(11 000); λ_{max} (0.01 N NaOH in C_2H_5OH) 217 nm (ϵ 9230), 265 (8530); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 2.8–3.0 (2 H, H-5'a, H-5'e), 3.07 (1 H, d of d, J_{gem} = 13.6 Hz, $^3J_{ea}$ = 2.8 Hz, H-3'e), 3.15–3.35 (2 H, H-6'a, H-6'e), 3.37 (1 H, d of d, J_{gem} = 13.6 Hz, $^3J_{aa}$ = 9.8, H-3'a), 5.65 (1 H, d, J_{H-6} = 8.2 Hz, H-5), 5.80 (1 H, d of d, $^3J_{aa}$ = 9.8 Hz, $^3J_{ae}$ = 2.8 Hz, H-2'a), 7.78 (1 H, d, J_{H-5} = 8.1 Hz, H-6), 10 (br s, CONHCO). Anal. ($C_8H_{10}N_2O_2S_2$) C, H, N; S: calcd, 27.84; found, 26.57.

1-(1,4-Dithian-2-yl)thymine (17). The procedure for coupling 2-(benzoyloxy)-1,4-dithiane (**14**; 0.441 g, 1.83 mmol) with thymine (0.231 g, 1.83 mmol) was identical with that used for preparing **15**. Evaporation of the solvent gave a white solid (0.56 g), which was recrystallized from CH_3OH to give **17**: yield 0.30 g (67%); TLC R_f 0.33 [1:1 (v/v) petroleum ether (bp 35–60 °C)–ethyl acetate]; mp 217–218 °C; UV λ_{max} (C_2H_5OH) 212 nm (ϵ 9590), 270 (11 000); λ_{max} (0.01 N HCl in C_2H_5OH) 212 nm (ϵ 9680), 270 (10 900); λ_{max} (0.01 N NaOH in C_2H_5OH) 218 nm (ϵ 10 500), 270 (8580); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 1.85 (3 H, d, $^4J_{H-6}$ = 1.2 Hz, CH_3), 2.8–3.0 (2 H, H-5'a, H-5'e), 3.0 (1 H, d of d, J_{gem} = 13.4 Hz, $^3J_{ea}$ = 2.6 Hz, H-3'e), 3.14–3.25 (1 H, d of t, J_{gem} = 14.0 Hz, ^3J = 4.0 Hz, H-6'e), 3.27–3.40 (1 H, m, J_{gem} = 14.0 Hz, $^3J_{aa}$ = 8.6 Hz, $^3J_{ae}$ = 4.6 Hz, H-6'a), 3.41 (1 H, d of d, J_{gem} = 13.4 Hz, $^3J_{aa}$ = 10.4 Hz, H-3'a), 5.81 (1 H, d of d, $^3J_{aa}$ = 10.4 Hz, $^3J_{ae}$ = 2.6 Hz, H-2'), 7.58 (1 H, quartet, $^4J_{CH_3}$ = 1.2 Hz, H-6), 10.03 (br s, CONHCO). Anal. ($C_9H_{12}N_2O_2S_2$) C, H, N; S: calcd, 26.25; found, 25.02.

1-(1,4-Dioxan-2-yl)-5-fluorouracil (20). The procedure for coupling 2-(benzoyloxy)-1,4-dioxane[10] (**19**; 1.11 g, 5.35 mmol) with 5-fluorouracil (0.70 g, 5.35 mmol) was identical with that used for preparing **8**. Evaporation of the solvent gave a white solid (1.78 g), which was recrystallized from methanol to give **20**: yield 0.81 g (70%); TLC R_f 0.16 [1:1 (v/v) petroleum ether (bp 35–60 °C)–ethyl acetate]; mp 217 °C; UV λ_{max} (C_2H_5OH) 207 nm (ϵ 8480) 267 (8560); λ_{max} (0.01 N HCl in C_2H_5OH) 207 nm (ϵ 8490), 267 (8540); λ_{max} (0.01 N NaOH in C_2H_5OH) 217 nm (ϵ 7700), 266 (6300); ^1H NMR (acetone-d_6, 300 K, 200 MHz) δ 3.6–3.8 (2 H, H-5'e, H-5'a), 3.63 (1 H, d of d, J_{gem} = 11.4 Hz, $^3J_{aa}$ = 8.8 Hz, H-3'a), 3.85–3.97 (1 H, t of d, H-6'a), 3.90 (1 H, d of d, J_{gem} = 11.4 Hz, $^3J_{ea}$ = 3.3 Hz, H-3'e), 3.99–4.07 (1 H, d of t, H-6'e), 5.68 (1 H, m, $^3J_{aa}$ = 8.8 Hz, $^3J_{ae}$ = 3.3 Hz, ^5J_F = 1.7 Hz, H-2'a), 7.92 (1 H, d, J = 7.0 Hz, CH=CF), 10.49 (br s, CONHCO); ^{19}F NMR δ −99, (d of d, $J_{CH=CF}$ = 7.0 Hz, $^5J_{2'a}$ = 1.6 Hz, CH=CF). Anal. ($C_8H_9N_2O_4F$) C, H, N, F.

Screening for Biological Activity Using Cell Cultures. All cell-growth experiments were performed using plastic plates containing 24 wells, 16 mm in diameter (2.0-cm^2 surface area). The medium for the MDAY-D2 cells was Alpha MEM (Gibco, Grand Island, NY) and for the L1210 and K-562 it was RPMI 1640 (Gibco). All media contained 10% fetal calf serum (Flow Laboratories, Rockville, MD) and antibiotics (penicillin and streptomycin).[22]

Compounds tested for biological activity were dissolved in Me_2SO and then diluted with the above media to give the desired concentrations. The cells used for screening were suspended in fresh medium at a concentration of 10^3–10^4 cells per milliliter; 1 mL of this cell suspension was added to each well. On the following day the test compounds were added to the cells in 1 mL of medium. Two wells of cells were used for each concentration of the test compound. Each of the controls received 1 mL of medium containing 1% Me_2SO, so that all cultures contained a final concentration of 0.5% of Me_2SO by volume. Cells in two of the control wells were counted each day (using a Coulter counter) to monitor the growth of the cells. In 5–6 days after the addition of the test compounds or just before the control cultures had attained their maximal cell densities, the cells in each well were counted.

ID_{50}'s were obtained from log–log plots of the compound concentration vs. cell numbers at the end of the incubation period, the cell numbers of the control cultures being taken as 100% (see also Table I).

Acknowledgment. The authors are grateful to the Natural Sciences and Engineering Research Council of Canada for its financial support of this work. They also thank Dr. R. S. Kerbel, Cancer Research Division, Department of Pathology, Queen's University, for kindly providing screening facilities.

(22) The media used was kindly prepared by Mrs. Majka Florian.

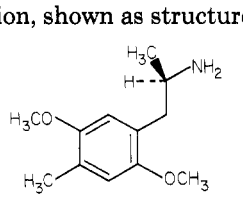
Isomeric Cyclopropyl Ring-Methylated Homologues of *trans*-2-(2,5-Dimethoxy-4-methylphenyl)cyclopropylamine, an Hallucinogen Analogue

James N. Jacob and David E. Nichols*

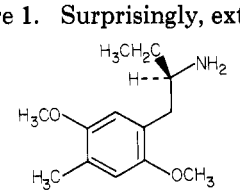
Department of Medicinal Chemistry and Pharmacognosy, School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907. *Received August 21, 1981*

The hallucinogen analogue *trans*-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine was modified by adding a 3-methyl group, either cis or trans with respect to the amino group. These two isomeric cyclopropyl ring-methylated compounds were then tested for activity in the mouse ear-scratch assay and for a contractile effect in the rat fundus preparation. Neither compound was found to possess appreciable activity when compared to the nonmethylated parent, in either assay.

A large number of substituted phenethylamine derivatives have been synthesized and evaluated for hallucinogen-like biological activity. One of the more well known and studied of these, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane, (DOM, STP), is quite potent, and the more active enantiomer has the *R* absolute configuration, shown as structure **1**. Surprisingly, extension of the α-methyl of **1** to the α-ethyl homologue **2** abolishes hallucinogenic activity.[1] The ethyl congener **2** also lacks potency, relative to **1**, in a number of other biological assays.[2-4] No satisfactory explanation for the difference in



1



2

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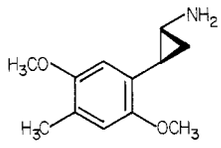
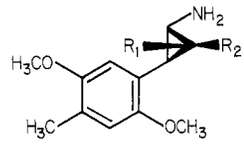
pharmacological activity between 1 and 2 has appeared. Solution NMR studies,[5] as well as theoretical conformational calculations,[6] have failed to identify a significant differences in molecular flexibility or allowed conformational states for the two homologues. As a result, steric interaction between the receptor and an α-ethyl group (but not an α-methyl group) has been invoked as an explanation.[5,6]

Previously, the cyclopropyl analogue 3 of DOM has been



3

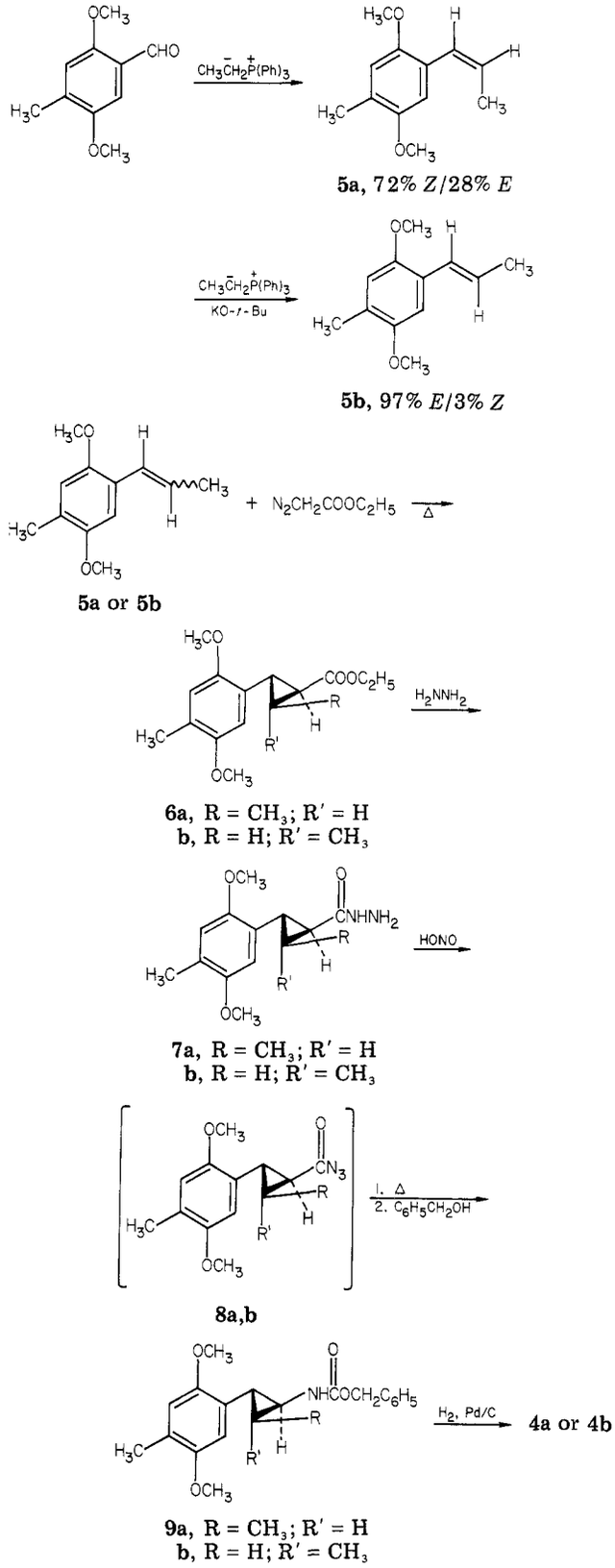


4a, R_1 = H; R_2 = CH_3
b, R_1 = CH_3; R_2 = H

shown to produce effects in animals similar to that produced by known hallucinogenic agents.[7-9] It was therefore of interest to determine whether addition of a methyl to C-3 of the cyclopropyl ring would have a deleterious effect on activity similar to the 1 to 2 transformation. Further, such ring-methylated congeners, **4a** and **4b**, could even be viewed as rigid analogues for conformational extremes of 2. If biological activity was observed for either **4a** or **4b**, it might be possible to identify a conformational region in which the α-ethyl of 2 could reside which would allow activity but which was for some reason inaccessible.

Chemistry. The synthesis of the two isomers **4a** and **4b** is detailed in Scheme I. Condensation of 2,5-dimethoxy-4-methylbenzaldehyde with triphenylphosphonium ethylide in the absence of excess base gave a 72:28 ratio of the *Z*/*E* olefins, **5a,b**. Since this mixture did not yield to separation on a preparative scale, the sequence was carried on and isomer separation was achieved at a later stage. In the presence of excess potassium *tert*-butoxide, the Wittig reaction gave almost exclusively (97%) the *E* olefin, **5b**. The olefins were then treated with ethyl diazoacetate at 180 °C. The cyclopropanation reaction was not efficient, although yields were modest if based on the actual amount of olefin reacted. The use of copper or rhodium catalysts failed to improve the conversion in this reaction. The distilled cyclopropane esters were then treated with hydrazine hydrate to convert the esters to the corresponding hydrazides **7a** and **7b**. Only at this stage did separation prove feasible, and it was possible to obtain the pure isomeric hydrazides by silica gel column chromatography, followed by recrystallization. Treatment of the hydrazides at 0 °C with nitrous acid gave the acyl azides. These were isolated and thermally rearranged to their respective isocyanates. Treatment of these with benzyl alcohol gave the *N*-carbobenzoxy derivatives **9a** and **9b**. Hydrogenolysis in ethanol at 5 °C over Pd/C afforded the amines, which were converted into the hydrochloride salts **4a** and **4b**. The amine salts appeared to slowly decompose, with changes in biological activity, if stored in solution or at room temperature. Thus, it was most convenient to store the carbamates **9a** and **9b** and carry out

Scheme I



5a, 72% *Z*/28% *E*

5b, 97% *E*/3% *Z*

5a or 5b

6a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

7a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

8a,b

9a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

hydrogenolysis on small samples, as required, just prior to biological activity testing.

The stereochemistry of **4a** and **4b** was verified by an alternate synthesis of the intermediate esters **6a** and **6b** and hydrazides **7a** and **7b**, utilizing the method of Johnson and Janige[10] (Scheme II). Chromatographic mobility and

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Scheme II

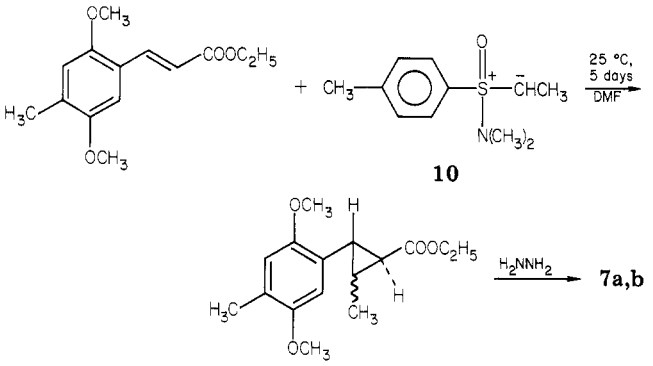

Table I. Number of Mouse Ear Scratches in the 30 min Following Intraperitoneal Injection of the HCl Salt of 1, 3, 4a, or 4b

drug	dose, mg/kg	no. of scratches [a]
saline		12.0 ± 5.0
1 [b]	1.00	52.4 ± 20.89
	2.00	109.2 ± 17.86
	4.00	79.0 ± 19.7
3	5.00	39.5 ± 13.8
	10.00	56.2 ± 25.0
	20.00	64.2 ± 36.0
4a	1.25	11.5 ± 3.5
	2.50	10.8 ± 3.8
	5.00	17.3 ± 6.8
	10.00	12.8 ± 10.5
	20.00	2.5 ± 2.0
4b	5.00	4.8 ± 3.0
	10.00	4.0 ± 2.0
	20.00	9.5 ± 2.5

[a] $n = 4$ for each treatment, with three mice per group. Values are mean ± SEM. [b] $n = 5$.

NMR and IR analysis showed these products to be identical with those obtained from the diazoacetate procedure. This confirmed that the relative stereochemistry of the aromatic ring and carboxyl was trans. As noted by Johnson and Janige,[10] the chemical shift of the 3-methyl group can be used to assign the cis or trans stereochemistry of the 3-methyl, relative to the aromatic ring. That is, the method of **9a** absorbs at δ 1.2, whereas the methyl of **9b** absorbs at δ 0.8, upfield from the methyl of **9a**. This is due to the anisotropic shielding experienced by a methyl which is cis to, and above, the π system of the aromatic ring.

Pharmacology. We previously reported that both **1** and **3** are active in eliciting the ear-scratch response in mice.[8] This assay has shown good correlation with human hallucinogenic potency for phenethylamine hallucinogens.[11] Furthermore, **2** is inactive in this model. Thus, both **4a** and **4b** were compared to **3** in the ear-scratch assay. The ability of these compounds to contract the rat stomach fundus preparation was also studied. The method used was essentially that described by Vane.[12]

Results and Discussion

As shown in Table I, neither **4a** nor **4b** elicit an increase in the ear scratches of mice. Likewise, compound **2** does not elicit ear scratching (unpublished data). However, during these studies we occassionally observed components of the "serotonin syndrome"[13] following administration of

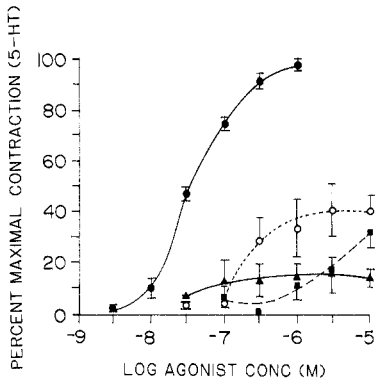

Figure 1. Effects of drugs on the isolated rat fundus preparation. Maximal responses were obtained on all tissues to 5-HT prior to studying drug effects. Serotonin (●, $n = 6$) was more potent than **3** (○, $n = 4$). Both **4a** (■, $n = 5$) and **4b** (▲, $n = 6$) were less potent than either serotonin or the nonmethylated parent **3**. Points are plotted as the mean, with vertical bars indicating the standard error.

4b. That is, head weaving, forepaw treading, and splayed hindlimbs were often elicited. Although the response was too unreliable to quantitate, it was never observed following administration of **4a**.

The studies in the rat fundus preparation parallel the findings in the mouse ear scratch assay (Figure 1). Previous workers have shown that **2** has less than $^1/_{500}$ the potency of **1** in ability to contract the rat stomach fundus.[4] In the present study, both **4a** and **4b** were only weakly active in the fundus. Only at the highest concentration did **4a** begin to demonstrate any appreciable agonist potency. Both compounds are clearly less active in the fundus preparation than is **3**. Thus, addition of a 3-methyl group to **3** either cis (**4a**) or trans (**4b**) to the amino group has a deleterious effect on activity, with no apparent stereoselectivity. Further speculation on the nature of this effect seems unwarranted at this time.

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 and are reported in reciprocal centimeters. NMR spectra were recorded on a Varian EM-360 or FT-80 spectrometer. 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; m, multiplet; br, broad. Gas chromatographic analyses were carried out on a Varian 2700 gas chromatograph using a 5 ft × $^1/_8$ in. stainless-steel column packed with 1.5% OV 101 on 100–120 mesh Chromasorb G. Nitrogen was used as the carrier gas. Elemental analyses were performed by the Purdue Microanalytical Laboratory and were within ±0.4% of the calculated values. Thin-layer chromatography (TLC) was performed on Macherey-Nagel Polygram SIL F/UV_{254} 0.25-mm precoated plastic plates.

(*Z*)- and (*E*)-1-(2,5-Dimethoxy-4-methylphenyl)propene (5a,b). (a) With 1 Equiv of Base. Ethyltriphenylphosphonium bromide (11.10 g, 0.03 mol, Aldrich Chemical Co.) in 50 mL of dry THF was stirred under a N_2 atmosphere with 3.36 g (0.03 mol) of commerical (Aldrich Chemical Co.) potassium *tert*-butoxide. The mixture was stirred for 2 h, resulting in an orange–red colored solution. A solution of 2,5-dimethoxy-4-methylbenzaldehyde (5.40 g, 0.03 mol) in 25 mL of dry THF was added dropwise to the reaction mixture. As the addition proceeded, the color changed to bright yellow. The mixture was stirred at room temperature for 0.5 h and refluxed overnight under an N_2 atmosphere. The reaction mixture was filtered, diluted with water, and extracted three times with $CHCl_3$. The combined extracts were washed with

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brine, dried ($MgSO_4$), filtered, and concentrated. The residue was taken up into a minimum of Et_2O, and the solution was decanted to remove triphenylphosphine oxide, which separated as a solid. The solid was washed with ether, and the combined ether solutions were concentrated and passed through a short silica gel column eluted with ethyl acetate–hexane (1:1), to remove remaining traces of triphenylphosphine oxide. The required olefin, along with some unreacted aldehyde, was rapidly eluted from the column. Concentration of this material gave a residue, which was taken up into 10 mL of EtOH and treated with 10 mL of saturated $NaHSO_3$ solution. The bisulfite adduct was removed by filtration and was repeatedly washed with ether. The combined filtrate and washings were concentrated to give the required product as a yellow liquid: yield 3.56 g (62%); bp 110–125 °C (0.15 mm); NMR ($CDCl_3$) δ 1.90 (d, 3, $CHCH_3$, J = 7 Hz), 2.2 (s, 3, Ar CH_3), 3.85 (s, 6, OCH_3), 6.0–6.5 (m, 2, vinyl CH), 6.75 (br s, 1, Ar H), 6.95 (br s, 1, ArH). GC analysis (column temp 160 °C, injector temp 190 °C, detector temp 190 °C) indicated the product to be 72% Z isomer (**5a**; R_t = 0.33 min) and 28% E isomer (**5b**; R_t = 0.44 min). Assignment was made based on NMR coupling constants after double irradiation of the pure trans olefin, prepared below, and gas chromatographic retention times.

(b) With 2 Equiv of Base. The Wittig reaction was repeated as above but using 2 equiv of potassium *tert*-butoxide. Thus, 5.4 g (0.03 mol) of the aldehyde and 11.1 g (0.03 mol) of ethyltriphenylphosphonium bromide with 6.72 g (0.06 mol) of potassium *tert*-butoxide yielded, after distillation, 2.89 g (50%) of the pure olefin, bp 105–110 °C (0.05 mm). Gas chromatographic analysis (see above) showed it to be 97% E (**5b**) and 3% Z (**5a**).

Double-Irradiation Study. Irradiation of the doublet at δ 1.90 ($CHCH_3$) caused collapse of the vinyl multiplets to give two mutually coupled doublets at δ 6.58 (J = 16 Hz) and 5.93 (J = 16 Hz), indicating the E olefin: NMR ($CDCl_3$) δ 1.90 (d of d, 3, vinyl CH_3, J = 6 Hz), 2.21 (s, 3, Ar CH_3), 3.79 and 3.80 (2 s, 6, OCH_3), 6.02–6.38 (m, 2, CH=CH), 6.88 (m, 1, Ar H), 7.25 (m, 1, Ar H), 7.25 (m, 1, Ar H). Anal. ($C_{12}H_{16}O_2$) C, H.

Ethyl 2-(2,5-Dimethoxy-4-methylphenyl)-3-methylcyclopropanecarboxylates 6a,b. 6a. (E)-1-(2,5-Dimethoxy-4-methylphenyl)propene (**5b**; 7.5 g, 0.039 mol) was stirred in a 15-mL three-necked flask that was fitted with a condenser and a pressure-equalizing addition funnel and heated to 180 °C under a nitrogen atmosphere. A mixture of ethyl diazoacetate (9.0 g, 0.079 mol) and the olefin (7.5 g, 0.039 mol) was placed in the addition funnel and was added in drops to the hot olefin over a period of 3.0 h at a rate such that the evolution of nitrogen subsided after the addition of each drop. The mixture was stirred at 190 °C for 12 h and was distilled under vacuum to recover 3.12 g of unreacted olefin and 2.56 g (23%) of the ester: bp 100–140 °C (0.10 mm); IR (Neat) 1740 (C=O), 1520, 1470, 1400 cm^{-1}; NMR ($CDCl_3$) δ 7.2 (m, 2, Ar H), 4.2 (q, 2, OCH_2CH_3), 3.85 (br s, 6, OCH_3), 2.51–2.66 (m, 1, CH), 2.25 (s, 3, Ar C h_3), 1.6–2.0 (m, 2, CH), 0.95–1.50 [m, 6, OCH_2CH_3 (both isomers)] CIMS, m/e 279 (M + 1). Anal. ($C_{16}H_{22}O_4$) C, H.

6b. The same procedure was followed as above for the cyclopropanation reaction using the Z/E 72:28 olefin mixture. Thus, from 21.42 g (0.112 mol) of olefin and 14.6 g (0.128 mol) of ethyl diazoacetate was obtained 8.61 g of recovered olefin and 9.70 g (30%) of the mixture of cyclopropyl esters, bp 110–140 °C (0.05 mm).

Conversion of Cyclopropyl Esters to Hydrazides 7a and 7b. A mixture of ethyl 2-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclopropanecarboxylate (**6a** or **6b**; 4.0 g, 0.014 mol) and 4.0 mL of hydrazine hydrate was heated at 100–110 °C for 4 days. The crude mixture of hydrazide thus obtained was purified by column chromatography using silica gel (Merck, 60–270 mesh, 200 g) and elution with 3% MeOH in $CHCl_3$: yield of hydrazide **7a** 0.57 g (32%); yield of hydrazide **7b** 0.56 g (31%); TLC (5% MeOH–$CHCl_3$; silica gel) R_f (**7a**) 0.34, R_f (**7b**) 0.25. **7a**: mp 155–157 °C (EtOH); IR (KBr) 3280, 1640, 1520, 1460, 1210 cm^{-1}; NMR ($CDCl_3$) δ 7.25 (br m, 1, NH), 6.7 (s, 1, Ar H), 6.45 (s, 1, Ar H), 3.8 and 3.83 (2 s, 6, OCH_3), 2.5 (m, 1, cyclopropyl H), 2.2 (s, 3, Ar CH_3), 1.7–1.5 (m, 2, cyclopropyl H), 1.2 (d, 2, $CHCH_3$); CIMS, m/e 265 (M + 1). Anal. ($C_{14}H_{20}N_2O_3$) C, H, N. **7b**: mp 165–166 °C (EtOH); IR (KBr) 3250, 1650, 1615, 1220 cm^{-1}; NMR ($CDCl_3$) δ 7.4 (br m, 3, $NHNH_2$), 6.8 (s, 1, Ar H), 6.65 (s, 1, Ar H), 4.0 (s, 6, OCH_3), 2.85 (m, 1, cyclopropyl H), 2.35 (s, 3, Ar CH_3), 1.8 (m, 1, cyclopropyl H), 1.5 (m, 1, cyclopropyl H), 0.96 (d, 3 $CHCH_3$, J = 6 Hz); CIMS, m/e 265 (M + 1). Anal. ($C_{14}H_{20}N_2O_3$) C, H, N.

(1*RS*,2*SR*,3*RS*)-1-Carbobenzoxamido-2-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclopropane (9a). The hydrazide **7a** (528 mg, 2.0 mmol) was taken up into 12 mL of 3 N HCl and cooled to 0 °C. To the cold suspension was added a solution of 217 mg (4.6 mmol) of $NaNO_2$ in 3 mL of H_2O. The reaction mixture was layered with 10 mL of Et_2O and was stirred for 0.5 h. The ether layer was separated and the H_2O layer was extracted twice with ether. The combined ether layers were washed with water, dried ($MgSO_4$), filtered, and concentrated to yield 0.526 g of azide (**8a**: IR 2160 (N_3), and 1720 (C=O) cm^{-1}.

Without further purification, the azide was heated in 10 mL of dry benzene for 2 h at reflux. Infrared analysis showed the absence of the azide absorption at 2160 cm^{-1} and the presence of a strong band at 2260 cm^{-1}. To the hot benzene solution of isocyanate was added 0.423 g of benzyl alcohol in 3 mL of benzene. The mixture was heated at reflux overnight. The solvent was evaporated and the residue was heated under high vacuum to remove excess benzyl alcohol. Purification of the residue over a silica gel column by elution with ethyl acetate–hexane (1:1) gave 0.516 g (73%) of carbamate **9a**. This was recrystallized from EtOH to yield 340 mg: mp 101–102 °C; NMR ($CDCl_3$) δ 7.45 (s, 5, C_6H_5), 6.7 (s, 1, Ar H), 6.5 (s, 1, Ar H) 5.2 (s, 2, $CH_2C_6H_5$), 5.1 (br m, 1, NH), 3.83 and 3.78 (2 s, 6, OCH_3), 2.9 (m, 1, cyclopropyl H), 2.2 (s, 3, Ar CH_3), 1.9 (m, 1, cyclopropyl H), 1.45 (m, 1, cyclopropyl H), 1.2 (br s, 3, $CHCH_3$). Anal. ($C_{21}H_{25}NO_4$) C, H, N.

(1*RS*,2*SR*,3*SR*)-1-Carbobenzoxamido-2-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclopropane (9b). Following a procedure similar to that for **9a**, 0.355 g (1.34 mmol) of hydrazide **7b** afforded 0.364 g (88%) of the carbobenzoxamido derivative: mp 95–96 °C (EtOH); IR (Neat) 3280–3380, 1680, 1500, 1200 cm^{-1}; NMR ($CDCl_3$) δ 7.37 (s, 5, C_6H_5), 6.67 (s, 2, Ar H), 5.15 (s, 2, $CH_2C_6H_5$), 3.78 (s, 6, OCH_3), 2.67 (m, 1, cyclopropyl H), 2.2 (s, 3, Ar CH_3), 1.2–1.6 (m, 2, cyclopropyl H), 0.8 (d, 3, $CHCH_3$, J = 6 Hz); CIMS, m/e 356 (M + 1). Anal. ($C_{21}H_{25}NO_4$) C, H, N.

(1*RS*,2*SR*,3*RS*)-1-Amino-2-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclopropane Hydrochloride (4a). A solution of the carbamate **9a** (100 mg, 0.282 mmol) in 15 mL of EtOH containing 40 mg of 10% palladium on charcoal was stirred at 5 °C under a H_2 atmosphere overnight. The solution was filtered and concentrated. The amine was converted to the hydrochloride using an equivalent amount (0.24 mL) of 1.2 N ethanolic HCl. Recrystallization from acetonitrile–ether gave 56 mg (77%): mp 192–193 °C dec; NMR ($CDCl_3$) δ 8.9 (br m, 3, NH_3^+), 6.6 (s, 1, Ar H), 6.45 (s, 1, Ar H), 3.78 and 3.73 (2 s, 6, OCH_3), 2.8 (m, 2, cyclopropyl H), 2.1 (s, 3, Ar CH_3), 1.8 (m, 1, cyclopropyl H), 1.45 (br s, 3, $CHCH_3$). Anal. ($C_{13}H_{20}NO_2Cl$) C, H, N.

(1*RS*,2*SR*,3*SR*)-1-Amino-2-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclopropane Hydrochloride (4b). A solution of the carbamate **9b** (54.7 mg, 0.154 mmol) in 10 mL of EtOH containing 30 mg of 10% palladium on charcoal was stirred overnight at 5 °C under an atmosphere of hydrogen. The catalyst was removed by filtration, and the solvent was concentrated to obtain a residue, which was converted to the hydrochloride with an equivalent amount (0.13 mL) of 1.2 N ethanolic HCl. This was recrystallized from EtOH–Et_2O to give white crystals: yield 25 mg (62%); mp 168–170 °C; NMR ($CDCl_3$) δ 8.85 (br m, 3, NH_3^+), 6.75 (s, 1, Ar H), 6.65 (s, 1, Ar H), 3.80 (s, 6, OCH_3), 2.5–2.8 (m, 2, cyclopropyl H), 2.15 (s, 3, Ar CH_3), 1.9 (m, 1, cyclopropyl H), 0.86 (d, 3, $CHCH_3$, J = 6 Hz). Anal. ($C_{13}H_{20}NO_2Cl$) C, H, N.

Ethyl 2-(2,5-Dimethoxy-4-methylphenyl)-3-methylcyclopropanecarboxylates 6a and 6b from Ethyl 2,5-Dimethoxy-4-methylcinnamate and Dimethylamino-*p*-tolyloxosulfonium Ethylide. Into a flame-dried, 15-mL, three-necked flask, fitted with a septum and N_2 inlet tube, was placed 284 mg (6.68 mmol) of NaH (as a 57% dispersion in mineral oil), and the flask was kept under N_2. The mineral oil was removed by washing with dry hexane several times, and traces of hexane were removed under vacuum. Dry DMF (distilled over CaH) (6 mL) was added to the flask and the suspension was cooled in an ice bath. Dimethylaminoethyl-*p*-tolyloxosulfonium fluoroborate (**10**; 1.5 g, 6.68 mmol) was added all at once to the flask. Vigorous hydrogen evolution occurred. After 5 min, the ice bath was removed and

the reaction was allowed to warm to 25 °C, resulting in a yellow solution. After 30 min, a solution of ethyl 2,5-dimethoxy-4-methylcinnamate (0.836 g, 3.34 mmol) in 2.0 mL of DMF was added. The mixture was stirred at 25 °C for 5 days. The reaction was cooled in an ice bath, and excess H_2O was added. The solution was extracted several times with ether. The ether extract was washed (brine), dried ($MgSO_4$), and filtered, and the filtrate was concentrated to yield 0.88 g of liquid residue. This material was taken up into a minimum amount of ether and crystallized to remove solid byproducts. Concentration of the mother liquor yielded 0.54 g of a yellow liquid. NMR and TLC analysis of this mixture showed its components to be identical with the cyclopropyl esters obtained by the diazoacetate procedure.

Conversion of Ethyl 2-(2,5-Dimethoxy-4-methylphenyl)-3-methylcyclopropanecarboxylates to the Hydrazide 7a or 7b. The mixture of ethyl 2-(2,5-dimethoxy-4-methylphenyl)-3-methylcyclopropanecarboxylates (obtained from the above reaction) was treated with 99% hydrazine hydrate as described above. Purification of the crude hydrazide over a silica gel column by eluting with 2% MeOH in $CHCl_3$ gave two major components, which had NMR and IR spectra and TLC properties identical with the hydrazides (**7a** and **7b**) obtained from esters formed by the diazoacetate method.

Rat Fundus Preparation. Responses to drugs were studied in the isolated rat fundus, prepared from 250- to 350-g male Sprague-Dawley rats which had been fasted overnight but allowed free access to water. Following the method of Vane,[12] strips of fundus, approximately 3 × 10 mm, were suspended in 25-mL organ baths containing Tyrode's solution, maintained at 37 °C, and oxygenated with 95% O_2–5% CO_2. The bathing solution contained 10^{-7} M iproniazid and scopolamine. Strips were placed under a 1-g initial tension, and contractions were measured using a Grass FT03 force-displacement transducer and recorded with a Gould preamplifier and recorder.

A complete dose–response curve was obtained to serotonin for each tissue. Dose–response curves were obtained in a noncumulative manner, with each drug concentration washed out before proceeding to a higher concentration. This gave more reliable responses and kept spontaneous activity of the tissue to a minimum. Only one test drug was used in each preparation. Responses are reported as the percent of the maximum contraction obtainable with serotonin. Points on the dose–response curves in Figure 1 are the means, with vertical bars indicating the standard error.

Mouse Ear Scratch. This was a modification of our previously published procedure.[11] Male, albino, Swiss-Webster derived mice (Laboratory Supply Co., Indianapolis, IN), 25–40 g, were group housed at 22–24 °C under a 12–12 h light–dark cycle with free access to food and water. Mice were given ip drug injections and were observed in groups of three. Drugs were injected in a volume of saline equal to 0.1 mL/10 g of body weight. Mice were observed continuously for 30 min, and the total number of scratches were recorded. A scratching episode, as described by Kulkarni,[14] consisted of "hindleg scratching of the back of the ear and subsequent return of the hindleg to the floor". Significant differences between treatment responses were identified using Student's *t* test.

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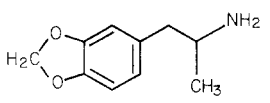
Effects of Certain Hallucinogenic Amphetamine Analogues on the Release of [^{3}H]Serotonin from Rat Brain Synaptosomes

David E. Nichols,*[†] David H. Lloyd,[†] Andrew J. Hoffman,[†] Maxine B. Nichols,[‡] and George K. W. Yim[‡]

Department of Medicinal Chemistry and Pharmacognosy and Department of Pharmacology and Toxicology, School of Pharmacy and Pharmacal Sciences, West Lafayette, Indiana 47907. *Received November 16, 1981*

The enantiomers of 3,4-(methylenedioxy)amphetamine (MDA), *p*-methoxyamphetamine (PMA), and *N*-Me-MDA (MDMA), along with their α,α-dimethylated derivatives, were evaluated for an effect on the release of [^{3}H]serotonin from rat whole brain synaptosomes. The amphetamine isomers were all potent in inducing the release of [^{3}H]serotonin at bath concentrations of 1 and 10 μM but were inactive at 0.1 μM. No significant difference in isomer potency was observed at the 10-μM concentration. However, at 1 μM the (+) isomer of MDMA was more effective in inducing release than was the (−) isomer. Since it is the (+) isomer which is clinically active, this result suggests that transmitter release may play a role in the biological activity of MDMA. By contrast, the α,α-dimethyl compounds were not effective in releasing serotonin, even at the highest bath concentration.

Hallucinogenic phenethylamine derivatives produce their central effects through a stereoselective process. In those cases which have been examined, the pharmacological effects are selectively elicited by the isomer possessing the *R* absolute configuration.[1–6] N-Methylation considerably attenuates or abolishes activity in this series, with the notable exception of 3,4-(methylenedioxy)amphetamine (MDA, **1**).[7] In the case of MDA a curious reversal



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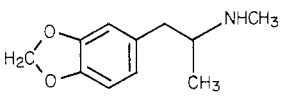

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of stereoselectivity is observed; (*S*)-(+)-*N*-Me-MDA [(*S*)-**2**, (*S*)-(+)-MDMA] is more potent than its optical isomer. Further, cross tolerance does not develop between **1** and **2**, possibly indicating different mechanisms of action.[7] It was previously argued that while (*R*)-**1** might possess a direct receptor action, the effects of (*S*)-**2** might be mediated by release of endogenous neurotransmitter.[7] This was based partly on the proposal by Cheng et al.[8] that

[†] Department of Medicinal Chemistry and Pharmacognosy.
[‡] Department of Pharmacology and Toxicology.

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