (15) that the *cis* isomer should have the larger coupling constant.

To confirm that *trans*-**10***a* → *cis*-**10***a* isomerism occurred in concentrated HCl, a solution of the former was heated at 80° and aliquots were removed at various time intervals and evaporated to give white solids whose i.r. spectra were examined. The ν_{max} 3150 cm^{-1} band (*cis* isomer) increased in size at the expense of the ν_{max} 3350 cm^{-1} band (*trans* isomer) with increasing solution time. Prolonged heating gave the ketone (**11***d*).

The experience gained during the preparation of compound **12***a* permitted a more rapid synthesis of 2-amino-4,7-dimethoxyindane (**12***b*). 4,7-Dimethoxy-2-isonitroso-1-indanone (**8***b*) was synthesized from 2,5-dimethoxybenzaldehyde (**4***b*) via the same sequence of reactions described above for the homolog (**8***a*). Catalytic reduction



cis - **10***a*



trans - **10***a*

of **8***b* in ethanolic hydrochloric acid gave an excellent yield of 2-amino-4,7-dimethoxy-1-indanone (**9***b*) hydrochloride, whereas the same reduction in ethanolic sodium hydroxide produced 2-amino-4,7-dimethoxy-1-indanol (**10***b*; ν_{max} 3350 cm^{-1}), assumed to be the *trans* isomer. Its reduction in dioxane – concentrated HCl proceeded smoothly and an excellent yield of 2-amino-4,7-dimethoxyindane (**12***b*) hydrochloride resulted.

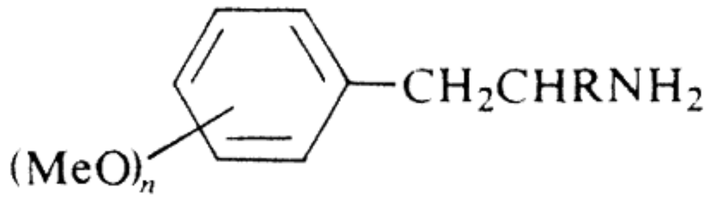
An attempt to prepare 2-amino-5-bromo-4,7-dimethoxyindane (**12***c*) was unsuccessful. Treatment of 3-(2,5-dimethoxyphenyl)propionic acid (**6***b*) with bromine water gave a monobromo derivative. Since the aromatic protons appeared as singlets (δ 6.80, 7.03) in a 60 MHz n.m.r. spectrum and were therefore *para* to each other, the product was identified as 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid (**6***c*). When this acid was heated in polyphosphoric acid, a low yield of 6-bromo-4,7-dimethoxy-1-indanone (**7***c*) was produced which was converted to the required 6-bromo-4,7-dimethoxy-2-isonitroso-1-indanone (**8***c*) by the action of ethyl nitrite. Catalytic reduction of this product, however, resulted in the removal of the bromine atom. Thus, catalytic reduction of **8***c* in ethanolic HCl yielded 2-amino-4,7-dimethoxy-1-indanone (**9***b*) hydrochloride, and a similar reduction in ethanol and sodium hydroxide gave the corresponding indanol (**10***b*) hydrochloride.

Some tertiary amines were also prepared in this study. When an aqueous solution of 2-amino-4,7-dimethoxy-5-methylindane (**12***a*) containing a slight excess of formaldehyde was hydrogenated catalytically, the product isolated was 4,7-dimethoxy-2-dimethylamino-5-methylindane (**16***f*) hydrochloride. In a similar manner, *cis*- and *trans*-2-dimethylamino-4,7-dimethoxy-6-methyl-1-indanol (**17***f*) hydrochlorides were prepared from *cis*- and *trans*-2-amino-4,7-dimethoxy-6-methyl-1-indanol (**10***a*) hydrochlorides, respectively. The *cis*- (ν_{max} OH, 3190 cm^{-1}) and *trans*-**17***f* hydrochlorides (ν_{max} OH, 3270 cm^{-1}) had similar melting points but a mixture melting point was depressed.

When 4,7-dimethoxy-6-methyl-1-indanone (**7***a*) was reacted with dimethylamine and paraformaldehyde in ethanolic HCl, a good yield of 4,7-dimethoxy-2-(dimethylamino)methyl-6-methyl-1-indanone (**18**) hydrochloride resulted. Reduction of this ketone with sodium borohydride gave the corresponding indanol (**17***g*) hydrochloride (ν_{max} OH, 3310 cm^{-1}), presumably the *trans* isomer, which was catalytically reduced in dioxane – concentrated HCl to 4,7-dimethoxy-2-(dimethylamino)methyl-5-methylindane (**16***g*) hydrochloride.

Various substituted 1-aminoindanes have been found to possess central nervous system activity (16, 17) and since the 1-indanones described above are also precursors of 1-aminoindanes, it was convenient to prepare selected examples of ring-methoxylated 1-aminoindanes to compare their pharmacological properties with their 2-amino counterparts.

The oximes (**19***a* and *b*) were readily obtained by the action of hydroxylamine on the appropriate ketone (**7**). Catalytic reduction of 4,7-dimethoxy-6-methyl-1-indanone oxime (**19***a*) in ethanol or reduction with lithium aluminum hydride gave a good yield of 1-amino-4,7-dimethoxy-6-methylindane (**20***a*). In contrast, a solvent system of acetic acid, ethanol, and sul-



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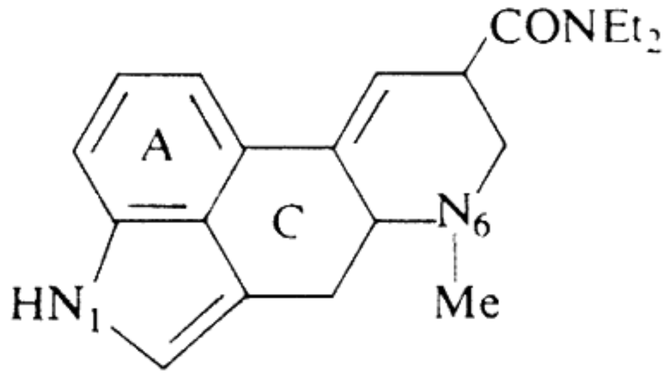

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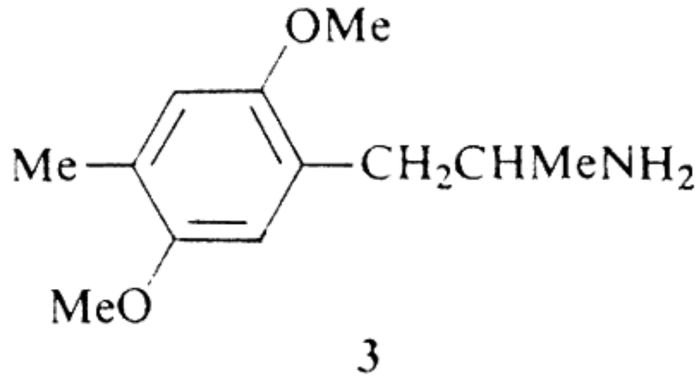

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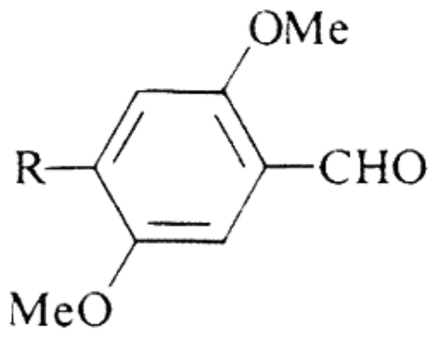

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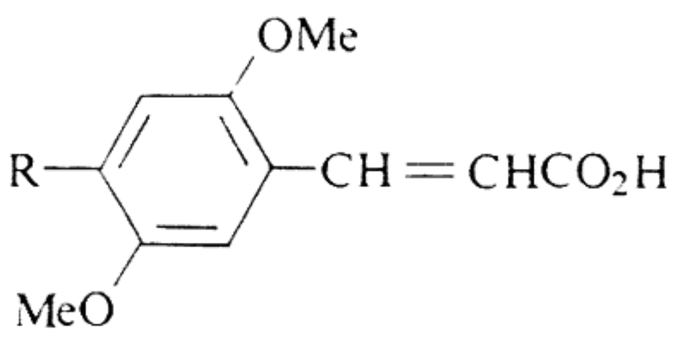

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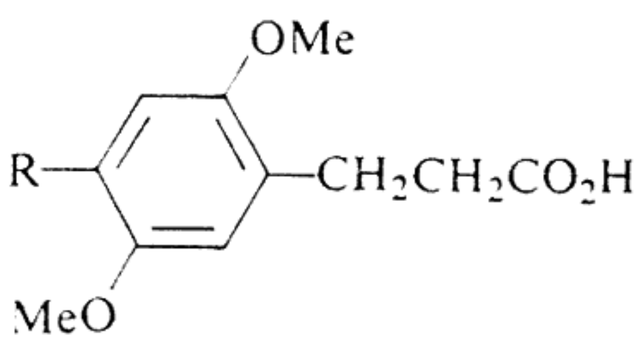

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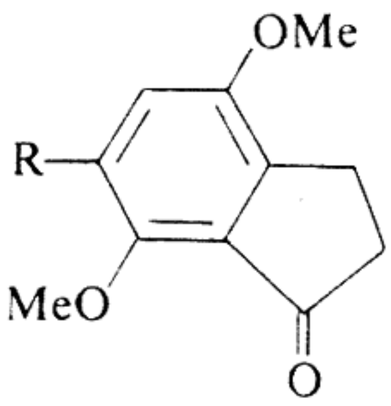

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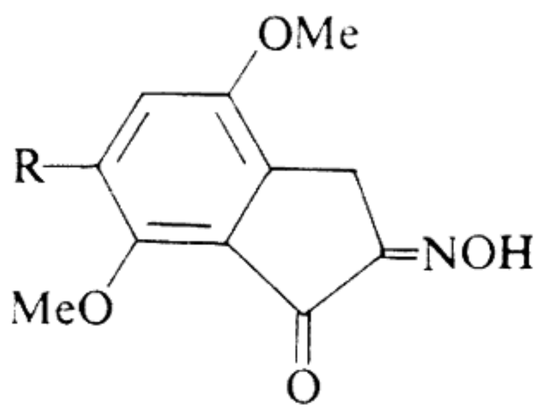

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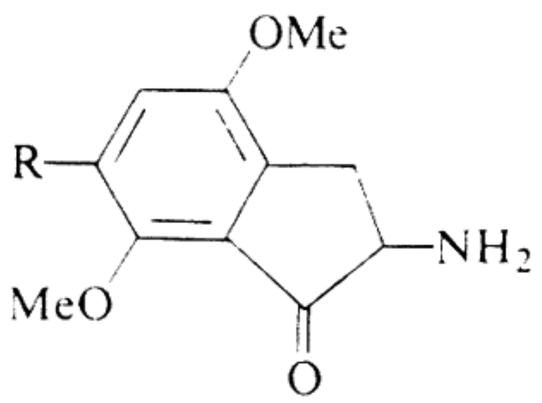

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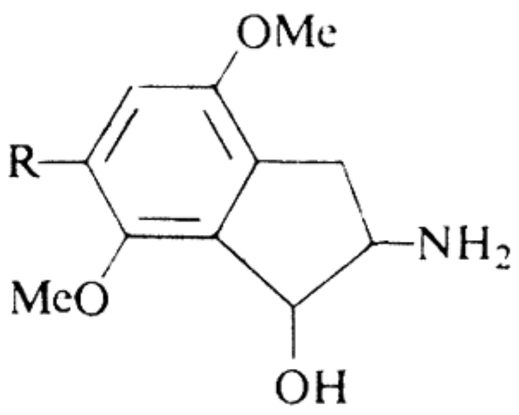

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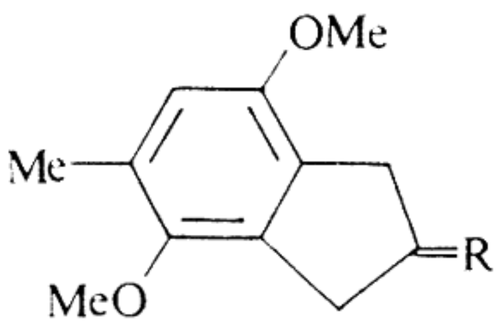

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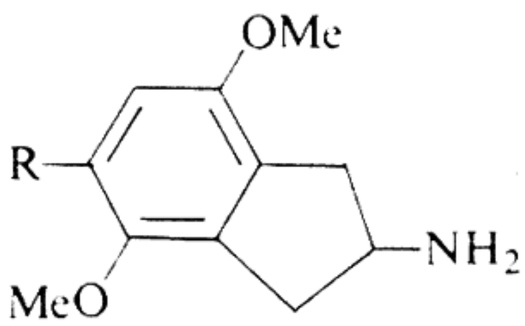

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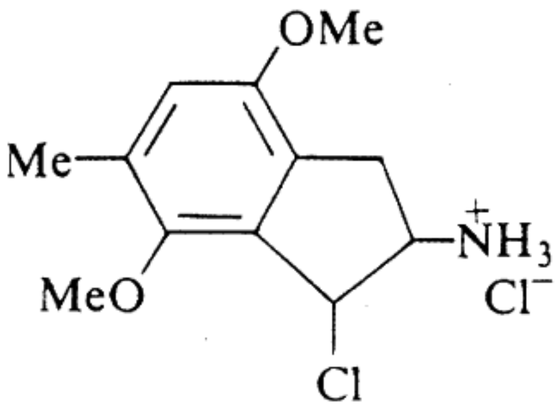

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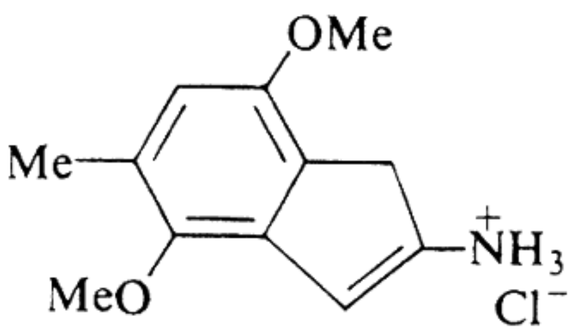

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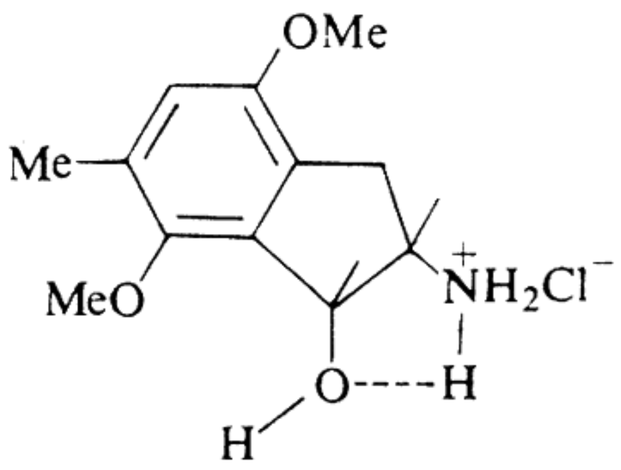

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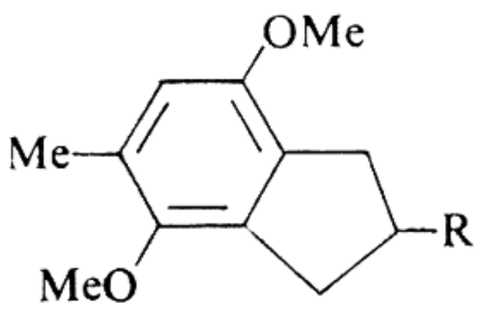

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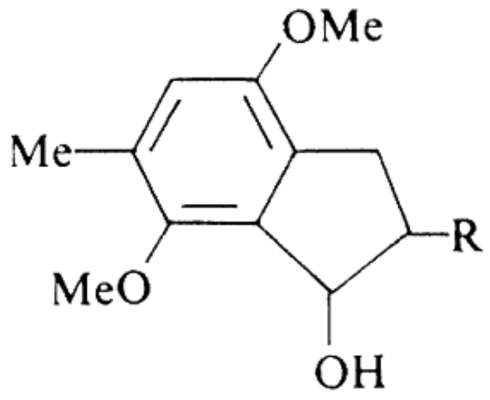

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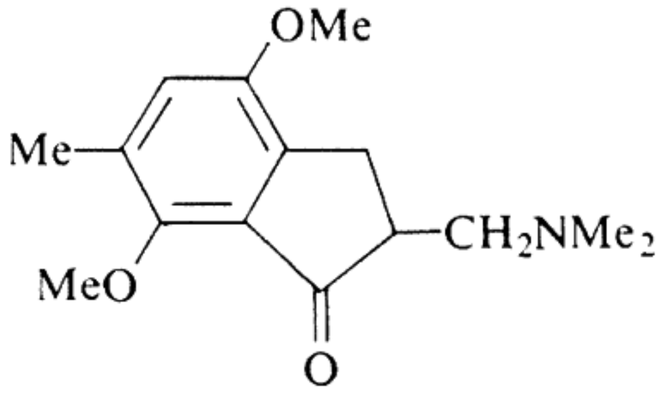

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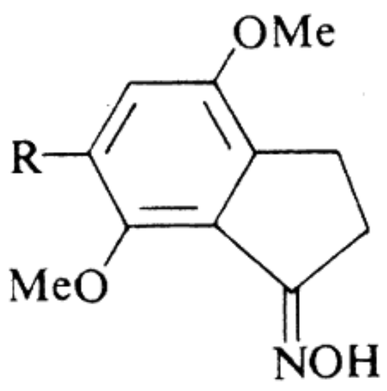

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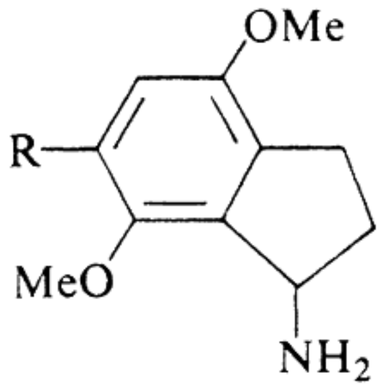

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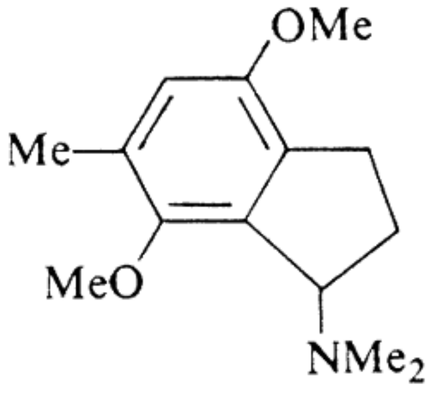

21

a R = Me
b R = H
c R = Br
d R = O
e R = NOH
f R = NMe_2
g R = CH_2NMe_2

furic acid proved necessary in the catalytic reduction of the oxime (**19***b*) to 1-amino-4,7-dimethoxyindane (**20***b*).

Two derivatives of **20***a* and *b* were also prepared. Treatment of **20***b* with a slight excess of bromine water gave a monobromo derivative, $C_{11}H_{16}BrNO_2$, assumed to be 1-amino-6-bromo-4,7-dimethoxyindane (**20***c*). The tertiary amine, 4,7-dimethoxy-1-dimethylamino-6-methylindane (**21**), was the product recovered when a solution of the indane **20***a* and formaldehyde was reduced catalytically.

Some of the aminoindanes just described were subjected to a simple preliminary pharmacological screening in which the effects of an oral or intraperitoneal dose in male rats (150–500 g) were compared with those caused by an oral dose of DOM (10 mg/kg) which reliably caused hypersalivation, pupillary dilation, retraction of scrotum, loss of orientation reflexes, hypomotility, and walking with a slinking gait. This revealed that compounds **12***a* (10 mg/kg oral dose) and **12***c* (30 mg/kg intraperitoneal dose) showed similar pharmacological responses as DOM, but were somewhat less active than DOM. The remaining compounds evaluated, *cis*-**10***a*, *trans*-**10***a*, **12***b*, **16***f*, **16***g*, **20***a*, and **21** were much less active.

Experimental

The conditions employed in the determination of melting points and elemental analyses, and in the recording of i.r. as Nujol mulls, n.m.r., and mass spectra are described in a previous publication (18). Compounds with structures **9**, **10**, **12**, **13**, **16**, **17**, **18**, **20**, and **21**, described below, are racemates. No attempts were made to isolate optically pure compounds.

trans-2,5-Dimethoxy-4-methylcinnamic Acid (5a)

A solution of 2,5-dimethoxy-4-methylbenzaldehyde (19), (9.2 g), malonic acid (12.0 g), dry pyridine (24 ml), and piperidine (0.6 ml) was heated on a steam bath for 3 h, then added to a mixture of concentrated HCl (35 ml) and ice (60 g). Crystallization of the product from ethanol gave the title compound as a yellow solid (11.4 g), m.p. 158–161°; i.r. ν_{max} 1618 (C=C), 1690 (C=O), 2500–2700 (OH) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.25 (s, 3H, CH_3), 3.84 and 3.85 (overlapping singlets, 6H, $(OCH_3)_2$), 6.46 (d, 1H, J = 16.5) and 8.14 (d, 1H, J = 16.5) (*trans* (20, 21) CH=CH), 6.76 (s, 1H) and 6.99 (s, 1H) (aromatic protons), 10.78 (s, br, 1H, exchanges with D_2O, COOH).

Anal. Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.95; H, 6.46.

3-(2,5-Dimethoxy-4-methylphenyl)propionic Acid (6a)

A solution of 2,5-dimethoxy-4-methylcinnamic acid (10.0 g) in ethanol was hydrogenated at room temperature and normal pressure under 10% palladium–charcoal (Pd–C) (0.5 g) until the theoretical amount of hydrogen was absorbed. The filtrate on evaporation gave the title compound, m.p. 108–110° (from ethanol); i.r. ν_{max} 1700 (C=O), 2500–2700 (OH) cm^{-1}.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.02; H, 7.19.

4,7-Dimethoxy-6-methyl-1-indanone (7a)

The acid (**6***a*, 10.0 g) was stirred in polyphosphoric acid (100 g) at 80° for 1.5 h. The dark yellow mixture was poured into ice water (300 ml), basified with excess $NaHCO_3$, and extracted with chloroform (3 × 200 ml). The washed (H_2O) organic solution was evaporated to

give the title indanone (6.8 g), m.p. 104–105.5° (from ethanol); i.r. ν_{max} 1710 (C=O) cm^{-1}; n.m.r. (DMSO-d_6) δ 2.21 (s, 3H, CH_3), 2.35–3.07 (m, 4H, CH_2 groups), 3.73 (s, 3H) and 3.80 (s, 3H) (OCH_3 groups), 7.07 (s, 1H, aromatic proton).

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.78; H, 6.94.

4,7-Dimethoxy-1-indanone (7b)

This compound was prepared in a similar manner in 58% yield from 3-(2,5-dimethoxyphenyl)propionic acid. The product had m.p. 124–125° (from ethanol) (lit. (22) m.p. 124–125°); i.r. ν_{max} 1701 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.73; H, 6.30. Found: C, 68.51; H, 6.19.

6-Bromo-4,7-dimethoxy-1-indanone (7c)

This compound (2.6 g), m.p. 109–110° (from ethanol) was prepared in a similar way from 3-(4-bromo-2,5-dimethoxyphenyl)propionic acid (10.0 g); i.r. ν_{max} 1700 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}BrO_3$: C, 48.73; H, 4.09. Found: C, 48.56; H, 4.08.

*4,7-Dimethoxy-2-isonitroso-6-methyl-1-indanone (**8a**)*

Freshly prepared ethyl nitrite was bubbled through a solution of 4,7-dimethoxy-6-methyl-1-indanone (11.0 g) in ethanol (100 ml) saturated with HCl gas, for 2 h at 35° then the reaction mixture was left at room temperature for 12 h. The crystalline solid which formed (6.8 g) had m.p. 219–220° (from ethanol); i.r. ν_{max} 1645 (C=N), 1730 (C=O), 3280 br (OH) cm^{-1}.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.07; H, 5.46; N, 5.72.

*4,7-Dimethoxy-2-isonitroso-1-indanone (**8b**)*

This was prepared in 72% yield in a similar manner from 4,7-dimethoxy-1-indanone. The product was purified by dissolving it in 10% NaOH, filtering and acidifying with concentrated HCl. Compound **8***b* had m.p. 233–234.5° (from ethanol); i.r. ν_{max} 1650 (C=N), 1732 (C=O), 3300 br (OH) cm^{-1}.

Anal. Calcd. for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01. Found: C, 59.50; H, 4.97.

*6-Bromo-4,7-dimethoxy-2-isonitroso-1-indanone (**8c**)*

This compound (1.25 g), m.p. 248–250° (from ethanol), was prepared in a similar way from 6-bromo-4,7-dimethoxy-1-indanone (3.0 g); i.r. ν_{max} 1648 (C=N), 1730 (C=O), 3300 br (OH) cm^{-1}.

Anal. Calcd. for $C_{11}H_{10}BrNO_4$: C, 44.02; H, 3.36. Found: C, 43.88; H, 3.28.

*2-Amino-4,7-dimethoxy-6-methyl-1-indanone (**9a**) Hydrochloride*

A suspension of 4,7-dimethoxy-2-isonitroso-6-methyl-1-indanone (2.0 g) in ethanol (200 ml) was hydrogenated at room temperature and normal pressure in the presence of 10% Pd–C (0.2 g) until incorporation of hydrogen was complete. The filtrate, initially colorless, slowly turned red on standing. Addition of concentrated HCl decolorized the solution and removal of the solvent gave the title compound as a white solid (1.81 g), m.p. 248–252° (from ethanol–ether); i.r. ν_{max} 1602, 1980, 2450–2630 ($\overset{+}{N}$—H), 1720 (C=O) cm^{-1}; n.m.r. (D_2O) δ 2.33 (s, 3H, CH_3), 2.49–3.71 (m, 2H, CH_2), 3.87 (s, 3H) and 3.95 (s, 3H) (OCH_3 groups), 4.15–4.57 (m, 1H, aliphatic CH), 7.31 (s, 1H, aromatic proton).

Anal. Calcd. for $C_{12}H_{16}ClNO_3$: C, 55.92; H, 6.26; N, 5.44. Found: C, 55.09; H, 6.40; N, 6.60.

*2-Amino-4,7-dimethoxy-1-indanone (**9b**) Hydrochloride*

This compound (4.5 g), m.p. 260–262°, was prepared in a similar manner from the isonitroso compound (**8***b*, 5.0 g), using ethanol (200 ml) and concentrated HCl (5 ml) as solvent; i.r. ν_{max} 1592, 1980, 2610–2700 ($\overset{+}{N}$—H), 1712 (C=O) cm^{-1}.

Anal. Calcd. for $C_{11}H_{14}ClNO_3$: C, 54.21; H, 5.79; N, 5.75. Found: C, 53.98; H, 5.98; N, 6.00.

*trans-2-Amino-4,7-dimethoxy-6-methyl-1-indanol (**10a**) Hydrochloride*

(*i*) A solution of 2-amino-4,7-dimethoxy-6-methyl-1-indanone hydrochloride (5.0 g) in 50% aqueous methanol (100 ml) was added dropwise to a stirred solution of sodium borohydride (5.0 g) in the same solvent (100 ml). Stirring was continued for a further 3 h, then the solution was acidified with concentrated HCl. The solution was concentrated (60 ml), basified ($NaHCO_3$), and extracted with chloroform (3 × 50 ml). Evaporation of the combined chloroform extracts yielded the indanol (**10***a*, 2.41 g), which was converted to its hydrochloride, m.p. 193–195° (from ethanol–ether); i.r. ν_{max} 1610, 1998, 2420–2650 ($\overset{+}{N}$—H), 3350 (OH) cm^{-1}; mass spectrum *m/e* (% relative abundance) 194 (100), 223 (95) ($C_{12}H_{17}NO_3$); n.m.r. (D_2O) δ 2.33 (s, 3H, CH_3), 2.50–4.23 (m, 3H, C_2—H and CH_2) overlapping 3.87 (s, 6H, $(OCH_3)_2$), 4.82 (s, 4H, DOH from $\overset{+}{N}H_3$, OH), 5.52 (d, 1H, J = 3.2 Hz, C_1—H), 6.98 (s, 1H, aromatic H).

Anal. Calcd. for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.98; N, 5.39. Found: C, 55.23; H, 7.16; N, 5.50.

(*ii*) A solution of 4,7-dimethoxy-2-isonitroso-6-methyl-1-indanone (10.0 g) in ethanol (100 ml) and sufficient 10% NaOH to effect solution was hydrogenated at room temperature and normal pressure in the presence of 10% Pd–C (1.0 g) until hydrogen uptake ceased. The filtrate was evaporated and the residue suspended in water (60 ml), then extracted with chloroform and further treated as described in preparation *i* immediately above. This produced **10***a* hydrochloride (6.92 g), m.p. 193–195°, with i.r. and mass spectra identical to the product of preparation *i*.

*trans-2-Amino-4,7-dimethoxy-1-indanol (**10b**) Hydrochloride*

This compound (1.98 g), m.p. 182–184° (from ethanol) was the product of the reduction of 4,7-dimethoxy-2-isonitroso-1-indanone (3.0 g) using method *ii* above; i.r. ν_{max} 1602, 2080, 2580–2660 ($\overset{+}{N}$—H), 3350 (OH) cm^{-1}.

Anal. Calcd. for $C_{11}H_{16}ClNO_3$: C, 53.77; H, 6.56; N, 5.70. Found: C, 53.68; H, 7.11; N, 6.02.

*4,7-Dimethoxy-5-methyl-2-indanone (**11d**)*

A solution of 2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (1.0 g) in concentrated HCl (20 ml) and water (10 ml) was heated under reflux. After 15 min a yellow oil separated from the solution. The reaction mixture was cooled, then extracted with chloroform (30 ml), and the latter extract reserved. The procedure was

repeated on the aqueous layer until evaporation of the chloroform extract gave no residue. The previous chloroform extracts were combined and evaporated to yield a pale yellow oil (0.56 g) which solidified on standing. Crystallization from ethanol yielded the title compound, m.p. 100–102°; i.r. ν_{max} 1750 (C=O) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.32 (s, 3H, CH_3), 3.40 (s, 2H) and 3.51 (s, 2H) (CH_2 groups), 3.71 (s, 3H) and 3.81 (s, 3H) (OCH_3 groups), 6.59 (s, 1H, aromatic proton); mass spectrum *m/e* (% relative abundance) 163 (100), 206 (90) ($C_{12}H_{14}O_3$). This compound was used, without further characterization, in the preparation of the oxime (**11***e*).

*4,7-Dimethoxy-5-methyl-2-indanone Oxime (**11e**)*

A solution of the indanone (**11***d*, 1.0 g) and hydroxylamine hydrochloride (2.0 g) in ethanol (10 ml) and pyridine (5 ml) was heated at 80° for 5 h then evaporated. The residue was suspended in water and the insoluble portion (0.98 g) was crystallized from ethanol and gave the title compound, m.p. 164–166°; i.r. ν_{max} 3250 br (OH) cm^{-1}; n.m.r. (DMSO-d_6) δ 10.66 (s, 1H, OH).

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.69; H, 6.92; N, 5.99.

*2-Amino-4,7-dimethoxy-5-methylindane (**12a**) Hydrochloride*

(*i*) A solution of 4,7-dimethoxy-5-methyl-2-indanone oxime (0.5 g) in ethanol (200 ml) and concentrated HCl (5 ml) containing PtO_2 (0.1 g) was hydrogenated at room temperature and normal pressure until the theoretical amount of hydrogen was absorbed. The filtrate was evaporated and the residue was triturated with water (25 ml) and filtered. The aqueous solution was evaporated under reduced pressure and the product obtained (0.18 g) was crystallized from ethanol–ether to give the title compound, m.p. 253–255°; i.r. ν_{max} 1610, 2220–2680 ($\overset{+}{N}$—H) cm^{-1}; n.m.r. (D_2O) δ 2.30 (s, 3H, CH_3), 2.90–3.55 (m, 4H, CH_2 protons), 3.83 (s, 3H) and 3.88 (s, 3H) (OCH_3 protons), 4.10–4.60 (m, 1H, CH), 6.83 (s, 1H, aromatic proton).

Anal. Calcd. for $C_{12}H_{18}ClNO_2$: C, 59.12; H, 7.45; N, 5.75. Found: C, 58.70; H, 7.64; N, 5.85.

(*ii*) A solution of the oxime (**11***e*, 0.5 g) in glacial acetic acid (50 ml) and concentrated H_2SO_4 (0.5 g) containing 10% Pd–C (0.13 g), was hydrogenated to completion at room temperature and normal pressure. To the filtrate was added a solution of NaOH (0.25 g) in water (2 ml), prior to evaporation. The residue was dissolved in water (50 ml), basified with 5% NaOH (3 ml) and extracted with chloroform (3 × 50 ml). The combined chloroform extract was saturated with HCl gas and evaporated to give the title compound (0.32 g), m.p. 253–255° (from ethanol–ether).

(*iii*) A solution of 2-amino-4,7-dimethoxy-6-methylindanol hydrochloride (0.5 g) in dioxane (20 ml) and concentrated HCl (20 ml) containing 10% Pd–C (0.1 g) was hydrogenated at room temperature and normal pressure. Hydrogen was slowly absorbed over 20 h. The filtrate was evaporated under reduced pressure and the residue obtained was suspended in cold acetone (10 ml) and filtered. The insoluble material (0.23 g) was the title compound, m.p. 252–255° (from ethanol–ether).

Products from reactions *ii* and *iii* had i.r. spectra superimposable on that of the product from reaction *i*.

*2-Amino-4,7-dimethoxyindane (**12b**) Hydrochloride*

This compound (0.91 g), m.p. 245–247° (from ethanol–ether) was the acetone-insoluble product obtained when 2-amino-4,7-dimethoxy-1-indanol (1.0 g) was treated in the manner described in reaction *iii* above; i.r. ν_{max} 1615, 2030, 2380–2700 ($\overset{+}{N}$—H) cm^{-1}; mass spectrum *m/e* (% relative abundance) 162 (100), 193 (86) ($C_{11}H_{15}NO_2$).

Anal. Calcd. for $C_{11}H_{16}ClNO_2$: C, 57.51; H, 7.02; N, 6.10. Found: C, 57.43; H, 7.16; N, 6.23.

*cis-2-Amino-4,7-dimethoxy-6-methyl-1-indanol (**10a**) Hydrochloride*

(*i*) The acetone solution remaining in the preparation of **12***a* hydrochloride by method *iii* was evaporated and the residue dissolved in water (25 ml), then filtered. The filtrate was basified (5% NaOH) and extracted with chloroform (3 × 25 ml). The combined chloroform extract was saturated with HCl gas and evaporated to yield the title compound (0.25 g), m.p. 206–208° (from ethanol–ether); i.r. ν_{max} 1602, 2480–2700 ($\overset{+}{N}$—H), 3150 br (OH) cm^{-1}; mass spectrum *m/e* (% relative abundance) 194 (100); 223 (75) ($C_{12}H_{17}NO_3$); n.m.r. (D_2O) δ 2.33 (s, 3H, CH_3), 2.60–4.20 (m, 3H, C_2—H and CH_2) overlapping 3.88 and 3.91 (singlets, 6H, $(OCH_3)_2$), 4.80 (s, 4H, DOH from $\overset{+}{N}H_3$, OH), 5.47 (d, 1H, J = 5.7 Hz, C_1—H), 6.95 (s, 1H, aromatic H).

Anal. Calcd. for $C_{12}H_{18}ClNO_3$: C, 55.49; H, 6.98; N, 5.39. Found: C, 55.26; H, 7.24; N, 5.68.

(*ii*) A solution of 2-amino-4,7-dimethoxy-6-methyl-1-indanone hydrochloride (0.5 g) in ethanol (50 ml) was hydrogenated at 50 p.s.i. and room temperature for 15 h (arbitrary) in the presence of 10% Pd–C (0.1 g) and $PdCl_2$ (0.1 g). The filtrate was evaporated and the residue was crystallized from ethanol–ether to give the title compound (0.31 g), m.p. 205–208°, whose i.r. spectrum was identical to that of the product obtained in reaction *i*.

*3-(4-Bromo-2,5-dimethoxyphenyl)propionic Acid (**6c**)*

A slight excess of bromine water was added dropwise over 4 h to a stirred solution of 3-(2,5-dimethoxyphenyl)-propionic acid (25 g) in dioxane (100 ml) and water (25 ml). The product precipitated from solution during the addition. The solid was collected by filtration and when the filtrate was diluted with water, more product precipitated. The combined solids when crystallized from ethanol yielded the title compound (22.2 g), m.p. 136–137°; i.r. ν_{max} 1702 (C=O), 2500–2700 (OH) cm^{-1}; n.m.r. ($CDCl_3$) δ 2.52–3.12 (m, 4H, CH_2 groups), 3.76 (s, 3H) and 3.81 (s, 3H) (OCH_3 groups), 6.80 (s, 1H) and 7.03 (s, 1H) (aromatic protons), 11.36 (s, br, 1H, exchanges with D_2O, OH).

Anal. Calcd. for $C_{11}H_{13}BrO_4$: C, 45.69; H, 4.53. Found: C, 45.63; H, 4.54.

*Catalytic Hydrogenation of 6-Bromo-4,7-dimethoxy-2-isonitroso-1-indanone (**8c**)*

(*i*) A solution of the title compound (0.60 g) in ethanol (50 ml) and concentrated HCl (3 ml) was hydrogenated at room temperature and normal pressure for 12 h (arbitrary) in the presence of 10% Pd–C (0.2 g). Evaporation of the filtrate gave 2-amino-4,7-dimethoxy-1-indanone (**9***b*) hydrochloride (0.48 g), m.p. 259–262° (from ethanol–ether). The i.r. was identical to that of **9***b*

hydrochloride described earlier, and a mixture m.p. was undepressed.

(*ii*) A solution of the title compound (1.0 g) in ethanol (100 ml) and 5% NaOH (5 ml) was hydrogenated as described in *i* immediately above. The filtrate was evaporated and the residue dissolved in chloroform (100 ml). The chloroform solution was washed with water (4 × 50 ml), then saturated with HCl gas and evaporated. The residue (0.64 g), m.p. 180–182° (from ethanol) was *trans*-2-amino-4,7-dimethoxy-1-indanol (**10***b*) hydrochloride. Its i.r. spectrum was superimposable on that of authentic **10***b* hydrochloride and a mixture m.p. was undepressed.

*4,7-Dimethoxy-2-dimethylamino-5-methylindane (**16***f*) Hydrochloride*

A solution of 2-amino-4,7-dimethoxy-5-methylindane hydrochloride (0.50 g) in water (30 ml) and 40% formaldehyde (0.6 g) was hydrogenated at room temperature and normal pressure for 12 h (arbitrary) over 10% Pd–C (0.5 g). The filtrate was basified (NH_4OH) and extracted with chloroform (3 × 30 ml). The washed (H_2O) chloroform extract was saturated with HCl gas and evaporated to give a pale yellow solid (0.21 g), m.p. 194–196° (from ethanol); i.r. ν_{max} 1599, 2440–2700 ($\overset{+}{N}$—H) cm^{-1}; mass spectrum *m/e* (% relative abundance) 71 (100), 235 (57) ($C_{14}H_{21}NO_2$).

Anal. Calcd. for $C_{14}H_{22}ClNO_2$: C, 61.86; H, 8.16; N, 5.15. Found: C, 61.87; H, 8.34; N, 5.42.

*cis-2-Dimethylamino-4,7-dimethoxy-6-methyl-1-indanol (**17***f*) Hydrochloride*

This compound (0.55 g), m.p. 234–236° (from ethanol–ether) was prepared in a similar manner from *cis*-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (1.0 g); i.r. ν_{max} 1610, 2480–2700 br ($\overset{+}{N}$—H), 3190 br (OH) cm^{-1}; n.m.r. (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 2.80–3.65 (m, 3H, C_2—H and CH_2) overlapping 2.96 (s, 6H, $N(CH_3)_2$), 3.78 and 3.80 (overlapping s, 6H, $(OCH_3)_2$), 5.31 (d, 1H, J = 5.50 Hz, C_1—H), 6.00–6.50 (br s, 1H, exchanges in D_2O, OH), 6.90 (s, 1H, aromatic H), 9.41–10.83 (br s, 1H, exchanges in D_2O, $\overset{+}{N}H$).

Anal. Calcd. for $C_{14}H_{22}ClNO_3$: C, 58.42; H, 7.71; N, 4.87. Found: C, 58.67; H, 7.97; N, 4.96.

*trans-2-Dimethylamino-4,7-dimethoxy-6-methyl-1-indanol (**17***f*) Hydrochloride*

This compound (0.38 g), m.p. 244–246° (from ethanol) was prepared in a similar manner from *trans*-2-amino-4,7-dimethoxy-6-methyl-1-indanol hydrochloride (0.8 g) except that in this instance the title compound base precipitated on the addition of NH_4OH and was removed, then dissolved in dry ether for conversion to the hydrochloride; i.r. ν_{max} 1610, 2460–2560 ($\overset{+}{N}$—H), 3270 br (OH) cm^{-1}; n.m.r. (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 2.87 (s, 6H, $N(CH_3)_2$), 2.92–3.65 (m, 3H, C_2—H and CH_2), 3.75 and 3.78 (overlapping s, 6H, $(OCH_3)_2$), 5.69 (d, 1H, J = 5.50 Hz, C_1—H), 5.86–6.53 (br s, 1H, exchanges in D_2O, OH), 6.83 (s, 1H, aromatic H), 11.50–12.10 (br s, 1H, exchanges in D_2O, $\overset{+}{N}H$).

Anal. Calcd. for $C_{14}H_{22}ClNO_3$: C, 58.42; H, 7.71; N, 4.87. Found: C, 58.72; H, 8.08; N, 4.80.

A mixture m.p. of *cis*-**17***f* hydrochloride and *trans*-**17***f* hydrochloride was depressed to 228°.

*4,7-Dimethoxy-2-(dimethylamino)methyl-6-methyl-1-indanone (**18**) Hydrochloride*

A solution of 4,7-dimethoxy-6-methyl-1-indanone (10.0 g), dimethylamine hydrochloride (4.05 g) and paraformaldehyde (3.0 g) in ethanol (150 ml) and concentrated HCl (0.2 ml) was heated under reflux for 3 h, concentrated and cooled. The title compound (7.2 g), m.p. 179–180° (from ethanol–acetone), crystallized from solution; i.r. ν_{max} 1710 (C=O), 2450–2550 br ($\overset{+}{N}$—H) cm^{-1}; n.m.r. (DMSO-d_6) δ 2.22 (s, 3H, CH_3), 2.83 (s, 6H, $N(CH_3)_3$), 3.00–3.65 (m, 5H, CH and CH_2 groups), 3.75 (s, 3H) and 3.84 (s, 3H) (OCH_3 groups), 7.18 (s, 1H, aromatic proton).

Anal. Calcd. for $C_{15}H_{22}ClNO_3$: C, 60.09; H, 7.40. Found: C, 59.87; H, 7.67.

*4,7-Dimethoxy-2-(dimethylamino)methyl-6-methyl-1-indanol (**17***g*) Hydrochloride*

A solution of 4,7-dimethoxy-2-(dimethylamino)methyl-6-methyl-1-indanone hydrochloride (2.0 g) in methanol (25 ml) was reduced to the indanol (**17***g*) with sodium borohydride (1.0 g) using essentially the same method as described above for the preparation of **10***a*, method *i*. The chloroform extract of the indanol (**17***g*) was saturated with HCl gas and evaporated to yield the title compound (1.1 g), m.p. 193–194° (from ethanol); i.r. ν_{max} 2450, 2610 br ($\overset{+}{N}$—H), 3310 br (OH) cm^{-1}.

Anal. Calcd. for $C_{15}H_{24}ClNO_3$: C, 59.69; H, 8.01; N, 4.64. Found: C, 59.69; H, 7.83; N, 4.65.

*4,7-Dimethoxy-2-(dimethylamino)methyl-5-methylindane (**16***g*) Hydrochloride*

A solution of 4,7-dimethoxy-2-(dimethylamino)methyl-6-methyl-1-indanol hydrochloride (1.0 g) in dioxane (20 ml) and concentrated HCl (20 ml) containing 10% Pd–C (0.5 g) was hydrogenated at 40 p.s.i. and room temperature for 12 h (arbitrary). The filtrate was evaporated and the residue obtained was shaken with dry acetone and filtered. The insoluble material (0.67 g) was crystallized from ethanol–ether to yield the title compound, m.p. 204–205°; i.r. ν_{max} 2560 br, 2610 br ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{15}H_{24}ClNO_2$: C, 63.00; H, 8.46; N, 4.90. Found: C, 62.52; H, 8.72; N, 4.54.

*4,7-Dimethoxy-6-methyl-1-indanone Oxime (**19***a*)*

A solution of 4,7-dimethoxy-6-methyl-1-indanone (7.0 g), hydroxylamine hydrochloride (7.0 g), and pyridine (8 ml) in ethanol (100 ml) was heated at 80° with stirring for 20 min and cooled. A solid precipitated and was washed repeatedly with 5% HCl then crystallized from methanol to yield the title compound (5.7 g), m.p. 228–231°; i.r. ν_{max} 3250 (OH) cm^{-1}.

Anal. Calcd. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83. Found: C, 65.10; H, 6.79.

*4,7-Dimethoxy-1-indanone Oxime (**19***b*)*

This compound (2.1 g), m.p. 230–232° (from ethanol) was obtained in the same manner from 4,7-dimethoxy-1-indanone (2.5 g); i.r. ν_{max} 3210 (OH) cm^{-1}.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 64.06; H, 6.56; N, 6.67.

*1-Amino-4,7-dimethoxy-6-methylindane (**20a**)*

(*i*) A suspension of finely powdered 4,7-dimethoxy-6-methyl-1-indanone (4.5 g) in sodium-dried ether (200 ml) was added slowly to a stirred suspension of lithium aluminum hydride (1.0 g) in the same solvent (100 ml). The mixture was heated under reflux for 30 h, cooled, and the excess hydride decomposed by the careful addition of cold water. The suspension was filtered and the insoluble material washed well with ether. The combined ether extract was dried ($MgSO_4$) and saturated with HBr gas. The title compound (4.8 g) precipitated, m.p. 214–215° (from ethanol); i.r. ν_{max} 1590, 1998, 2580–2680 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{12}H_{18}BrNO_2$: C, 50.01; H, 6.29; N, 4.86. Found: C, 50.04; H, 6.42; N, 4.86.

(*ii*) A solution of 4,7-dimethoxy-6-methyl-1-indanone oxime (2.0 g) in ethanol (50 ml) containing PtO_2 (0.1 g) was hydrogenated at room temperature and normal pressure for 12 h. The filtrate was evaporated and the residue dissolved in ether. This solution was saturated with HBr gas to yield the title compound (1.84 g), m.p. 214–215°.

*1-Amino-4,7-dimethoxyindane (**20b**) Hydrochloride*

A solution of 4,7-dimethoxy-1-indanone oxime (1.2 g) in glacial acetic acid (25 ml) and concentrated H_2SO_4 (1 ml) was hydrogenated over 10% Pd–C (0.3 g) until the theoretical volume of hydrogen was absorbed (6 h). The filtrate was neutralized ($NaHCO_3$) and evaporated. The residue was suspended in 5% $NaHCO_3$ solution (25 ml) and extracted with chloroform (3 × 25 ml). The chloroform extract was washed (H_2O), dried ($MgSO_4$), saturated with gaseous HBr and evaporated to yield the title compound (1.1 g), m.p. 225–226° (from ethanol); i.r. ν_{max} 1590, 1982, 2600–2700 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{11}H_{16}BrNO_2$: C, 48.19; H, 5.88; N, 5.11. Found: C, 48.06; H, 5.79; N, 4.82.

*1-Amino-6-bromo-4,7-dimethoxyindane (**20c**) Hydrochloride*

A slight excess of bromine water was added dropwise to a stirred solution of 1-amino-4,7-dimethoxyindane hydrochloride (0.5 g) in water (20 ml). The pale red solution was stirred for a further 2 h, basified (10% NaOH) and extracted with ether (2 × 50 ml). The ether solution was dried ($MgSO_4$), saturated with gaseous HCl and evaporated to give an oil which solidified on standing. This was assumed to be the title compound (0.21 g), m.p. 217–219°, (from ethanol–acetone); i.r. ν_{max} 1602, 2010, 2580–2680 ($\overset{+}{N}$—H) cm^{-1}; mass spectrum *m/e* (% relative abundance) 162 (100), 273 (58) ($C_{11}H_{14}{}^{81}BrNO_2$), 271 (60) ($C_{11}H_{14}{}^{79}BrNO_2$).

Anal. Calcd. for $C_{11}H_{15}BrClNO_2$: C, 42.81; H, 4.90; N, 4.54. Found: C, 42.70; H, 4.70; N, 4.79.

*1-Dimethylamino-4,7-dimethoxy-6-methylindane (**21**) Hydrochloride*

This compound (0.42 g), m.p. 209–211° (from ethanol) was prepared from 1-amino-4,7-dimethoxy-6-methylindane hydrochloride (1.5 g) using the method described for the synthesis of **16***f*-hydrochloride; i.r. ν_{max} 1602, 2300–2600 ($\overset{+}{N}$—H) cm^{-1}.

Anal. Calcd. for $C_{14}H_{22}ClNO_2$: C, 61.86; H, 8.16; N, 5.15. Found: C, 62.00; H, 8.17; N, 5.58.

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