such an interaction cause a decrease in androgenic activity. James and Roberts[5] have demonstrated that solubilities in organic solvents can be dependent on the area of the α face available for contact with that of a neighboring molecule. This in turn influences the distribution coefficient. While not disagreeing in principle with Ringold's theory, it is suggested that separation of steric and solubility effects may lead to a better understanding of these structural requirements.

Acknowledgments. One of us (M. A. Q. C.) thanks the University of Wales Institute of Science and Technology for a research scholarship. We are grateful to Dr. D. J. Bailey for his advice on the preparation and characterization of the esters and to Mr. D. M. Ellis for his guidance in the statistical evaluation of the results.

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Potential Psychotomimetics. 2.[1] Rigid Analogs of 2,5-Dimethoxy-4-methylphenylisopropylamine (DOM, STP)

David E. Nichols,[2] Charles F. Barfknecht,*

Division of Medicinal Chemistry, College of Pharmacy, University of Iowa, Iowa City, Iowa 52242

John P. Long,

Department of Pharmacology, University of Iowa, Iowa City, Iowa 52242

Robert T. Standridge, Henry G. Howell, Richard A. Partyka,

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201

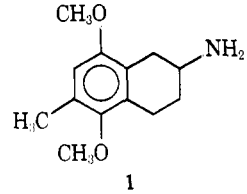
and Donald C. Dyer

Department of Pharmacology and the Anesthesia Research Center, School of Medicine, University of Washington, Seattle, Washington 98195. *Received May 11, 1973*

2-Amino-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalene and 2-amino-4,7-dimethoxy-5-methylindan were prepared as rigid analogs of psychotomimetic phenylisopropylamines. Neither compound appeared to have psychotomimetic activity in rats. The effect of the aminotetralin derivative on 5-HT receptors in rat fundus strips and sheep umbilical arteries was also studied.

Early investigators studied 2-amino-1,2,3,4-tetrahydronaphthalene derivatives (aminotetralins) as lysergic acid congeners.[3,4] More recently, other workers have approached aminotetralins as rigid analogs of psychotomimetic phenylisopropylamines.[1,5,6] Cooper and Walters[7] found that for mescaline-like activity, racemic *trans*-2-(3,4,5-trimethoxyphenyl)cyclopropylamine was much more potent than the cis isomer. Although this finding supports a transoid conformation of the ethylamine side chain of psychotomimetics at the receptor, it does not indicate the relative conformation of the side chain with respect to the plane of the aromatic ring. Since 2,5-dimethoxy-4-methylphenylisopropylamine (DOM, STP) is a potent hallucinogen, it was decided to prepare and test compounds **1** (DOM-AT) and **2** (DOM-AI) to determine whether they possessed similar activity. Compound **1** was prepared by two independent routes, outlined in Schemes I and II, and the aminoindan derivative **2** was prepared as shown in Scheme III.

Examination of Dreiding models indicates that for **1** the distance from the center of the aromatic ring to the amino nitrogen is approximately 5.2 Å. When the nitrogen is in an axial conformation, it is approximately 1.3 Å above the plane of the ring, but when it is equatorial it lies nearly in the plane of the ring. For **2**, which is a rigid structure, the Ar–N distance is about 4.6 Å and the nitrogen is about 1.2 Å above the plane of the aromatic ring. Thus, based on recently proposed correlations,[8,9] **1** would be predicted to most closely correspond to the structure of LSD.



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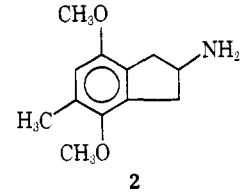
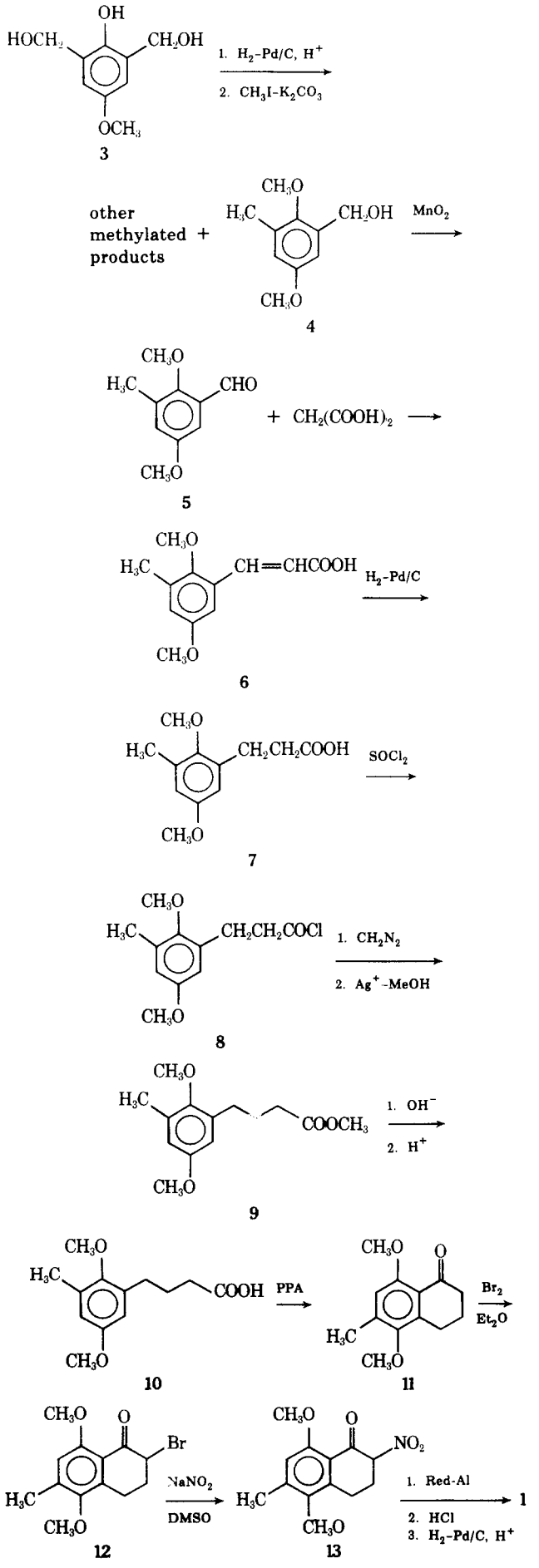


2

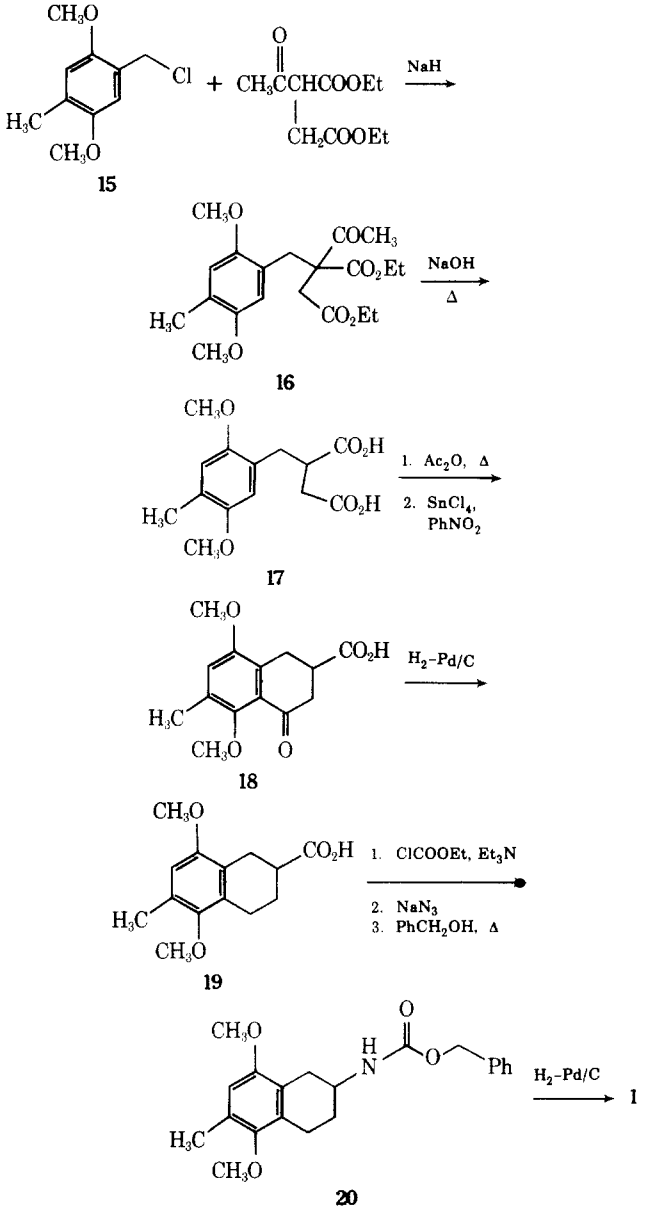
Experimental Section

A. Chemistry. All boiling points are uncorrected. Melting points were determined in open glass capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab Ltd., Indianapolis,

Scheme I



Scheme II

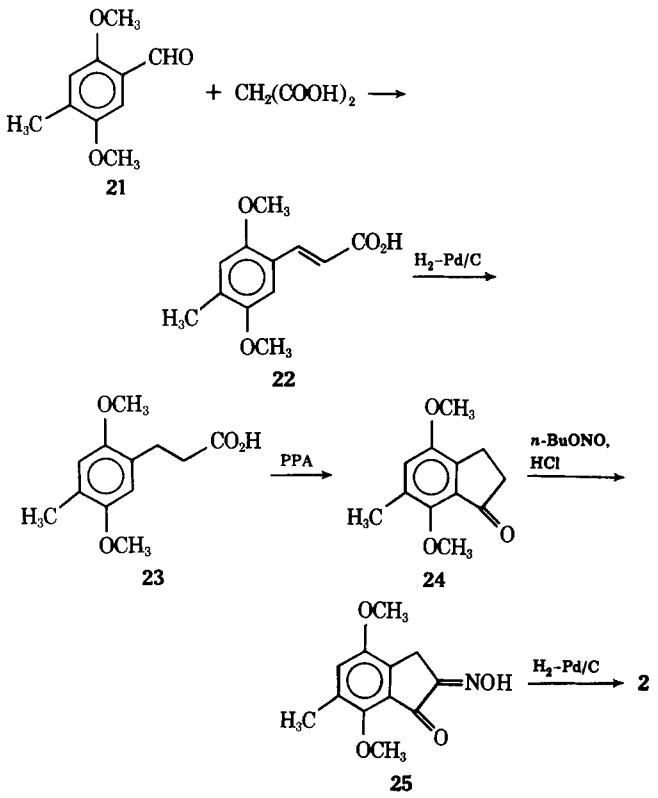


Ind., by the Division of Medicinal Chemistry, University of Iowa, and by the Analytical section of Bristol Labs. Where analyses are indicated by symbols of the elements, the analytical results obtained were within ±0.4% of the theoretical values. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates T-60 spectrometer using tetramethylsilane as an internal standard.

Catalytic Reduction of 3. A solution of 184 g (1.0 mol) of 2,6-di(hydroxymethyl)-4-methoxyphenol[10] in 1 l. of 95% EtOH was warmed to 50° and 1.5 ml of concentrated H_2SO_4 added. The mixture was shaken over 2.0 g of 10% Pd/C in a 2-l. Parr bottle at 50 psig. The reduction was stopped at 3.5 hr, at which time 1.0 mol of H_2 had been absorbed. The catalyst was removed by filtration and the filtrate was stirred with solid $NaHCO_3$ until the alcoholic solution was no longer acidic. (Failure to completely neutralize the acid at this point results in decomposition of the reduction products.) The neutral solution was then filtered. Tlc analysis (silica gel–ether) showed three components of R_f 0.66, 0.62, and 0.35. The solvent was removed *in vacuo* and the residual mass used directly in the next step.

2,5-Dimethoxy-3-methylbenzyl Alcohol (4). The total residue from the reduction of 3 was dissolved in 250 ml of dry Me_2CO. Methyl iodide, 153 g (1.08 mol), and 141 g (1.02 mol) of anhydrous K_2CO_3 were added and the mixture was stirred and heated at reflux for 48 hr. The reaction was cooled and filtered, the Me_2CO was removed *in vacuo*, and the residue was taken up into Et_2O. The Et_2O solution was filtered, washed with 10% NaOH to

Scheme III



remove unalkylated phenolic products, and then washed with H_2O until the washings were neutral. The Et_2O was dried (Na_2SO_4) and removed, and the residual oil was vacuum distilled. The fraction with bp 94–96° (0.1 mm) was collected [lit.[11] bp 109–116° (0.6 mm)]: yield 83.6 g (45.5% based on **3**). The thin-layer chromatographic mobility (R_f 0.22 silica gel–ether) and ir and nmr spectra of this material were identical with those of authentic material prepared by the method of Sayigh, *et al.*[11]

2,5-Dimethoxy-3-methylbenzaldehyde (5). To a solution of 54.6 g (0.30 mol) of **4** in 500 ml of dry C_6H_6, 173.9 g (2.0 *M*) of activated MnO_2 (Winthrop Special Chemicals Div.) was added. The mixture was heated at reflux and stirred overnight maintaining continuous H_2O removal with a Dean-Stark tube (12.5 ml of H_2O collected). The MnO_2 was removed by filtration (Celite) and the C_6H_6 distilled off under reduced pressure. The residue was recrystallized from hexane: mp 42.5–43° (lit.[11] mp 40–41°); yield 45.1 g (83.5%).

2,5-Dimethoxy-3-methylcinnamic Acid (6). The aldehyde **5** (79.2 g, 0.44 mol), 95.5 g (0.82 mol) of malonic acid, 190 ml of pyridine, and 3.6 ml of piperidine were heated on the steam bath for 2.5 hr. The mixture was cooled and poured with stirring into a mixture of 300 ml of concentrated HCl and 1200 ml of ice–H_2O. The solid was collected by filtration and recrystallized from EtOH–H_2O: mp 166–167°; yield 94.7 g (97%). *Anal.* ($C_{12}H_{14}O_4$) C, H.

3-(2,5-Dimethoxy-3-methylphenyl)propionic Acid (7). The cinnamic acid **6** (44.5 g, 0.2 mol) was dissolved in 800 ml of 95% EtOH and shaken over 2 g of 10% Pd/C at 40 psig of H_2 pressure. The theoretical amount of H_2 was taken up in less than 1 hr. The catalyst was removed by filtration and the residue recrystallized from C_6H_6–hexane: mp 87.5–88.5°; yield 44.1 g (98.2%). *Anal.* ($C_{12}H_{16}O_4$) C, H.

3-(2,5-Dimethoxy-3-methylphenyl)propionyl Chloride (8). The reduced acid **7** (22.4 g, 0.10 mol) was dissolved in 80 ml of dry Et_2O. $SOCl_2$, 53 ml (0.74 mol), was added and the solution heated at reflux for 4.5 hr. The Et_2O and excess $SOCl_2$ were removed *in vacuo* and the acid chloride was vacuum distilled: bp 129–130° (1.0 mm). *Anal.* ($C_{12}H_{15}ClO_3$) C, H.

Methyl 4-(2,5-Dimethoxy-3-methylphenyl)butyrate (9). Following the method of Elmore and King,[12] 18.75 g (77.5 mmol) of the acid chloride **8** was slowly added, in two portions, to two 340-ml portions of an Et_2O solution of CH_2N_2, each portion containing 5.1 g (0.121 mol) of CH_2N_2. The solutions were allowed to sit overnight at room temperature and then the Et_2O was removed under reduced pressure. The residual yellow oil was taken up into 180 ml of MeOH, and a 10% solution of silver benzoate in Et_3N was added dropwise. Gas evolution began after addition of a few drops and the silver benzoate solution was added at a rate sufficient to maintain vigorous N_2 evolution. After reaction had slowed considerably, the solution was heated to reflux for 0.5 hr. After cooling, the mixture was filtered and the MeOH removed *in vacuo*. The residual oil was vacuum distilled: bp 122–124° (0.15 mm); yield 17.1 g (88%). An analytical sample was crystallized as fine white needles from Et_2O–hexane, mp 33–33.5°. *Anal.* ($C_{14}H_{20}O_4$) C, H.

4-(2,5-Dimethoxy-3-methylphenyl)butyric Acid (10). The ester **9** (7.7 g, 30 mmol) was refluxed 4 hr with a solution of 6 g of KOH pellets in 20 ml of H_2O. The solution was cooled, acidified with concentrated HCl, and extracted several times with Et_2O. The Et_2O was dried (Na_2SO_4) and removed under reduced pressure, and the residue was recrystallized from hexane: mp 39.5–40.5°; yield 6.93 g (97%). *Anal.* ($C_{13}H_{18}O_4$) C, H.

3,4-Dihydro-5,8-dimethoxy-6-methyl-1(2*H*)-naphthalenone (11). Compound **10** (5 g, 22 mmol) was stirred with 100 g of PPA for 35 min at 80°. The reaction was poured over 300 g of ice–H_2O and the resulting oil extracted into Et_2O. The Et_2O was washed with H_2O and 5% $NaHCO_3$ and dried (Na_2SO_4). The residual oil obtained after removal of the solvent was vacuum distilled, bp 149–150° (0.1 mm), and the desired tetralone obtained as an extremely viscous pale yellow oil: yield 4.0 g (86.5%). *Anal.* ($C_{13}H_{16}O_3$) C, H.

2-Bromo-3,4-dihydro-5,8-dimethoxy-6-methyl-1(2*H*)-naphthalenone (12). By a modification of the method of Wilds,[13] 3.9 g (17.7 mmol) of the tetralone **11** was dissolved in 100 ml of dry Et_2O and cooled to 5°. A solution of 2.84 g (17.8 mmol) of Br_2 in 10 ml of $CHCl_3$ was added dropwise over 0.5 hr. A yellow precipitate initially formed which dissolved on stirring a further 3 hr. The solution was washed with 2 × 100 ml of H_2O, 2 × 150 ml of 5% $NaHCO_3$, and then with water until the washing were neutral. The Et_2O was dried (Na_2SO_4) and removed under reduced pressure. The residue was recrystallized from EtOAc–hexane: mp 77–78°; yield 4.3 (81%). *Anal.* ($C_{13}H_{15}BrO_3$) C, H.

2-Nitro-3,4-dihydro-5,8-dimethoxy-6-methyl-1(2*H*)-naphthalenone (13). Following a modification of the method of Kornblum, *et al.*,[14] 3.89 g (13 mmol) of the bromo ketone **12** was added to a solution of 1.79 g (26 mmol) of $NaNO_2$ and 2.27 g (14 mmol) of phloroglucinol in 12 ml of dry DMSO, and the mixture was stirred for 2 hr. The solution was then poured into 250 ml of cold H_2O and the precipitated solid collected by filtration and recrystallized from absolute EtOH (carbon): mp 141–142°; yield 2.2 g (63.7%). *Anal.* ($C_{13}H_{15}NO_5$) C, H, N.

2-Amino-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalene Hydrochloride (1). The nitrotetralone **13**, 1.51 g (5.7 mmol), was dissolved in 100 ml of dry C_6H_6 and added to a stirring solution of 13.15 g (45.6 mmol) (as a 70% solution) of bis(2-methoxyethoxy)aluminum hydride (Red-Al, Aldrich) in 50 ml of C_6H_6. After addition, 50 ml of C_6H_6 was added to the reaction. The solution was heated at reflux with stirring for 8 hr and then cooled and excess Red-Al decomposed by addition of 100 ml of H_2O. The C_6H_6 layer was separated and the H_2O phase filtered to remove alumina salts and then extracted with 3 × 100 ml of $CHCl_3$. The $CHCl_3$ and C_6H_6 solutions were combined and dried (Na_2SO_4), and the solvents were removed under reduced pressure. The residue was taken up into Et_2O–$CHCl_3$ (4:1) and dry HCl added to precipitate the salt. The aminotetralol salt as isolated was very hygroscopic and was dried in a vacuum dessicator: yield 0.97 g (62%); mp (crude) 80–84°. The crude amino alcohol hydrochloride **14**, 950 mg (3.48 mmol), 19 ml of AcOH, 0.5 ml of 70% $HClO_4$, and 500 mg of 10% Pd/C were placed in a 500-ml Parr bottle and shaken at an initial H_2 pressure of 50 psig. Shaking was continued for 5 hr at room temperature, at which time H_2 uptake had ceased with about 75% of the theoretical amount absorbed. The catalyst was removed by filtration. To the filtrate was added 1.6 g of KOAc; the mixture was stirred for 10 min and then filtered to remove precipitated $KClO_4$. The filtrate was concentrated *in vacuo* and the residual oil taken up into 50 ml of H_2O and basified with 10% NaOH solution. The basic solution was extracted with 3 × 50 ml of Et_2O; the Et_2O extracts were combined and washed with H_2O until the washings were neutral. The Et_2O was removed under reduced pressure and the residual oil diluted with C_6H_6 and reduced *in vacuo* several times to remove traces of H_2O. The residual brown oil was taken up into dry Et_2O and the HCl salt precipitated with dry HCl gas and collected by filtration. The salt was twice recrystallized from *i*-PrOH–Et_2O (charcoal) to

Table I. Effect of DOM-AT (1) on the Conditioned Avoidance Response

Dose, μmol/kg	Effect
10	Increase in response time and slight disruptive effect immediately after injection lasting for 30–40 min
20	Similar effect to above but somewhat more pronounced
40	Initial disruption somewhat less and after 40–50 min a stimulant effect similar to 1 mg/kg of *d*-amphetamine sulfate.[a] Rats initially appeared sedated, had reduced activity between trials, and assumed a relaxed posture with feet hanging between the bars of the floor grid. Subjectively the effects seemed to resemble more closely those observed previously for 2-amino-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (5,8-ADT),[b] producing a decrease in spontaneous activity while leaving the animals alert
80	Immediate severe hindlimb ataxia which produced an increase in response time and disruption.[c] When, after approximately 30 min, use of the hindlimbs was regained, amphetamine-like stimulant activity was observed, with a corresponding enhancement of performance over controls. Heavy salivation and pilomotor erection were evident at this dose

[a] See ref 20. [b] See ref 24. [c] Two albino rats (175 and 180 g) which were given iv injections of 20 and 40 μmol/kg, respectively, of DOM-AT (1) immediately became flaccid, walked backward, and showed pilomotor erection and hindlimb ataxia. These rats also appeared sedated but could respond to external stimuli.

Table II. Effect of DOM-AI (2) on the Conditioned Avoidance Response

Dose, μmol/kg	Effect
40–80	Very slight increase in initial response time
120	Effects similar to 40 mol/kg of DOM-AT (1), having almost no initial effect but followed by slightly enhanced performance 40–50 min after injection. Heavy salivation was frequently noted at this dose
160	Marked increase in response time with some disruption of the CAR. Heavy salivation was noted at this dose

yield 388 mg (43.5%) of white crystals, mp 237.5–238.5° (overall yield from nitrotetralone, 27%). Recrystallization from MeCN gave mp 239–240.5°. *Anal.* $C_{13}H_{20}ClNO_2$) C, H, N, Cl.

Diethyl 2-Acetyl-2-(2,5-dimethoxy-4-methylbenzyl)succinate (16). To a stirred solution, under N_2, of 48.4 g (0.224 mol) of diethyl acetylsuccinate in 250 ml of anhydrous DMF was added, portionwise, 9.43 g (0.224 mol) of 57% NaH dispersion in mineral oil. A vigorous reaction occurred, heat was evolved, and the mixture assumed a deep reddish-brown color. When the reaction had moderated, the mixture was heated at 45–50° until H_2 evolution had ceased (*ca.* 30 min). The heat source was removed and a solution of 45 g (0.224 mol) of 2,5-dimethoxy-4-methylbenzyl chloride (15)[15] in 250 ml of anhydrous DMF was added over a period of 3 min. After a few minutes the color of the mixture lightened, a finely divided solid began to separate, and heat was again evolved. The temperature was maintained at 45–50° for 1 hr and the reaction mixture was then stirred at ambient temperature under N_2, for 18 hr.

The mixture was poured into ice-H_2O and the oil which separated was extracted into Et_2O. The solvent was evaporated, the residue was dissolved in MeCN, and mineral oil was removed by extraction with pentane (two portions). The MeCN was evaporated and the product was stripped of volatiles at 70° (4 mm). There was obtained 79.4 g (93%) of the ester 16 as a thick amber oil. Glc showed this material to be 97% pure and it was used directly in the next step.

Distillation provided an analytical sample, bp 158–166° (0.15 mm), as a thick straw-colored oil. *Anal.* ($C_{20}H_{28}O_7$) C, H.

2-(2,5-Dimethoxy-4-methylbenzyl)succinic Acid (17). A mixture of 76.4 g (0.201 mol) of acetyl succinate 16 and 24.1 g (0.603 mol) of NaOH in 1 l. of H_2O was stirred and refluxed for 17 hr. The solution was cooled and a small amount of insoluble oil was removed by Et_2O extraction. The alkaline solution was chilled (ice-H_2O) and acidified with concentrated HCl. The oily product solidified upon stirring and scratching. The solid was filtered, washed with H_2O, air-dried, pulverized, washed thoroughly with H_2O, and finally oven-dried to give 48.2 g of crude material. This was dissolved in a minimum amount of boiling $MeNO_2$ (*ca.* 400 ml); the solution was filtered, seeded, and cooled to 0° with occasional agitation. As soon as precipitation was complete, the colorless crystals were filtered, washed, and oven-dried (110°) to yield 38.7 g (68%) of 17, mp 161–163°. *Anal.* ($C_{14}H_{18}O_6$) C, H.

5,8-Dimethoxy-6-methyl-4-oxo-1,2,3,4-tetrahydro-2-naphthoic Acid (18). A solution of 17.5 g (62 mmol) of diacid 17 in 175 ml of Ac_2O was heated at reflux for 2 hr. The Ac_2O was removed under reduced pressure; the solid anhydride was flashed down with three portions of toluene and stripped at 100° (4 mm).

The anhydride was suspended in 175 ml of nitrobenzene and 18 ml (40.2 g, 154 mmol) of anhydrous $SnCl_4$ was added all at once. The mixture was stirred under anhydrous conditions at ambient temperature for 66 hr. The dark solution was poured into 700 ml of ice-H_2O and 100 ml of concentrated HCl; the mixture was layered with 700 ml of Skellysolve B and stirred until the product separated as a tan solid. This solid was filtered and washed well with Skellysolve B and with H_2O. The wet cake was stirred with *ca.* 300 ml of dilute $KHCO_3$ solution for 5 min. The mixture was filtered and the filtrate was acidified with concentrated HCl. The solid was filtered, washed with H_2O, and oven-dried (110°). The brownish melt thus obtained, when pulverized, had mp 133–134.5°. The yield of 18 was 11.9 g (73%). *Anal.* ($C_{14}H_{16}O_5$) C, H.

5,8-Dimethoxy-6-methyl-1,2,3,4-tetrahydro-2-naphthoic Acid (19). To a solution of 6.4 g (24.2 mmol) of keto acid 18 in 100 ml of glacial AcOH was added 2 ml of 60% aqueous $HClO_4$ and 1.5 g of 10% Pd/C. The mixture was hydrogenated at an initial gauge pressure of 3 atm; after 35 min the pressure drop corresponded to theoretical H_2 uptake. Sodium acetate (1.5 g) was added, the mixture was agitated, and the solids were filtered. The filtrate was concentrated under reduced pressure until a solid began to separate. Dilution with H_2O gave a colorless solid which was recrystallized from MeOH-H_2O. The yield of 19 was 5.31 g (83%), mp 150.5–152°. *Anal.* ($C_{14}H_{18}O_4$) C, H.

2-Carbobenzoxamido-5,8-dimethoxy-6-methyl-1,2,3,4-tetrahydronaphthalene (20). The acid 19 was converted to the corresponding isocyanate by the general method of Weinstock[16] utilizing 4.0 g (16 mmol) of 19 and proportionate quantities of other reagents. The oily isocyanate was dissolved in 25 ml of anhydrous benzyl alcohol and the solution was heated on the steam bath, under anhydrous conditions, for 6 hr.

The excess benzyl alcohol was removed under reduced pressure, giving an oil which crystallized upon standing. Recrystallization from Skellysolve C provided 5.22 g (92%) of 20 as fluffy, straw-colored needles, mp 134–136°. *Anal.* ($C_{21}H_{25}NO_4$) C, H, N.

5,8-Dimethoxy-6-methyl-1,2,3,4-tetrahydro-2-naphthylamine Hydrochloride (1). A suspension of 4.0 g (11.3 mmol) of carbamate 20 and 0.5 g of 10% Pd/C in 200 ml of anhydrous MeOH was hydrogenated at an initial gauge pressure of 3 atm for 30 min. Filtration of the catalyst and evaporation of the solvent gave 2.7 g of a yellowish oil. Salt formation with dry HCl in Et_2O gave a gelatinous mass; evaporation of the mixture provided a solid which was dissolved in MeOH. The solution was filtered through hard filter paper and the filtrate was evaporated. The residue was recrystallized to give 1.77 g (61%) of pure 1 as described above.

2,5-Dimethoxy-4-methylcinnamic Acid (22). A solution of 25 g (0.139 mol) of 2,5-dimethoxy-4-methylbenzaldehyde (21), 29.2 g (0.280 mol) of malonic acid, 50 ml of anhydrous pyridine, and 2 ml of anhydrous piperidine was allowed to react according to the method of Koo, *et al.*[17] After acidification, the solid product was filtered, washed with 1 l. of ice-H_2O, and recrystallized from EtOH-H_2O: mp 163–166°; yield 31 g (99%). *Anal.* ($C_{12}H_{14}O_4$) C, H.

3-(2,5-Dimethoxy-4-methylphenyl)propionic Acid (23). A mixture of 31 g (0.139 mol) of 22, 1.5 g of 10% Pd/C, and 200 ml of absolute EtOH was hydrogenated at 50 psi for 1 hr. The catalyst and solvent were removed and the solid was recrystallized

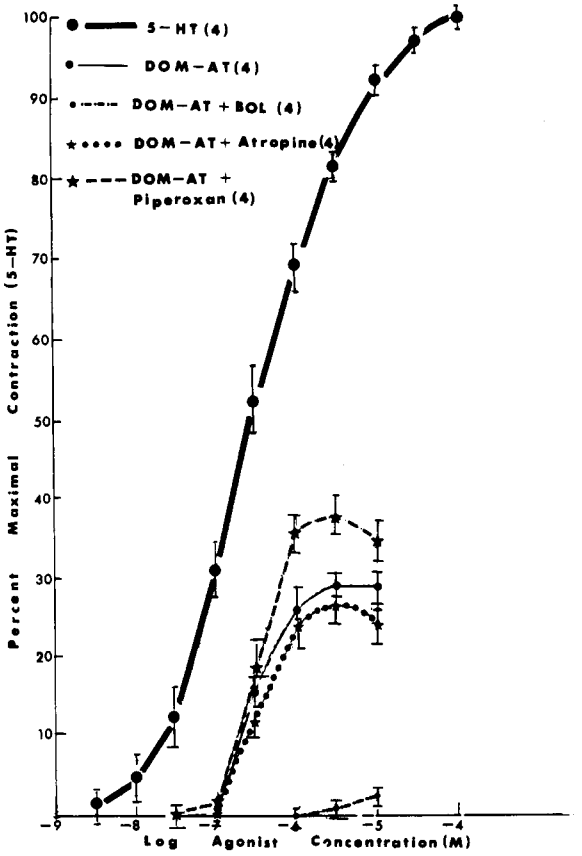


Figure 1. Isolated sheep umbilical arteries. Contractions produced by DOM-AT were not blocked by either atropine (1.2×10^{-7} *M*) or piperoxan (3.7×10^{-7} *M*) but were antagonized by 2-bromolysergic acid diethylamide (BOL, 2.5×10^{-7} *M*). All antagonists were equilibrated with tissue for 15 min prior to adding DOM-AT. Numbers in parentheses indicate the number of experiments. Vertical bars are ±S.E.M.

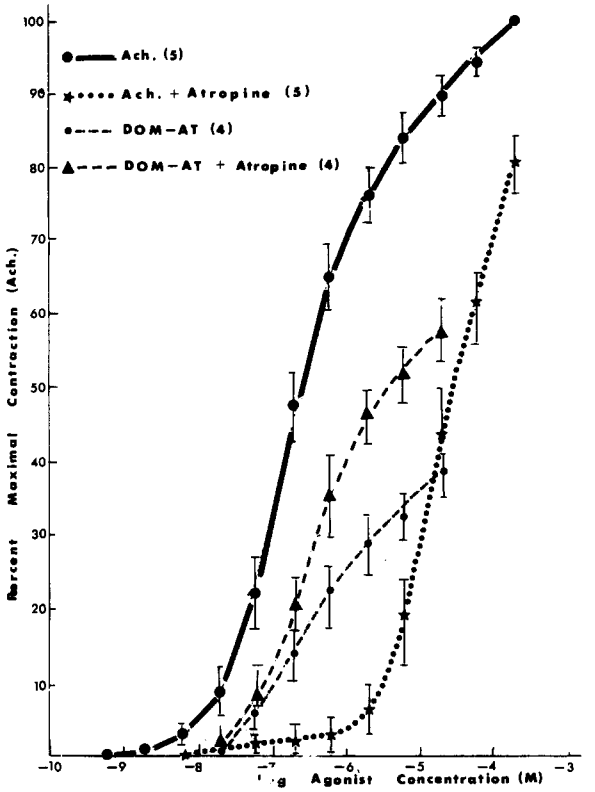


Figure 2. Isolated rat fundus strips. Maximal responses were obtained on all tissues to acetylcholine prior to studying the effect of DOM-AT. Atropine (5×10^{-7} *M*) was equilibrated with tissue for 10 min prior to adding either DOM-AT or ACh. It is clear that atropine greatly blocked responses to acetylcholine but not DOM-AT. The numbers in brackets indicate the number of experiments. Vertical bars are ±S.E.M.

from CH_3NO_2: mp 111–112°; yield 28.1 g (90.5%). *Anal.* ($C_{12}H_{16}O_4$) C, H.

4,7-Dimethoxy-5-methyl-3-indanone (24). The procedure of Koo was essentially followed.[18] To 50 g of stirred polyphosphoric acid was added 2.25 g (0.01 mol) of **23** portionwise. The mixture was allowed to remain at ambient temperature 1 hr, heated to 100° for 10 min, and then cooled, and 100 ml of ice-H_2O was added. Extraction with ether was followed by washing with H_2O, saturated $NaHCO_3$, and saturated NaCl. Drying (Na_2SO_4) and removal of solvent gave 2.2 g of crystalline material. After recrystallization from Skellysolve B, there was obtained 2.1 g (99%) of needles, mp 105–107°. *Anal.* ($C_{12}H_{14}O_3$) C, H.

2-Nitroso-4,7-dimethoxy-5-methyl-3-indanone (25). Following the method of Huebner,[19] a solution of 5 g (0.024 mol) of **24**, 3.5 ml (0.030 mol) of *n*-butyl nitrite, and 15 ml of absolute EtOH was stirred at 10–15° while 1 ml of concentrated HCl was added dropwise. The mixture was slowly warmed at 45° and maintained at this temperature for 1.25 hr. (CAUTION: When 45° was approached, the reaction became very exothermic and cooling was required to maintain 45°.) The mixture was cooled and diluted with 50 ml of cold H_2O and the solid was removed by filtration. After recrystallization from MeCN, there was obtained 3.5 g (60%) of product, mp 230–231°. *Anal.* ($C_{12}H_{13}NO_4$) C, H, N.

2-Amino-4,7-dimethoxy-5-methylindan Hydrochloride (2). A mixture of 2.05 g (0.0087 mol) of **25**, 1 g of 10% Pd/C, 100 ml of glacial acetic acid, and 1 ml of concentrated H_2SO_4 was shaken with H_2 at 55 psi for 16 hr. The catalyst was removed and the solution was made strongly basic (40% NaOH) and extracted with ether. The combined extracts were washed with water and saturated NaCl and dried ($NaSO_4$). After removing the solvent, the resulting oil was dissolved in anhydrous ether and treated with etheral HCl until precipitation was complete. Recrystallization from *i*-PrOH–Skellysolve B afforded 0.95 g (45%) of product, mp 263–265°. *Anal.* ($C_{12}H_{17}NO_2HCl$) C, H, N, Cl.

B. Conditioned Avoidance Studies. Compounds 1 and 2 were tested for an effect on the conditioned avoidance response as detailed previously.[20] Compounds were administered ip as the hydrochloride salts dissolved in physiological saline at a concentration such that animals received 0.01 ml per 10 g of body weight.

C. Studies at Serotonin Receptors. Responses to drugs were studied on isolated rat fundus strips prepared from albino rats (Sprague–Dawley) according to the method of Vane.[21] The fundus strips were suspended in 10-ml isolated organ baths and bathed in Krebs–Henseleit solution containing one-fourth the usual calcium concentration. The temperature of the bath was maintained at 37° and the Krebs–Henseleit solution was oxygenated with 95% O_2–5% CO_2. Isotonic contractions under a 1-g load were magnified tenfold and recorded on a kymograph. All tissues were allowed to equilibrate in the isolated organ bath for 30–45 min before initiating the experiment. The maximum contraction of all tissues was established either by adding 5-hydroxytryptamine or acetylcholine in cumulative amounts by micropipets. Responses to DOM-AT were also studied by adding it to the bath in cumulative amounts by micropipets. When 2-bromolysergic acid diethylamide (BOL) or atropine were used as antagonists, they were incubated 10 min with the tissue prior to adding either acetylcholine, 5-HT, or DOM-AT. Sheep umbilical arteries were prepared as previously described.[22]

Results

In our conditioned avoidance response (CAR) studies, mescaline exhibits a disruptive effect at 100 μmol/kg.[20] DOM shows a stimulant effect at 5 μmol/kg, a pronounced disruptive effect at 10 μmol/kg, and severe disruption, usually followed by death, at 20 μmol/kg. Neither 1 nor 2 showed this profile of activity and no deaths occurred at substantially higher doses. Tables I and II outline the observed activity of the compounds. From these results it appears that DOM-AT (1) may have two components of activity, as evident by the immediate sedation and ataxia at low to moderate doses which at higher doses is later followed by stimulation. DOM-AI 2 appears somewhat similar to 1 but less potent.

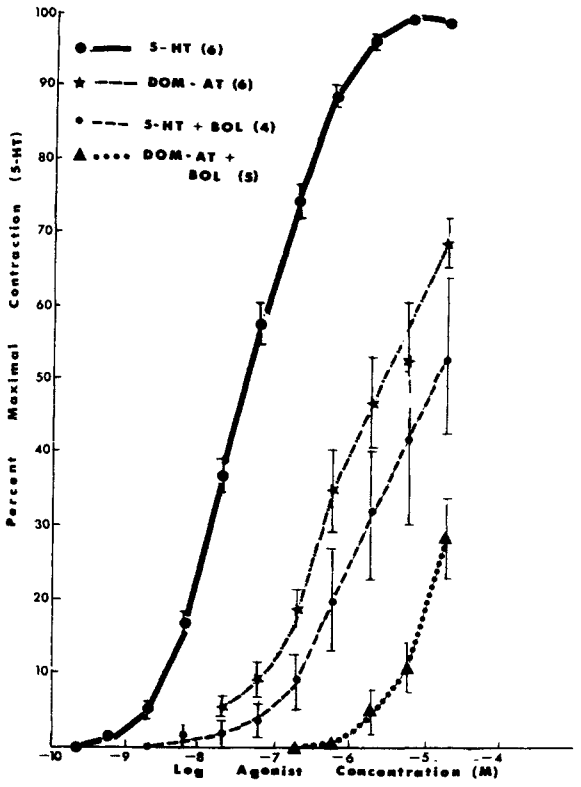


Figure 3. Isolated rat fundus strips. Maximal responses were obtained on all tissues to 5-HT prior to studying the effect of DOM-AT. 2-Bromolyseric acid diethylamide (BOL, 5×10^{-7} *M*) was equilibrated with tissue for 10 min before adding either 5-HT or DOM-AT. The numbers in brackets indicate the number of experiments. Vertical bars are ±S.E.M.

Although **1** is more potent than **2**, it does not produce a mescaline or DOM-like response in the dose ranges tested. However, certain features of the amphetamine type psychotomimetics are absent from **1** and **2**. In particular, most psychotomimetics show a stimulant profile at low doses, whereas for **1** and **2** sedation seems more apparent. The absence of these "classical" side effects complicates interpretation of the results in rats.

On rat fundus strips and sheep umbilical arteries (Figures 1-3) **1** (DOM-AT) clearly shows activity at 5-HT receptors. This is in contrast to similar studies done with 5,8-ADT.[1] Increased activity at 5-HT receptors may be related simply to substitution at the 6 position, although it is apparent from examination of space-filling molecular models that steric crowding forces the 5-methoxyl of DOM-AT (**1**) out of the plane of the aromatic ring. This twisting might also account for increased activity at 5-HT receptors of DOM-AT over 5,8-ADT. In the nmr spectra of DOM and 5,8-ADT, both methoxyls appear as a singlet at δ 3.78 (free base in $CDCl_3$); for DOM-AT two separate signals are recorded at δ 3.70 and 3.80. Twisting probably partially accounts for the upfield shift of the 5-methoxyl.[23] A similar situation also exists for DOM-AI (**2**). Molecular models indicate the 4-methoxyl to be forced out of plane. The nmr spectrum shows two methoxyl absorptions at δ 3.77 and 3.82. The lower activity of **2** would appear to be attributable to the unfavorable side-chain conformation.

Discussion

In our earlier report[1] it was suggested that 5-HT receptor stimulation might be related to psychotomimetic activity. It is difficult to determine if DOM-AT (**1**), which appears to have more 5-HT agonist activity than 5,8-ADT[1] or DOM-AI[25] (**2**), is psychotomimetic. It seems to have a rapid sedative effect at low doses which may account for its slight disruptive effect. Of course, fusion of the aliphatic chain into the aromatic ring may have altered the steric and electronic properties of the system and it is possible that neither **1** nor **2** is a good model for psychotomimetic activity. In any case, based on the higher potency of **1** as compared with **2**, it would appear that 5-HT receptors are of a geometry which accommodates the ethylamine side chain when it is in an extended transoid conformation.

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