the period of conversion. Blood pressure was recorded in the usual fashion and a lead II electrocardiogram was recorded to visually monitor the arrhythmia.

Registry No. (±)-I, 99495-88-2; (±)-I (base), 99495-87-1; (+)-I, 99495-93-9; (+)-I (base), 99495-92-8; (+)-I ·(+)-α-bromocamphor-π-sulfonic acid, 99495-89-3; (−)-I, 99495-94-0; (−)-I (base), 99495-90-6; (−)-I ·(−)-α-bromocamphor-π-sulfonic acid, 99495-91-7; (+)-α-bromocamphor-π-sulfonic acid ammonium salt, 14575-84-9; (−)-α-bromocamphor-π-sulfonic acid ammonium salt, 55870-50-3.

Synthesis and Evaluation of 2,3-Dihydrobenzofuran Analogues of the Hallucinogen 1-(2,5-Dimethoxy-4-methylphenyl)-2-aminopropane: Drug Discrimination Studies in Rats

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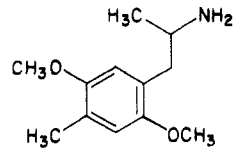
Two analogues, 6-(2-aminopropyl)-5-methoxy-2,3-dihydrobenzofuran and 6-(2-aminopropyl)-5-methoxy-2-methyl-2,3-dihydrobenzofuran, of the hallucinogenic agent 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM) were synthesized and tested in the two-lever drug discrimination paradigm. In rats trained to discriminate saline from LSD tartrate (0.08 mg/kg), stimulus generalization occurred to both of the 2,3-dihydrobenzofuran analogues but at doses more than 10-fold higher than for DOM. A possible explanation for this dramatic attenuation of LSD-like activity could involve a highly directional electrophilic binding site on the receptor that cannot accept the orientation of the unshared electron pairs on the heterocyclic oxygen atom in the benzofurans.

In our continuing investigations of the structure–activity relationships of hallucinogenic drugs, we have been directing attention to the importance of aromatic ring substituents in substituted "amphetamine" type hallucinogens. A prototype of this class of drug is 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (**1**; DOM, STP). Several years ago it was communicated by another worker that the 2,3-dihydrobenzofuran analogues of DOM **2** and **3** were highly potent hallucinogens.[1]



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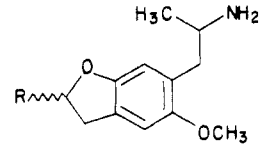


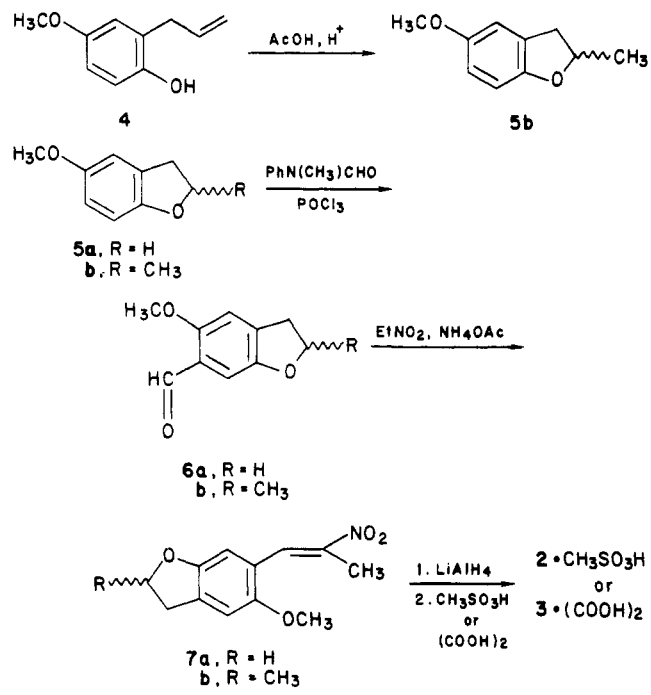
2, R = H
3, R = CH_3

We were intrigued by these reports and the possiblity that the diastereomers of **3** could be resolved to afford four isomers. These would provide useful probes of the stereochemical requirements of the binding site, if any, for the para substituent of the substituted amphetamine hallucinogens.

We therefore synthesized **2** and **3** to begin studies directed toward this goal. However, evaluation of these two compounds in the two-lever drug discrimination paradigm, in rats trained to discriminate between saline and LSD tartrate (0.08 mg/kg), revealed a dramatic attenuation of LSD-like activity in rats when compared with **1**. This report, therefore, details the synthesis of **2** and **3** and the evaluation in rats for LSD-like activity.

Chemistry. Both compounds **2** and **3** were obtained by elaboration of the 2,3-dihydrobenzofurans **5a** and **5b**. Treatment of these with phosphorus oxychloride and *N*-methylformanilide under conditions of the Vilsmeier–Haack reaction led to the corresponding benzaldehydes **6a** and **6b**, respectively. A major side reaction was formylation at the 7-position of the dihydrobenzofuran ring, but recrystallization of **6a** and **6b** from hexane effectively removed this isomeric aldehyde. Condensation of the benzaldehydes with nitroethane, followed by reduction of the resulting nitroolefin with lithium aluminum hydride and formation of the salt, gave the desired compounds **2** and **3**, as their methanesulfonate and oxalate salts, respectively.

Scheme I



Preparation of the starting 2,3-dihydrobenzofuran **5a** was accomplished following the method of Tanaka.[2]

The 2-methyl-2,3-dihydrobenzofuran **5b** was prepared by acid-catalyzed cyclization of 2-allyl-4-methoxyphenol, which was obtained by thermal Claisen rearrangement of the corresponding allyl ether. The acid-catalyzed cyclization of **4** was best accomplished following the method of Darling and Wills,[3] using reflux in glacial acetic acid containing a catalytic amount of sulfuric acid. A variety of other attempts with various acids failed, although py-

(1) Trampota, M., personal communication, 1980.

(2) Tanaka, S. *J. Am. Chem. Soc.* **1951**, *73*, 872.

(3) Darling, S. S.; Wills, K. D. *J. Org. Chem.* **1967**, *32*, 2794.

0022-2623/86/1829-0302$01.50/0

Table I. Drug Discrimination Data

compd	dose, mg/kg	no. responding on LSD lever	% responding on LSD lever	ED_{50}, mg/kg	95% CI
1[a]				0.148	0.094–0.234
2	0.25	1/8	13	2.12	1.25–5.61
	1.0	1/8	13		
	4.0	5/8	63		
	8.0	6/8	75		
	10.0	10/12	83		
3	0.5	0/8	0	5.50	3.88–7.79
	2.0	0/8	0		
	4.0	3/8	38		
	8.0	5/8	63		
	16.0	7/8	88		
8	0.5	1/8	13	1.713	0.67–1.98
	1.0	4/8	50		
	2.0	6/8	75		
	3.0	8/10	80		
	4.0	8/8	100		

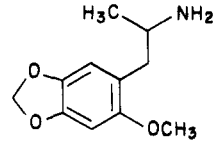
[a] See ref 5 for data from earlier study.

ridinium chloride afforded the desired material in very poor yield.[4]

Results and Discussion

The testing data are summarized in Table I. Also included in the table is the ED_{50} value for DOM (1), taken from an earlier study.[5] Complete LSD stimulus generalization occurred to both 2 and 3. For 2, maximum LSD-appropriate responding of 83% occurred at a dose of 10.0 mg/kg. The ED_{50} for 2 of 2.12 mg/kg may be compared to the ED_{50} for 1 to see that 2 is about 14-fold less potent than DOM. However, in a preliminary clinical study, compound 2 had no detectable central effects at an acute oral dosage of 30 mg of the methanesulfonate salt.[6] If 2 possesses psychotomimetic action in humans, it would be at least 5- to 10-fold less potent than DOM. The ED_{50} for 3 indicates that it is about 40 times less potent than 1 in rats.

The explanation for the decreased hallucinogen-like activity for 2 and 3 is rather perplexing. One would not anticipate that there would be significant electronic differences between 1 and 2. The additional hydrophobicity in the form of the 2-methyl group in 3 ought also, by virtue of known structure–activity relationships for hallucinogenic amphetamines, to have increased hallucinogenic activity. However, 3 is even less potent than 2. This is all the more difficult to explain in light of the fact that 2-methoxy-4,5-(methylenedioxy)amphetamine (8; MMDA-2) is active



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and produces clear central effects at an oral dosage of 25 mg of the hydrochloride,[7] although the ED_{50} found in this study indicates it is only slightly more active than 2 in rats. MMDA-2 simply represents an oxygen isostere of compound 2. One explanation centers around the possibility of a very directionally sensitive electrophilic site on the receptor that binds to the unshared electron pair of the 5-methoxy in 1 and the heterocyclic oxygen in 2 or 3. If this binding site has very restricted conformational mobility, it is possible that the unshared electron pair of the oxygen must be directed "syn" with respect to the position para to the isopropylamine side chain. In both 2 and 3 the electrons are rotated 180° from such an orientation. It is known that the simple addition of a 4-substituent to 2,5-dimethoxy-substituted phenylisopropylamines increases hallucinogenic activity in a dramatic way.[8,9] Nearly any para substituent will suffice, either electronegative or electron donating. Although there is some evidence that there may be a hydrophobic binding region at this location of the receptor,[9] this seems inadequate to explain the critical importance of the para substituent. On the other hand, if there is an electrophilic site to bind the unshared electron pair of the 5-methoxy of 1, the simple presence of the 4-methyl group, and the resulting nonbonded interaction between it and the 5-methoxy, will force the methoxy to adopt a conformation that directs the electron pairs of the methoxy oxygen toward the para substituent.

We recently commented extensively on the possible need for electron-pair directionality at serotonin receptors.[10] It is also possible that the methoxy group might adopt a nonplanar conformation. But in any case, the methyl of the 5-methoxy group in 1 cannot lie "syn" with respect to the 4-methyl group. Thus, the substituent at the 4-position could be seen as presenting a steric boundary that forces correct orientation of the 5-methoxy function. For both 2 and 3 the alkoxy function is completely locked, apparently in a conformation that precludes significant receptor activation.

However, the biological activity of 8 is not consistent with this explanation, since the 5-oxygen function is locked into a conformation nearly identical to that of 2, but there are at least two other possiblities to consider. First, it is possible that metabolic cleavage of the dioxole ring can occur, and that it is actually a metabolite of 8 that is active, whereas metabolic cleavage of 2 or 3, if it occurred, would yield different metabolites. On the other hand, the *4-oxygen* function of MMDA-2 is oriented so that its unshared electron pairs are aligned along a vector nearly parallel to that of the electron pair of the 5-methoxy of 1. A binding orientation on the receptor, translated from

(4) Sen, A. B.; Rastogi, R. P. *J. Ind. Chem. Soc.* **1953**, *30*, 355.
(5) Oberlender, R. A.; Kothari, P. J.; Nichols, D. E.; Zabik, J. E. *J. Med. Chem.* **1984**, *27*, 788.
(6) Shulgin, A. T., personal communication, 1984.
(7) Shulgin, A. T. *Experientia* **1964**, *15*, 366.
(8) Nichols, D. E.; Glennon, R. A. "Hallucinogens: Neurochemical, Behavioral, and Clinical Perspectives"; Raven Press: New York, 1984; pp 95–142.
(9) Nichols, D. E.; Shulgin, A. T.; Dyer, D. C. *Life Sci.* **1977**, *21*, 569.
(10) Nichols, D. E. "VIIIth International Symposium on Medicinal Chemistry"; Vol. 2; Dahlbom, R., Nilsson, J. L. G., Eds.; Swedish Pharmaceutical Press: Stockholm, 1985; pp 103–115.

the "normal" mode of binding for molecules such as 1, could allow the electron pair from the *4-oxygen* of 8 to be accommodated by the electrophilic site on the receptor that normally interacts with the *5-oxygen* of 1. The lower potency for 3 as compared to 2 might indicate that the 2-methyl group of 3 protrudes into a sterically sensitive region of the receptor. This is interesting to keep in mind when considering possible active conformations of homologues of 1, where the 4-methyl is extended to longer alkyls such as ethyl or propyl.

In any case, it seems that a good deal of additional study would be required to firmly establish the reason for the diminished LSD-like activity for compounds 2 and 3.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra (80 MHz) were recorded on a Varian FT-80 spectrometer, and 470-MHz ^{1}H NMR spectra were recorded on a Nicolet NTCFT-470 MHz spectrometer (Purdue University Biomedical Magnetic Resonance Laboratory). Chemical shifts are reported in δ values (parts per million) relative to an internal reference of Me_4Si in $CDCl_3$. Abbreviations used in NMR analysis are as follows: br s = broad singlet, d = doublet, dd = doublet of doublets, m = multiplet, q = quartet, s = singlet, t = triplet. Chemical-ionization mass spectral analysis was performed on a Finnegan 2000 spectrometer. Microanalysis was performed at the Purdue Microanalysis Laboratory, and all values were within 0.4%.

5-Methoxy-2-methyl-2,3-dihydrobenzofuran (5b). A solution of 45 g (274 mmol) of 4 in 100 mL of glacial acetic acid with 2 mL of concentrated H_2SO_4 was heated at reflux under nitrogen with stirring for 20 h. The solvent was removed by rotary evaporation, 30 g of NaOH pellets were added to the residual oil, and the mixture was swirled for 5 min. The brown oil was decanted and vacuum distilled to afford 21.6 g (48%) of a light yellow oil: bp 88 °C (1.3 mmHg) [lit.[3] bp 68–70 °C (0.3 mmHg)]; NMR ($CDCl_3$) δ 6.74–6.62 (m, 3, Ar H), 4.87 (s, 1, OCH), 3.72 (s, 3, OCH_3), 3.21 (q, 1, benzylic CH), 2.80 (q, 1, benzylic CH), 1.43 (d, 3, CH_3).

6-Formyl-5-methoxy-2,3-dihydrobenzofuran (6a). A mixture of 6.6 g of $POCl_3$ (43 mmol) and 5.7 g (42 mmol) of *N*-methylformanilide was swirled and allowed to incubate at room temperature for 30 min. To this was added 2.38 g (15.8 mmol) of **5a**. The mixture was heated to about 65 °C on the steam bath, under nitrogen, with stirring for 3 h. The reaction was then poured into water and extracted with methylene chloride (2 × 50 mL). The combined organic exract was washed with H_2O and 5% $NaHCO_3$, dried ($MgSO_4$), and filtered. After solvent removal the residue was extracted with boiling hexanes (4 × 50 mL). The desired aldehyde crystallized to yield 1.57 g (56%): mp 79–80 °C; NMR ($CDCl_3$) δ 10.37 (s, 1, CHO), 7.19 (s, 1, Ar H), 6.89 (s, 1, Ar H), 4.57 (t, 2, CH_2O), 3.88 (s, 3, OCH_3), 3.24 (t, 2, CH_2). Anal. ($C_{10}H_{10}O_3$) C, H.

6-Formyl-5-methoxy-2-methyl-2,3-dihydrobenzofuran (6b). Following a procedure similar to that for **6a**, 4 g (24 mmol) of **5b** gave 3.6 g (78%) of **6b**: mp 80–82 °C; NMR ($CDCl_3$) δ 10.35 (s, 1, CHO), 7.14 (s, 1, Ar H), 6.84 (s, 1, Ar H), 4.92 (s, 1, OCH), 3.86 (s, 3, OCH_3), 3.30 (q, 1, benzylic CH), 2.86 (q, 1, benzylic CH), 1.45 (d, 3, CH_3, J = 6.3 Hz); CIMS, 193 (M + 1). Anal. ($C_{11}H_{12}O_3$), C, H.

5-Methoxy-6-(2-nitro-1-propenyl)-2,3-dihydrobenzofuran (7a). A mixture of 1.14 g (6.4 mmol) of aldehyde **6a** and 500 mg of NH_4OAc (6.4 mmol) in 25 mL of nitroethane was heated on the steam bath under nitrogen until TLC indicated disappearance of starting aldehyde. The mixture was concentrated by rotary evaporation and the residue was diluted with 50 mL of H_2O and extracted with methylene chloride (2 × 30 mL). The organic extract was washed with H_2O, dried (Na_2SO_4), and filtered. After solvent removal, the orange oil was crystallized from MeOH to yield 870 mg (58%) of orange needles: mp 89–91 °C; NMR ($CDCl_3$) δ 8.52 (s, 1, =CH), 7.19 (s, 1, Ar H), 6.89 (s, 1, Ar H), 4.57 (t, 2, OCH_2), 3.90 (s, 3, OCH_3), 3.24 (t, 2, CH_2), 2.31 (s, 3, CH_3). Anal. ($C_{12}H_{13}NO_4$) C, H, N.

5-Methoxy-2-methyl-6-(2-nitro-1-propenyl)-2,3-dihydrobenzofuran (7b). Following a procedure similar to that for **7a**, 1.48 g of aldehyde **6b** gave, after recrystallization from MeOH, 1.55 g (81%) of yellow-orange crystals: mp 89–90 °C; NMR ($CDCl_3$) δ 8.25 (br s, 1, =CH), 6.80 (s, 1, ArH), 6.70 (s, 1, Ar H), 4.90 (m, 1, OCH), 3.82 (s, 3, OCH_3), 3.20 (q, 1, benzylic CH, J = 8.7 Hz), 2.88 (q, benzylic CH, J = 8.7 Hz), 2.38 (d, 3, CH_3, J = 1 Hz), 1.47 (d, 3, CH_3, J = 6.2 Hz); CIMS, 250 (M + 1). Anal. ($C_{13}H_{15}NO_4$) C, H, N.

6-(2-Aminopropyl)-5-methoxy-2,3-dihydrobenzofuran. The nitro compound **7a** (500 mg, 2.13 mmol) was reduced with 480 mg (12.6 mmol) of $LiAlH_4$ in dry THF. After usual workup, the free base was obtained as an amber oil, 0.36 g (82%). Preparation of the methane sulfonic acid salt gave 421 mg (66%), following recrystallization from EtOH–ether: mp 141–144 °C; NMR ($CDCl_3$, free base) δ 6.76 (s, 1, Ar H), 6.58 (s, 1, Ar H), 4.53 (t, 2, OCH_2), 3.17 (t, 2, CH_2), 3.75 (s, 3, OCH_3), 3.06 (m, 1, CH), 2.57 (t, 2, CH_2), 1.41 (s, 2, NH_2), 1.09 (d, 3, CH_3). Anal. ($C_{11}H_{18}NO_5S$) C, H, N.

6-(2-Aminopropyl)-5-methoxy-2-methyl-2,3-dihydrobenzofuran (3). Similar to the preparation of **2**, 1.14 g of **7b** was reduced with 0.35 g of $LiAlH_4$ to afford 0.85 g (84%) of the free base as an amber oil, following bulb-to-bulb distillation (101 °C bath, 0.05 mmHg). The hydrochloride salt proved to be hygroscopic, so the oxalate salt was prepared and used for testing: mp 216–218 °C; NMR (470 MHz, Me_2SO-d_6) δ 6.88 (s, 1, Ar H), 6.54 (s, 1, Ar H), 4.85 (sextet, 1, OCH, J = 6.3 Hz), 3.73 (s, 3, OCH_3), 3.35 (m, 1, C_α-H), 3.27 (dd, 1, C_3H), 2.83 (dd, 1, C_β-H), 2.76 (dd, 1, C_3-H), 2.63 (dd, 1, C_β-H), 1.36 (d, 3, 2 CH_3, J = 6.3 Hz), 1.08 (d, 3, CH_3, J = 6.5 Hz); CIMS, 222 (free base) (M + 1).

Pharamcology. Animals. Thirty male, Sprague–Dawley rats, weighing 200–240 g at the start of the experiment, were obtained from Murphy Breeding Labs, Inc. Plainfield, IN. Rats were housed individually. Discrimination training was carried out as described previously,[5] and rats were trained to discriminate intraperitoneal injections of saline from 0.08 mg/kg of LSD tartrate (NIDA). Rats were found deprived to about 85% of their free-feeding weight. Food (Lab Blox) was provided once daily, approximately 1 h after removal from the testing chambers.

Apparatus. Standard operant chambers (Coulbourn Instruments) within sound-attenuated, ventilated cubicles, with a white house light and masking white noise were used. Each chamber contained two response levers separated by a pellet delivery system through which 45 mg of food pellets (Bioserv, dustless) were dispensed. Solid-state and computer-controlled programming and data acquisition equipment was located in an adjacent room.

Rats were trained on a fixed-ratio 50 (FR50) schedule. Daily training sessions lasted 15 min. Drug treatments were administered 30 min prior to testing. Drug test sessions lasted until the rat emitted 50 responses on either lever or until 5 min had passed. If the rat did not emit 50 presses on either lever within 5 min, he was scored as disrupted and was not included in calculations.

Drugs. Drugs were administered in a volume of 0.10 mL of sterile physiological saline per 100 g of body weight. LSD tartrate was obtained from the National Institute on Drug Abuse.

Data Analysis. During test sessions, rats were scored either as drug positive or drug negative, depending on whether they emitted the first 50 responses on the LSD-appropriate or saline-appropriate lever, respectively. The percent responding within each treatment group was calculated.

Acknowledgment. This work was supported by funds from Grant DA02189 from the National Institute on Drug Abuse, Chemical Pharmacology Training Grant GM 709504 (R.A.O.), and Biomedical Research Support Grant 2-S07-RR05586-15 and PUBMRL Grant RR01077.

Registry No. **2**, 99355-77-8; **2**·$MeSO_3H$, 99355-78-9; **3**, 99355-74-5; **3**·$(CO_2H)_2$, 99355-79-0; **4**, 584-82-7; **5a**, 13391-30-5; **5b**, 13391-29-2; **6a**, 99355-75-6; **6b**, 85258-19-1; **7a**, 99355-76-7; **7b**, 85258-21-5; **8**, 23693-18-7.