with HOAc. The precipitate was separated, washed with H_2O, and dried to yield 0.7 g (73%) of 8 after recrystallization from HOAc, mp 217 °C dec. Anal. ($C_{15}H_{16}N_2O_4S$) C, H, N.

Method I. 2-Butyl-4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]-pyrimidine-7-carboxylic Acid (2e). A mixture of 8 (1.0 g, 0.0031 mol), 25 mL of concentrated HCl, and 25 mL of H_2O was refluxed in a wax bath under a N_2 atmosphere at a bath temperature of 142 °C for 17 h and 45 min. The suspension was cooled to room temperature, and the precipitate was separated, washed with H_2O, and then washed with Et_2O and dried to yield 0.6 g (64%) of 2e after recrystallization from EtOH, mp 252–254 °C. Anal. ($C_{15}H_{14}N_2O_3S$) C, H, N.

Method J. 2-Butyl-4-oxo-*N*-1*H*-tetrazol-5-yl-4*H*-pyrido-[1,2-*a*]thieno[2,3-*d*]pyrimidine-7-carboxamide (3d). A mixture of 8 (3.2 g, 0.01 mol) and CDI (9.93 g, 0.06 mol) in 100 mL of DMF was heated in a wax bath under a N_2 atmosphere with stirring at 100 to 108 °C for 70 min, cooled, and stirred at room temperature for 1 h. To the previous mixture was added 5-aminotetrazole monohydrate (2.06 g, 0.02 mol), and the mixture was heated at 100–108 °C for 90 min. The solvent was evaporated, the residue dissolved in DMF, filtered, and cooled, and the precipitate was collected and washed with MeOH to yield 1.2 g (34%) of **3d** after recrystallization from pyridine, mp 293 °C dec. Anal. ($C_{16}H_{15}N_7O_2S$) C, H, N.

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Synthesis and Serotonin-like Activity of 2-Amino-5,8-dimethoxy-6-methyl-1,2-dihydronaphthalene

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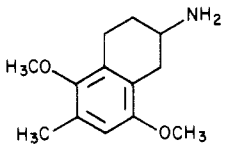
As a new type of rigid analogue for hallucinogenic phenethylamines, 2-amino-5,8-dimethoxy-6-methyl-1,2-dihydronaphthalene was synthesized. Evaluation in the rat fundus preparation showed it to be a much weaker serotonin agonist than its 1,2,3,4-tetrahydro homologue. Both the dihydro and tetrahydro compounds were able to elicit the serotonin syndrome in rats, but with the dihydro compound also appearing weaker in this assay. Both rigid analogues were less potent than the known hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM).

Our continuing interest in structure-activity relationships of centrally active phenethylamines has led us to examine several rigid congeners of hallucinogenic 1-phenyl-2-aminopropanes ("amphetamines").

In particular, several years ago the synthesis and pharmacology were reported for the tetrahydronaphthalene congener 1 of the known hallucinogenic agent



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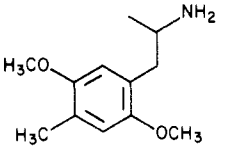

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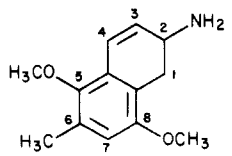

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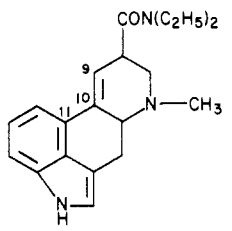

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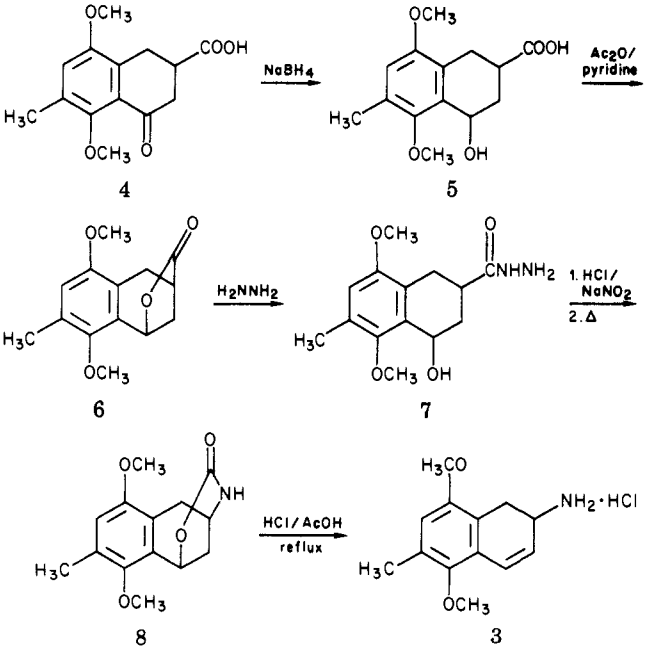
1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, STP, 2).[1] Compound 1 was found to be nondisruptive in the conditioned avoidance response in rats and to possess pharmacological effects quite different from hallucinogens such as DOM (2). The tetrahydronaphthalene congener 1 also proved to be a weak serotonin agonist in the rat fundus preparation.[1]

Scheme I



Recently, we reported that 2-amino-1,2-dihydronaphthalene possessed amphetamine-like action in mice and rats.[2] This is to be contrasted with the sedative activity of 2-amino-1,2,3,4-tetrahydronaphthalene.[3] This

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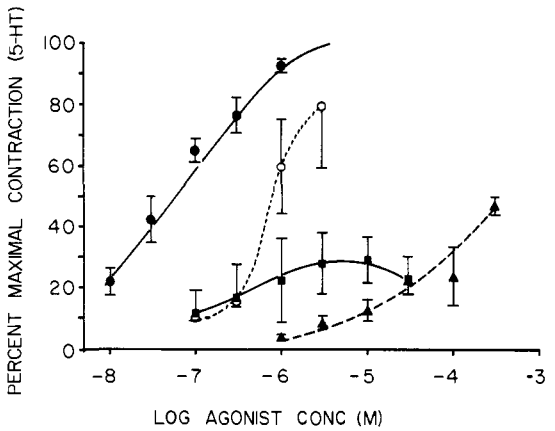

Figure 1. Effects of drugs on the isolated rat fundus preparation. Maximal responses were obtained on all tissues to 5-HT prior to studying drug effects. Serotonin (●, $n = 4$) was more potent than (−)-DOM (○, $n = 3$), which in turn was more potent than 1 (■, $n = 4$) and 3 (▲, $n = 5$). Contractions induced by all drugs were completely blocked by 10^{-6} M methysergide or cinanserin.

reversal of pharmacological effect suggested that certain parallels might occur upon introduction of a double bond into the 3,4 position of compound 1 to give the dihydronaphthalene 3.

The presence of the double bond in compound 3 could have several effects. First, it would tend to flatten the reduced ring. Second, using our recently developed hypothesis regarding binding similarities between phenethylamines and tryptamines,[4,5] it would provide a center of electron density corresponding approximately to the 10,11 region of LSD, 4, the most potent hallucinogen known.

This report details the synthesis and preliminary pharmacological examination of compound 3, which was compared with both 1 and 2 in the rat fundus and for the ability to elicit the "serotonin syndrome" in rats.[6,7]

Chemistry. The synthesis of compound 3 is shown in Scheme I. Keto acid 4 was prepared as previously described.[1] Following modifications of Violland et al.'s[8] procedure, the keto acid was reduced with borohydride to give the hydroxy acid 5. This was dehydrated to the tricyclic lactone 6 using acetic anhydride in pyridine. Treatment of the lactone with hydrazine hydrate gave the acid hydrazide 7, which was converted to the acyl azide with nitrous acid. The azide was not characterized but was immediately isolated and subjected to conditions of the Curtius rearrangement. The resulting isocyanate spontaneously cyclized to the cyclic carmabate 8. Treatment of the carbamate with HCl in acetic acid at reflux effected both carbamate hydrolysis and dehydration to yield the desired 3 as the hydrochloride salt.

Pharmacology. Compounds 1–3 were all compared for their ability to contract the rat stomach fundus preparation.[9] These compounds were also evaluated in rats for the ability to elicit the "serotonin syndrome."[6,7]

Table I. Incidence of the Serotonin Syndrome following Intraperitoneal Administration of the Hydrochloride Salts of Racemic 1, 2, or 3

		incidence				
drug	dose, mg/kg:	1	2	4	8	16
1·HCl		nt[a]	0/3	0/3	3/3	3/3
2·HCl (DOM)		1/4	5/7	5/7	7/7	nt
3·HCl		nt	0/3	1/3	0/3	2/3

[a] Not tested.

Results

Figure 1 shows the dose–response curves for serotonin (5-HT) and compounds 1–3 in the rat stomach fundus preparation. Responses to all compounds were completely antagonized by 10^{-6} M bath concentrations of methysergide, cinanserin, or metergoline, indicating that the contractions were mediated by interaction with serotonin receptors. It was previously shown that both 1 and 2 interact directly with serotonin receptors.[1,10] However, the present studies do not indicate whether the effect of 3 is direct or whether it occurs as a result of release of endogenous 5-HT. There is the possibility that these compounds may be interacting with more than one type of tryptamine receptor in the fundus.[11,12] Inspection of the dose–response curves clearly indicates the ordering of potency with DOM (2) being the most active and 3 being least active. However, at very high concentrations it is interesting that the maximum contraction which can be produced by 3 is significantly greater ($p < 0.05$) than that elicited by 1.

These in vitro results are generally confirmed in the whole animal assay. Seen in Table I are the results of the assay for ability to elicit the serotonin syndrome. Using the protocol described by Sloviter et al.,[7] animals were only scored when all three of the behavioral symptoms were present—forepaw padding, splayed hindlimbs, and head weaving or tremor. Neither 1 nor 3 was as potent as DOM. Although these data do not allow quantitative comparisons to be made, it does appear that 1 is also more potent than 3. The quantal nature of the scoring only indicates the presence or absence of the serotonin syndrome and not the frequency or intensity of the response. In the evaluations it was clear that 1 produced a quantitative response comparable in magnitude to DOM, when rats were given approximately equieffective doses of the two drugs. However, 3 did not elicit the intensity of response which was produced by either 1 or 2 at any dose tested.

Clearly, the introduction of the 3,4 double bond into 3 has not enhanced serotonin-like activity. It was originally envisioned that this modification would increase the similarity to lysergic acid, since it would tend to flatten the molecule and might provide a center of electron density corresponding to the 10,11 position of LSD. That these speculations were not borne out can possibly be attributed to at least two factors. First, the pK_a of compound 3 was measured and found to be 8.93 ± 0.05. This is about 0.6 pK unit lower than the pK_a of either 1 or 2. Although decreased basicity could be an explanation, there are several compounds that are potent serotonin agonists which have lower pK_a values. For example, the pK_a of LSD is 7.8.[13] The measured pK_a for 2-(2,5-dimethoxy-4-

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methylphenyl)cyclopropylamine, a DOM analogue with potent hallucinogen-like properties in several animal models,[14] was found to be 8.11 ± 0.04. Clearly, pK cannot be the sole factor.

Another possible explanation is the out-of-plane twisting of the 5-methoxy group. In an earlier study[1] it was noted that one of the methoxys of compound 1 was shifted upfield in the NMR spectrum. Model building clearly indicates that the 5-methoxy is sterically prevented from lying coplanar with the aromatic ring. However, in 2 both methoxys are allowed coplanarity with the aromatic ring and are observed as a single absorption in the NMR. The introduction of the 3,4 double bond in 3 does not significantly relieve this problem. There is again an observed upfield shift for one of the methoxys of about 0.1 ppm. The resulting lack of overlap between the n electrons of O(5) and the π cloud of the aromatic ring could be a significant factor in the decreased activity of both 1 and 3, relative to 2. It does not, however, indicate why 3 is less potent than 1.

Further speculation for the activity difference, at least in vitro, could be directed at the effect of extended conjugation from the aromatic ring through the 3,4 double bond. In contrast to our expectations, the effects on orbital energies and the ability to undergo electronic interactions with the receptor could be affected in a deleterious way. Furthermore, the binding orientation at the receptor could be different than the one suggested by our hypothesis, with less favorable complementarity for serotonin agonist action.

Experimental Section

Chemistry. Melting points were determined in open glass capillaries using a Mel-Temp apparatus and are uncorrected. IR spectra were recorded on a Beckman IR-33 instrument; frequencies are expressed in reciprocal centimeters. NMR spectra were recorded on a Varian EM-360 or FT-80 instrument. Chemical shifts are reported in parts per million with Me_4Si as the internal reference. The multiplicities are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Chemical-ionization mass spectra were obtained on a DuPont 21-492 spectrometer. Elemental analyses were performed by the Purdue Microanalytical laboratory and were within ±0.4% of the calculated values.

5,8-Dimethoxy-6-methyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid (5). A solution of 24 g (90.9 mmol) of 4,[1] dissolved in 300 mL of H_2O containing 3.63 g (90.9 mmol) of NaOH and 3.45 g (90.9 mmol) of $NaBH_4$, was stirred overnight at room temperature. The aqueous solution was acidified with 6 N HCl to pH 3. The solid which separated was collected by filtration, washed with ice-cold water on the filter, and air-dried. Recrystallization from MeOH–H_2O gave 20.55 g (85%) of colorless crystals; mp 111–112 °C; IR ($CHCl_3$) 3600–2400 (COOH, OH), 1700 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 6.7 (s, 1, ArH), 5.2 (br t, 1, CH), 3.8 (s, 6, OCH_3), 3.4–2.2 (m, 5, CH_2), 2.3 (s, 3, CH_3). Due to the facile dehydration to 6, as well as to the 3,4-dehydro acid, this material could not be purified to give a satisfactory elemental analysis. Mass spectral analysis (CI) gave M + 1 = 267.

6,9-Dimethoxy-8-methyl-4,5-dihydro-1,4-methano-2-benzoxepin-3(1*H*)-one (6). To a solution of 15.3 g of acetic anhydride in 200 mL of pyridine was added 20 g (74.9 mmol) of 5. The reaction was stirred for 3 h at reflux. The mixture was cooled and the solvent was removed under reduced pressure. The oily residue was taken up into 200 mL of Et_2O and the ether solution was washed twice with 50-mL portions of 1 N HCl, followed by 2 × 50 mL of 10% Na_2CO_3 and 2 × 50 mL of H_2O. The ether solution was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to yield an oily residue. Recrystallization from ether gave 12.23 g (65.6%) of colorless crystals: mp 105–107 °C; IR ($CHCl_3$) 1770 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 6.73 (s, 1, ArH), 5.87 (m, 1, C_4H), 3.7 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), 2.9–2.1 (m, 5, CH), 2.3 (s, 3, CH_3). Anal. ($C_{14}H_{16}O_4$) C, H.

5,8-Dimethoxy-6-methyl-4-hydroxy-1,2,3,4-tetrahydro-2-naphthoic Acid Hydrazide (7). A solution of 10 g (40.1 mmol) of 6 in 200 mL of 95% EtOH containing 40 mL of hydrazine hydrate was heated at reflux for 2 h. Removal of the solvent and excess hydrazine hydrate yielded an off white solid. The crude product was recrystallized from 95% EtOH to yield 7.1 g (80%) of colorless crystals: mp 155–156 °C; IR ($CHCl_3$) 3640–3200 (OH, NH_2), 1660 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 6.67 (s, 1, ArH), 5.16 (br t, 1, CHOH), 3.9 (s, 6, OCH_3), 2.8–1.9 (m, 5, CH, CH_2), 2.3 (s, 3, CH_3). Anal. ($C_{14}H_{20}N_2O_4$) C, H, N.

7,10-Dimethoxy-9-methyl-1,4,5,6-tetrahydro-1,5-methano-2,4-benzoxazecin-3-one (8). Sufficient concentrated HCl was added to a suspension of 6 g (21.4 mmol) of 9 in 100 mL of H_2O to effect solution. This was layered with 100 mL of toluene and cooled to 0 °C in an ice–salt bath. The solution was stirred slowly while adding, dropwise, a solution of 1.55 g (22.4 mmol) of $NaNO_2$ in 50 mL of H_2O. After complete addition and when the two layers had turned clear, the toluene layer was separated. The aqueous layer was twice extracted with 50-mL portions of toluene. The combined organic layers were dried ($MgSO_4$) and filtered, and the filtered solution was heated at reflux for 1.5 h. At the end of this period, the reaction was cooled and reduced under vacuum to yield a yellowish solid. Recrystallization from EtOH yielded 5.18 g (92%) of 8: mp 280 °C dec; IR ($CHCl_3$) 3420 (NH), 1690 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 6.73 (s, 1, ArH), 5.7 (m, 1, C_4H), 3.8 (s, 3, OCH_3), 3.7 (s, 3, OCH_3), 3.1–1.2 (m, 5, CH, CH_2), 2.2 (s, 3, CH_3). Anal. ($C_{14}H_{17}NO_4$) C, H, N.

5,8-Dimethoxy-6-methyl-1,2-dihydro-2-aminonaphthalene Hydrochloride (3). To 100 mL of a 1:4 v/v mixture of concentrated HCl and AcOH was added 4 g (15.2 mmol) of the cyclic carbamate 8. The mixture was blanketed with N_2 and heated at reflux for 3 h. The solvent was removed under reduced pressure, and the dark brown mass thus obtained was repeatedly recrystallized from CH_3CN to yield 2.55 g (66%) of tan crystals: mp 189–191 °C; NMR (free base in $CDCl_3$) δ 6.8 (s, 1, ArH), 5.8–6.2 (m, 2, =CH), 3.8 (s, 3, OCH_3), 3.7 (s, 3, OCH_3), 3.0–2.0 (m, 3, CH_2, CH), 2.2 (s, 3, CH_3). Anal. ($C_{13}H_{17}ClNO_2$)-C, O_2) C, H, N.

Pharmacology. Rat Fundus Preparation. Responses to drugs were studied in the isolated rat fundus, prepared from 300–400 g male Sprague–Dawley rats which had been fasted overnight but allowed free access to water. Following the method of Vane,[9] fundus strips were suspended in 25-mL organ baths and bathed in Tyrode's solution. The bath was maintained at 37 °C and oxygenated with 95% O_2–5% CO_2. Tissue strips were placed under an initial 1-g tension, and contractions were measured using a Grass FTO3 transducer and recorded on a Grass polygraph.

Drugs were added in cumulative amounts with micropipets, and contractions were expressed as the percent of the maximum response obtainable with serotonin in that tissue. Only one test drug was used in each preparation.

Serotonin Behavioral Syndrome. The behavioral syndrome elicited by serotonin receptor activation was evaluated as described by Sloviter et al.[7] Male Sprague–Dawley rats, 200–300 g, were used for these experiments. Animals were allowed free access to food and water and were maintained on a 12-h light/dark cycle. Drugs were injected intraperitoneally in a volume of saline of 0.1 mL per 100 g of body weight. The serotonin syndrome was considered to be present only if all three of the symptoms (forepaw padding, splayed hindlimbs, and head weaving or head tremor) were elicited simultaneously. We found a considerably higher potency in our studies when evaluating the standard hallucinogenic agent, (±)-DOM, as compared with the results reported by Sloviter et al.[15] Apparently, these workers used the less potent (+) isomer of DOM, whereas we used the racemic material.

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