yielded 0.6 g (18%) of the crystalline product **6**, found to be pure by TLC (silica gel; benzene/acetone, 8:2, v/v): R_f 0.6; mp 115–116 °C.

Preparation of 6 from Compound 10. Commercial sodium hydride (0.063 g, 57% NaH in oil, 1.5 mmol) was freed from oil by rinsing it with benzene (3 × 5 mL). It was then added to a solution of **10** (0.331 g, 1 mmol) in benzene (20 mL). The reaction mixture was stirred for 48 h and filtered, and the filtrate was concentrated under vacuum. Recrystallization of the remaining solid from ethyl ether/petroleum ether at −10 °C gave 0.250 g (86%) of pure **6**, mp 115–116 °C.

***N*,*N*:*N*′,*N*′-Di-1,2-ethanediyl-*N*″-(2,2,6,6-tetramethyl-4-piperidyl)phosphorothioic Triamide (12a).** To a stirred solution of **9**[7,17] (1.82 g, 10 mmol) in benzene/methylene chloride (100 mL, 2:1, v/v) at 0–4 °C was added a solution of 4-amino-2,2,6,6-tetramethylpiperidine (**11c**; 3.13 g, 20 mmol) in methylene chloride (50 mL). The reaction mixture was allowed to warm to room temperature, and the stirring was continued for 16 h. The mixture was filtered, and the filtrate was concentrated under vacuum. The remaining solid was dispersed in benzene (30 mL), and the dispersion was filtered. The filtrate was concentrated. The remaining solid was mixed with ethyl ether (30 mL), and the solution was filtered. Concentration of the filtrate gave a solid, which on recrystallization from petroleum ether yielded 2.2 g (70%) of crystalline **12a**. TLC analysis (neutral alumina; benzene/methanol, 9:1, v/v) indicated a pure product **12a**: R_f 0.7; mp 121–122 °C; IR (Nujol mull) 3350 (NH), 1430, 1240, 920 cm^{-1}; MS 303 (M^+ + 1, 100), 287 (16), 260 (21); ^{1}H NMR ($CDCl_3$/Me_3Si), δ 1.1 (d, 12 H, 4 CH_3), 1.7–2.2 (m, 13 H, 2 CH_2, 4 CH_2N, NH), 2.5 (t, 1 H, CHN), 3.7 (broad, 1 H, NH). Anal. ($C_{13}H_{27}N_4PS$) C, H, N (±0.35).

***N*,*N*:*N*′,*N*′-Di-1,2-ethanediyl-*N*″-methyl-*N*‴-(2,2,6,6-tetramethyl-4-piperidyl)phosphorothioic Triamide (12b).** To a stirred solution of **9**[7,17] (1.82 g, 10 mmol) in benzene/methylene chloride (200 mL, 1:1, v/v) at 0–4 °C was added all at once a solution of **11b** (3.4 g, 20 mmol) in methylene chloride (50 mL). The reaction mixture was allowed to warm to room temperature, and the stirring was continued for 72 h. The solution was then concentrated under vacuum, and the remaining solid was mixed with benzene (80 mL) and filtered, and the filtrate was concentrated to 10 mL. The concentrate was chromatographed on a neutral alumina column (1 × 14 in.) with benzene/ethyl acetate (8:2, v/v) as eluant. The fractions were monitored by TLC (neutral alumina; benzene/methanol, 9:0.8, v/v). Concentration of the fractions containing the pure compound, R_f 0.7, under vacuum gave 1.2 g (36%) of the crystalline **12b**: mp 94–95 °C; IR (Nujol mull) 1450, 1370, 1250, 920 cm^{-1}; MS, *m/e* 317 (M^+ + 1, 100), 301 (24); ^{1}H NMR ($CDCl_3$/Me_4Si) δ 1.3 (d, 12 H, 4 CH_3), 1.8–2.7 (m, 12 H, 2 CH_2, 4 CH_2N), 2.9–3.3(m, 4 H, CH_3N, CHN), 5 (broad, 1 H, NH). Anal. ($C_{14}H_{29}N_4PS$) C, H, N (±0.35%).

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Registry No. 1, 52-24-4; **2a**, 2226-96-2; **2b**, 14691-88-4; **3a**, 51585-38-7; **3b**, 89486-95-3; **4a**, 51526-59-1; **4b**, 33683-34-0; **5**, 89486-96-4; **6**, 89486-97-5; **7a**, 78996-69-7; **7b**, 89486-98-6; **7c**, 89486-99-7; **8**, 89487-00-3; **9**, 62679-38-3; **10**, 89487-01-4; **11a**, 42585-33-1; **11b**, 40327-96-6; **11c**, 36768-62-4; **12a**, 89487-02-5; **12b**, 89487-03-6; **13a**, 2896-70-0; **13b**, 826-36-8; **14**, 70484-16-1; **15**, 89487-04-7; **16a**, 51526-57-9; **16b**, 64566-76-3; $PSCl_3$, 3982-91-0; $ClCH_2CH_2NH_2$, 689-98-5; aziridine, 151-56-4; phosphorisocyanatidic dichloride, 870-30-4; 4-(dichlorophosphinoaminocarbonyl)-1-oxy-2,2,6,6-tetramethylpiperidine, 89487-05-8.

Substituent Branching in Phenethylamine-Type Hallucinogens: A Comparison of 1-[2,5-Dimethoxy-4-(2-butyl)phenyl]-2-aminopropane and 1-[2,5-Dimethoxy-4-(2-methylpropyl)phenyl]-2-aminopropane

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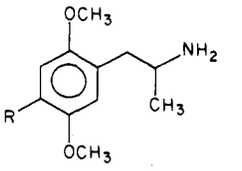
Two novel hallucinogen analogues related to 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, STP) were synthesized and evaluated in the two-lever drug discrimination paradigm by using 0.08 mg/kg of LSD as the training drug stimulus. The two compounds differ from each other only with respect to the point of branching in the 4-alkyl group. However, pharmacological evaluation revealed a clear difference in potency and degree of LSD generalization for the two isomers. Branching adjacent to the ring, as in the 4-(2-butyl) analogue, may provide steric interference to the formation of the drug–receptor complex, while branching one methylene unit removed from the ring, as in the 4-(2-methylpropyl) analogue, poses less of a steric problem for the drug–receptor interaction. This is consistent with the idea that formation of a charge-transfer complex between the hallucinogen molecule and the receptor may be one of the features of this drug–receptor interaction.

In the 1-phenylisopropylamine hallucinogens, "substituted amphetamines", maximum activity resides in compounds with the 2,4,5 aromatic trisubstitution pattern.[1] Greatest potency results when the substituent at the 4-position is an alkyl or halogen (**1**).[2] Variation of the 4-alkyl group in 1-(2,5-dimethoxy-4-alkylphenyl)isopropylamine has shown that optimum activity resides in analogues containing a straight chain, while branching adjacent to the ring drastically attenuates activity.[3,4]

It has been suggested that a planar surface may serve as a model for the interaction of hallucinogenic phenethylamines with the receptor.[5,6] Furthermore, present evidence suggests that binding to the receptor may involve



1, R = alkyl; halogen
2, R = $CH_2CH(CH_3)_2$
3, R = $CH(CH_3)CH_2CH_3$

the formation of a charge-transfer complex.[7–9] The steric bulk of the 4-alkyl group may therefore have an important

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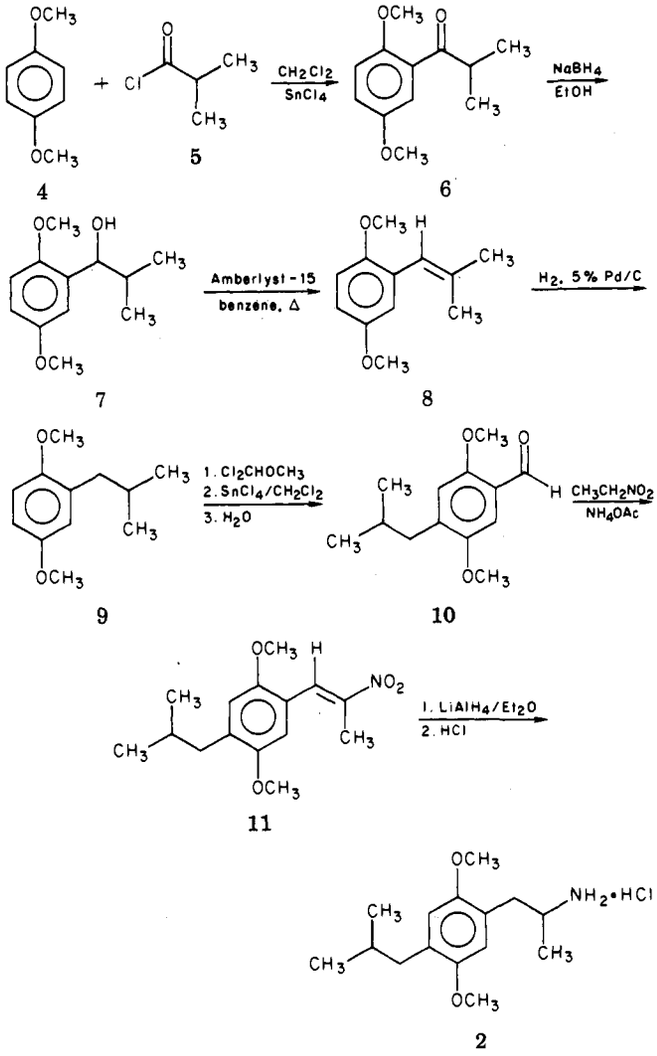
Table I. Results of Drug Discrimination Assay

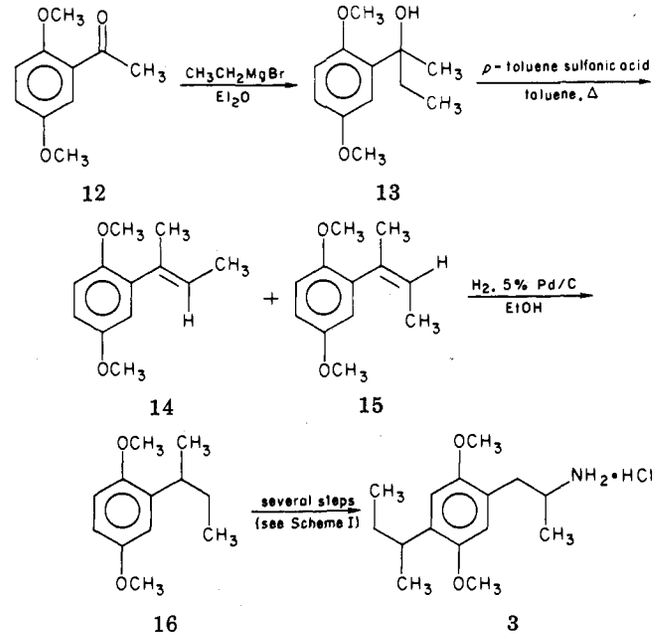
compd	dose range, mg/kg	no. of doses	no. of test sessions per drug[a]	highest % LSD correct responses (dose, mg/kg)[b]	ED_{50}, mg/kg	95% confidence interval
LSD	0.005–0.08	5	23	100 (0.04)	0.0077	0.0036–0.0162
DOM	0.125–0.5	4	30	99 (0.5)	0.148	0.094–0.234
2	0.125–2.0	5	24	95 (1)	0.536	0.227–1.26
3	0.5–16	6	26	70 (4)	1.800	0.244–13.25

[a] Four to nine rats were used per dose of compound. [b] Average responding after saline administration never exceeded 15%.

Scheme I



Scheme II



influence on the ability of the electron-rich aromatic ring of the hallucinogen molecule to closely approach an electron acceptor on the receptor surface. Reports in the literature have indicated that such steric factors have deleterious effects on electron donor–acceptor complex formation.[10,11] The possibility of such steric interference by the alkyl group in 1-phenylisopropylamine hallucinogens has been clearly demonstrated by model calculations of conformational energies.[12]

One may predict, a priori, that the 4-isobutyl analogue (**2**), where branching is removed from the aromatic ring by one methylene unit, will retain a higher potency than the 4-*sec*-butyl analogue (**3**), where the branching is adjacent to the ring. This report describes the synthesis and pharmacological evaluation of compounds **2** and **3** in the two-lever drug discrimination paradigm.[13] For comparison purposes, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, STP) was included in the assay.

Chemistry. The synthesis of the hydrochloride salt of **2** used for the pharmacological evaluation was accomplished in eight steps as outlined in Scheme I. Friedel–Crafts acylation of *p*-dimethoxybenzene (**4**) with isobutyryl chloride (**5**) yielded the ketone **6**, which was then reduced with $NaBH_4$ to the alcohol **7**. Initial attempts to dehydrate the alcohol with *p*-toluenesulfonic acid were improved by use of the sulfonic acid type cation-exchange resin, Amberlyst-15. The resulting olefin **8** was then hydrogenated to the saturated alkane **9**. The aldehyde **10** was formed

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in the reaction of **9** with Cl_2CHOCH_3, followed by H_2O. Subsequent condensation of **10** with nitroethane yielded the nitropropene **11**, which was reduced with $LiAlH_4$ to form the free base **2**, which was converted to the hydrochloride salt.

A similar procedure was followed in the synthesis of **3** (Scheme II), proceeding from the Grignard reaction of **12** with ethylmagnesium bromide. The resulting carbinol **13** was dehydrated with *p*-toluenesulfonic acid to yield a mixture of the two isomeric olefins **14** and **15**, which was subsequently hydrogenated. The alkane **16** was carried forward to yield **3** in a manner identical with that shown in Scheme I. Although **3** is a mixture of diastereomers, they did not resolve on TLC, nor did repeated recrystallizations of the hydrochloride salt alter the melting point of this mixture. Therefore, **3** may be comprised of equal amounts of four optical diastereomers.

Results and Discussion

The results of the drug discrimination assay are presented in Table I. Based on the ED_{50} values, the 4-isobutyl analogue **2** was found to be 3.4 times more potent than the 4-*sec*-butyl analogue **3**. A comparison of the two compounds shows that the LSD cue completely generalized (95%) to that produced by **2** at one-fourth the dose at which **3** produced its maximum degree of generalization of only about 70%. Complete generalization for **3** did not occur, since disruption resulted from higher doses, disruption being defined as failure to complete 32 responses within the 55-min experimental period. However, an ED_{50} value was calculated for approximate potency comparison.

These results suggest that **2** and DOM produce an interoceptive cue in the rat that is sufficiently similar to the training drug, 0.08 mg/kg of LSD, to substitute for it as a stimulus. The cue produced by **3** probably has some overlapping stimulus properties but cannot completely substitute for LSD.

It should be noted that **3** is a mixture of diastereomers, by virtue of the fact that this molecule contains two chiral centers, whereas **2** is simply a racemic mixture. We have no information as to whether or not a binding site for the 2-butyl substituent would exhibit a stereoselective preference for one of the four optical diastereomers.

In previous studies[14] of the 1-(4-alkyl-2,5-dimethoxyphenyl)isopropylamine series, rats were trained to discriminate a dose of 1.0 mg/kg of (±)-DOM (**1**, R = CH_3) from saline under a VI-15 schedule of reinforcement. This drug stimulus generalized to the enantiomers of DOET (**1**, R = CH_2CH_3), DOPR (**1**, R = $CH_2CH_2CH_3$), and DOBU (**1**, R = $CH_2CH_2CH_2CH_3$). Generalization was not observed in testing with DOTB [**1**, R = $C(CH_3)_3$] and DOAM (**1**, R = $CH_2CH_2CH_2CH_2CH_3$). Another study by Glennon et al.[15] reported that within the 4-alkyl derivatives of 2,5-DMA, only DOM produced generalization when administered to 5-OMe-DMT trained rats.

It is still too early to make conclusive remarks on the mechanistic components of the behavioral effects of this series of compounds, but judging from results of this and previous studies, the variation of the alkyl substituent on 1-(4-alkyl-2,5-dimethoxyphenyl)isopropylamine has a clear effect on the potency and the degree to which these compounds generalize to a hallucinogenic training drug. Branching adjacent to the aromatic ring, as in DOTB and **3**, lowers the degree of generalization to the training drugs (±)-DOM, 5-OMe-DMT, or LSD.

These results are consistent with the idea that steric bulk, introduced by various 4-alkyl groups, may influence the formation of a charge-transfer complex at the receptor. There is a clear difference between the potency (ED_{50}) and the degree of generalization of **2**, relative to that of **3**. The moving of the methyl branch in the 4-alkyl group of **3** to a more distal site as in **2** can be viewed as a modification that leads to reduced interference with the ability of the drug molecule to approach the receptor. The log *P* values for these two compounds are expected to be nearly identical, and one would not expect lipophilicity to be an important factor. However, other differential factors, such as metabolism, transport, and binding to different receptor populations, cannot be excluded at this time.

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 instrument and are reported in δ values (parts per million) relative to an internal standard of tetramethylsilane. Elemental analyses were performed by the microanalysis laboratory, Chemistry Department, Purdue University, and are within 0.4% of the calculated values.

2′,5′-Dimethoxy-2-methylpropiophenone (6). To a solution of 4.56 g (30 mmol) of 2,5-dimethoxybenzene (**4**) and 3.20 g (30 mmol) of isobutyryl chloride (**5**) in 50 mL of dry CH_2Cl_2 in an ice bath was added 7.8 g (33 mmol) of $SnCl_4$ dropwise over 45 min while stirring. Following addition, the reaction was allowed to warm to room temperature (30 min) and then heated at reflux on a steam bath for 2 h. The reaction was cooled and then poured over crushed ice (10 g), and the CH_2Cl_2 layer was washed with 2 × 50 mL of 6 N HCl, followed by 2 × 100 mL of H_2O, and then dried (Na_2SO_4) overnight. The solution was filtered, and the filtrate was concentrated by rotary vacuum evaporation. The yellow residue was purified by vacuum distillation to afford 4.48 g (72%) of the ketone: bp 88 °C (0.04 mm); ^1H NMR ($CDCl_3$) δ 1.14 (d, 6, CH_3, J = 6.9 Hz), 3.44 (m, 1, CH, J = 6.9 Hz), 3.77 and 3.82 (2 s, 6, OCH_3), 6.93 (m, 3, Ar H). Anal. ($C_{12}H_{16}O_3$) C, H.

1-(2,5-Dimethoxyphenyl)-2-methylpropanol (7). The reduction of 4.48 g (21.5 mmol) of **6** was accomplished by treatment with 0.81 g (21.5 mmol) of $NaBH_4$ in 25 mL of dry EtOH. The mixture was stirred at room temperature for 2.5 h and then concentrated under vacuum. The residue was partitioned between CH_2Cl_2 and H_2O, and the organic phase was reduced by rotary vacuum evaporation. The resulting light yellow oil was purified by vacuum distillation to yield 3.25 g (72%) of the alcohol: bp 97 °C (0.05 mm); ^1H NMR ($CDCl_3$) δ 0.80 (d, 3, CH_3, J = 6.7 Hz), 1.01 (d, 3, CH_3, J = 6.7 Hz), 2.00 (m, 1, CH), 2.48 (d, 1, OH), 3.77 and 3.79 (2 s, 6, OCH_3), 4.48 [t, 1, C(OH)H], 6.80 (m, 3, Ar H). Anal. ($C_{12}H_{18}O_3$) C, H.

1-(2,5-Dimethoxyphenyl)-2-methylpropene (8). To a solution of 4.5 g (21.4 mmol) of **7** in 50 mL of benzene was added 0.4 g of Amberlyst-15 cation-exchange resin. After the solution was refluxed for 1.5 h, the resin was filtered off, and the benzene was reduced under vacuum, yielding 3.9 g (95%) of the crude alkene. The product was purified by vacuum distillation: bp 92 °C (0.06 mm); ^1H NMR ($CDCl_3$) δ 1.81 (s, 3, CH_3), 1.92 (s, 3, CH_3), 3.74 (s, 6, OCH_3), 6.28 (s, 1, =CH), 6.78 (m, 3, Ar H). Anal. ($C_{12}H_{16}O_2$) C, H.

1-(2,5-Dimethoxyphenyl)-2-methylpropane (9). A solution of 1.00 g (5.2 mmol) of the alkene **8** in 40 mL of EtOH containing 150 mg of 5% Pd/C was shaken under an H_2 atmosphere at an initial pressure of 50 psig for 3 h. Concentration of the filtrate after removal of the catalyst gave a quantitative yield of chromatographically pure product. Vacuum distillation afforded the pure saturated compound: bp 72 °C (0.4 mm); ^1H NMR ($CDCl_3$) δ 0.90 (d, 6, CH_3, J = 6.7 Hz), 1.90 (m, 1, CH, J = 6.7 Hz), 2.45 (d, 2, CH_2, J = 7.2 Hz), 3.76 (s, 6, OCH_3), 6.76 (m, 3, Ar H). Anal. ($C_{12}H_{18}O_2$) C, H.

2,5-Dimethoxy-4-(2-methylpropyl)benzaldehyde (10). A solution of 0.5 g (2.58 mmol) of **9** and 1.34 g (5.16 mmol) of $SnCl_4$ in 20 mL of dry CH_2Cl was stirred and cooled in an ice bath to

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5 °C. Dropwise addition of 0.45 g (3.87 mmol) of Cl_2CHOCH_3 over 30 min was followed by reflux for 3 h. After cooling, the reaction mixture was poured over 5 g of ice and the CH_2Cl_2 layer was then washed with 3 × 30 mL of 6 N HCl and 3 × 30 mL of H_2O. Drying (Na_2SO_4), filtering, concentrating, and purifying by vacuum distillation afforded 0.40 g (70%) of pure aldehyde: bp 104 °C (0.15 mm); ^1H NMR ($CDCl_3$) δ 0.91 (d, 6, OCH_3, J = 6.5 Hz), 1.90 (m, 1, CH), 2.53 (d, 2, CH_2, J = 7.0 Hz), 3.80 and 3.88(2 s, 6, OCH_3), 6.74 (s, 2, Ar H), 10.30 (s, 1, COH). Anal. ($C_{13}H_{18}O_3$) C, H.

1-[2,5-Dimethoxy-4-(2-methylpropyl)phenyl]-2-nitropropene (11). A mixture of 3.79 g (17 mmol) of the aldehyde and 1.3 g (17 mmol) of ammonium acetate in 50 mL of $EtNO_2$ was refluxed for 2.5 h. The remaining $EtNO_2$ was removed by rotary vacuum evaporation, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic layer was concentrated, and the product was recrystallized from methanol to afford 3.12 g (66%) of 11 as yellow needles: mp 72 °C; ^1H NMR ($CDCl_3$) δ 0.91 (d, 6, CH_3, J = 6.5 Hz), 1.93 (m, 1, CH), 2.41 (d, 3, CH_3, J = 1 Hz), 2.51 (d, 2, CH_2, J = 7.1 Hz), 3.78 and 3.83 (2 s, 6, OCH_3), 6.70 and 6.77 (2 s, 2, Ar H), 8.28 (s, 1, =CH). Anal. ($C_{15}H_{21}NO_4$) C, H, N.

1-[2,5-Dimethoxy-4-(2-methylpropyl)phenyl]-2-aminopropane Hydrochloride (2). A solution of 1.24 g (32.4 mmol) of $LiAlH_4$ in 100 mL of dry ether was stirred while 3.0 g (10.8 mmol) of 11 dissolved in 25 mL of dry ether was added dropwise over 10 min. The mixture was then refluxed on a steam bath for 2 h. The $LiAlH_4$ was quenched with 3.72 mL of H_2O in 10 mL of THF and allowed to stir for 3 h. The precipitate was filtered off and the ether was washed with 2 × 30 mL of H_2O and dried (Na_2SO_4) overnight. The ether was removed by rotary vacuum evaporation, and the free base was dissolved in 21 mL of 0.5 N ethanolic HCl. Recrystallization from 2-propanol–ethyl acetate afforded 1.63 g (60%) of fine white crystals: mp 164–166 °C; ^1H NMR (D_2O) δ 0.88 (d, 6, CH_3, J = 6.5 Hz), 1.38 (d, 3, CH_3, J = 6.5 Hz), 1.71 (br s, 2, CH_2), 1.77 (m, 1, CH), 2.44 (d, 2, CH_2, J = 6.9 Hz), 2.98 (m, 1, CH), 3.75 and 3.78 (2 s, 6, CH_3), 6.61 and 6.69 (2 s, 2, Ar H), 8.30 (br s, 3, NH_3). Anal. ($C_{15}H_{26}NClO_2$) C, H, N.

2-(2,5-Dimethoxyphenyl)-2-butanol (13). A Grignard reagent was prepared from 13.29 g (0.122 mol) of EtBr in 150 mL of dry ether. A solution of 20 g (0.111 mol) of 2,5-dimethoxyacetophenone 12 in 150 mL of ether was added, and the reaction was vigorously stirred and heated at reflux overnight. After cooling, the mixture was treated with cold saturated NH_4Cl solution. The aqueous layer was extracted twice with ether, the combined ether extract was dried (Na_2SO_4) and filtered, and the filtrate was concentrated under vacuum to afford 18.7 g (80%) of crude alcohol: bp 109–111 °C (0.9 mm); ^1H NMR ($CDCl_3$) δ 0.78 (t, 3, CH_3, J = 7.5 Hz), 1.52 (s, 3, CH_3), 1.85 (m, 2, CH_2), 3.80 and 3.75 (2 s, 6, OCH_3), 4.08 (br s, 1, OH), 6.81 (m, 2, Ar H), 6.98 (m, 1, Ar H). Anal. ($C_{12}H_{18}O_3$) C, H.

(*E*)- and (*Z*)-2-(2,5-Dimethoxyphenyl)-2-butene (14 **and** 15). A solution of 22.47 g (0.107 mol) of the alcohol 13 in 250 mL of toluene was treated with 200 mg of *p*-toluenesulfonic acid and heated at reflux overnight. The cooled reaction was washed with 3 × 50 mL of 1 N NaOH and then with water and dried ($MgSO_4$). Filtration and concentration afforded 20.29 g (98.8%) of the crude alkene, which was purified by vacuum distillation: bp 71–74 °C (0.3 mm); ^1H NMR ($CDCl_3$) δ 1.76–1.40 (m, 3, CH_3), 1.96 (br s, 3, CH_3), 3.70 (s, 6, OCH_3), 5.60 (m, 1, =CH), 6.73 (m, 3, Ar H). Anal. ($C_{12}H_{16}O_2$) C, H.

2-(2,5-Dimethoxyphenyl)butane (16). A solution of 13.4 g of the alkene mixture 14 and 15 in 150 mL of 95% EtOH was shaken over 500 mg of 5% Pd/C under an atmosphere of H_2 at an initial pressure of 50 psig. Reduction was complete in about 2 h, and the catalyst was removed by filtration. The filtrate was concentrated by rotary vacuum evaporation, and the residual oil was purified by vacuum distillation to afford 12.08 g (90%) of the title compound: bp 72 °C (0.15 mm); ^1H NMR ($CDCl_3$) δ 0.83 (t, 3, CH_3, J = 7.6 Hz), 1.16 (d, 3, CH_3, J = 6.9 Hz), 1.47 (m, 2, CH_2), 3.13 (m, 1, CH), 3.73 (s, 6, OCH_3), 6.76 (m, 3, Ar H). Anal. ($C_{12}H_{18}O_2$) C, H.

2,5-Dimethoxy-4-(2-butyl)benzaldehyde (17). To a solution of 14.55 g (75 mmol) of 16 in 150 mL of dry CH_2Cl_2 in an ice bath was added 30.3 g (0.16 mol) of $TiCl_4$. While stirring in the ice bath, 8.63 g (75 mmol) of Cl_2CHOCH_3 was added dropwise. Following addition, the reaction was stirred at ice-bath temperature for 30 min, allowed to warm to room temperature, and then heated at reflux for 1 h. The reaction was cooled and then poured over crushed ice, and the methylene chloride layer was washed with 3 × 50 mL of 6 N HCl and 3 × 50 mL of H_2O and then dried (Na_2SO_4). The solution was filtered, and the filtrate was reduced by rotary vacuum evaporation. The residue was taken up into $CHCl_3$ and slowly percolated through a 50-g pad of silica gel to remove Ti salts. The filtrate was concentrated, redissolved in ether, and shaken vigorously with a saturated solution of $NaHSO_3$. The solid bisulfite adduct was washed well with EtOH and ether and then decomposed by dissolving it in H_2O and then treating the resulting solution with Na_2CO_3. The purified aldehyde was extracted into ether, the ether was dried (Na_2SO_4) and filtered, and the filtrate was concentrated to afford 13.83 g (83%) of the product as a pale yellow oil. Purification by vacuum distillation gave bp 93–95 °C (0.2 mm); ^1H NMR ($CDCl_3$) δ 0.85 (t, 3, CH_3), 1.20 (d, 3, CH_3), 1.67 (br m, 2, CH_2), 3.20 (br m, 1, CH), 3.86 and 3.93 (2 s, 6, OCH_3), 6.93 and 7.40 (2 s, 2, Ar H), 10.26 (s, 1, COH). Anal. ($C_{13}H_{18}O_3$) C, H.

1-[2,5-Dimethoxy-4-(2-butyl)phenyl]-2-nitropropene (18). A mixture of 12.5 g (56.4 mmol) of the aldehyde 17 and 2.43 g of ammonium acetate in 50 mL of $EtNO_2$ was heated on the steam bath with stirring overnight. The reaction mixture was concentrated by rotary vacuum evaporation, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic phase was concentrated, and the residue was chromatographed over a 100-g column of silica gel using $CHCl_3$ elution. The pooled fractions containing the yellow product were concentrated and recrystallized from MeOH to afford 12.73 g (82%) of 18 as fine yellow needles: mp 58–60 °C; NMR ($CDCl_3$) δ 0.86 (t, 3, CH_3, J = 7.2 Hz), 1.20 (d, 3, CH_3, J = 7 Hz), 1.55 (m, 2, CH_2), 2.42 (d, 3, CH_3, J = 0.9 Hz), 3.12 (m, 1, CH), 3.79 and 3.84 (2 s, 6, OCH_3), 6.76 and 6.78 (2 s, 2, Ar H), 8.28 (s, 1, =CH). Anal. ($C_{15}H_{21}NO_4$) C, H, N.

1-[2,5-Dimethoxy-4-(2-butyl)phenyl]-2-aminopropane Hydrochloride (3). The reduction of 3.46 g (13 mmol) of 18 was accomplished in dry ether by using 1.50 g (39 mmol) of $LiAlH_4$. Standard workup, followed by conversion of the free base to the hydrochloride salt and recrystallization from CH_3CN, afforded 2.25 g (73%) of the desired product: mp 168–170 °C; NMR ($CDCl_3$) δ 0.83 (t, 3, CH_3, J = 7.2 Hz), 1.17 (d, 3, CH_3, J = 6.9 Hz), 1.39 (d, 3, CH_3, J = 6.4 Hz), 1.52 (br m, 2, CH_2), 1.72 (br s, 2, CH_2), 3.00 (br m, 2, Ar CH, CHN), 3.76 and 3.79 (2 s, 6, OCH_3), 6.67 (s, 1, Ar H), 6.70 (s, 1, Ar H), 8.29 (br s, 3, NH_3).

Pharmacology. Animals. Sixteen male, Sprague–Dawley rats, weighing 200–240 g at the start of the experiment, were obtained from Murphy Breeding Labs, Inc., Plainfield, IN. For the 1st week, all rats were group housed (eight per cage) with food and water available ad libitum. The animals were housed in an environmentally controlled room at a temperature between 22 and 24 °C and a 14/10 h light/dark cycle. Following the initial acclimatization period, the rats were housed in pairs and started on a restricted food regimen: a limited amount of rat chow (Lab Blox) was provided to allow for an approximately 1-g gain in body weight per rat per day. Body weight was monitored daily; a few rats were assigned new cage mates to minimize competition for food. Food was provided once daily, approximately one hour after the rats were removed from the operant chambers. Water was available continuously, except during training and testing sessions.

Apparatus. Standard operant chambers (Coulbourn Instruments) consisting of modular test cages enclosed within sound attenuated, ventilated cubicles were used. Each chamber contained two response levers separated by a pellet trough into which 45-mg food pellets (Bioserv, dustless) were delivered from an electronically operated pellet dispenser. Solid-state programming and recording equipment was located in an adjacent room.

Drug Administration. A solution of *d*-LSD tartrate (NIDA) was prepared in saline such that administration of 1.0 mL/kg gave the desired training dosage of 0.08 mg/kg. Injections of either saline or LSD were administered intraperitoneally 30 min before the start of discrimination sessions.

Discrimination Training. In order to minimize the effects due to side preference, the rats were divided into two subgroups as follows: SAL-R/LSD-L and SAL-L/LSD-R. If the right lever (R) was correct when saline (SAL) was administered, then the

left lever (L) was correct when LSD was administered. The conditions were reversed for the other group.

From the first discrimination session onward, an injection of either LSD or saline was given prior to the session. Discrimination training was carried out 7 days per week. Initially rats were shaped to press the left lever, which was programmed to deliver a food pellet for each lever press (FR1). Once the rats acquired the lever-pressing response, the number of responses required for the delivery of the pellet was gradually increased until a fixed ratio of 32 (FR32, one reinforcement for every 32 lever presses) was achieved. Initially, only responding on the left lever was reinforced, so half the rats received saline and the other half received LSD.

Once three consecutive days of training on the FR32 schedule with a criteria of 85% correct responding on the left lever had been achieved, responding on the left lever was made inconsequential and the right lever was activated for the second phase. At this time, the rats that originally received LSD, received saline, and the rats that originally received saline, now received LSD. Discrimination training was again carried on until the rats were responding on the drug-appropriate lever on a FR32 schedule of reinforcement.

The third and final phase of discrimination training involved administration of the first training drug (either LSD or SAL) for 3 consecutive daily sessions, followed by administration of the second training drug for 3 more daily sessions. Following this, the first drug was again administered for 3 consecutive days, followed by the second drug for 2 more days. Finally, the first training drug was administered for 2 days. If responding during this last phase of discrimination training fulfilled the criteria of 85% responding on the appropriate lever, the stimulus generalization test procedure was initiated. If not, the rats were kept on discrimination training until the criterion was achieved.

Stimulus Generalization. The drug discrimination training required 5–6 weeks. Those rats that also successfully met the criteria of 85% correct responses on the appropriate levers in the final phase were included in the stimulus generalization procedure. During this phase of the study, test sesions were run on Wednesdays and Saturdays, with training sessions conducted on Monday, Tuesday, Thursday, and Friday. All injections were given 30 min before the session. The animals received no treatment on Sundays. In order to receive a test drug on Wednesday or Saturday, the animals were required to satisfy the 85% correct lever response criteria on both preceding training days. If the criterion was not satisfied, the testing session was used as a training session. The rates of responding for the LSD and saline training sessions were not significantly different.

During all phases of the experiment, the training sessions were of 15-min duration, and lever responses on both levers were recorded and the results were expressed as percent responding on the appropriate lever. On testing days, the session was terminated following 32 responses on either lever. No reinforcement was given. This was designated the lever selected by the rat in response to the drug cue. In all cases, responding on the incorrect lever had no programmed consequence.

Several preliminary experiments to determine appropriate dosages to use for new compounds were carried out; these data were discarded. Based on these initial experiments, dosages were selected for each test compound. The drug treatments in this study, including LSD, were randomized over the entire experimental period.

Data Analysis. An ED_{50} was calculated for LSD and for each test compound by the method of Litchfield and Wilcoxon.[16] This was defined as the dose at which responses were equally distributed on the drug and saline appropriate levers.

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Registry No. **2**, 89556-64-9; **2** (free base), 89556-70-7; **3**, 89556-69-4; **3** (free base), 89556-71-8; **4**, 150-78-7; **5**, 79-30-1; **6**, 89556-60-5; **7**, 26172-15-6; **8**, 35205-30-2; **9**, 89556-61-6; **10**, 89556-62-7; **11**, 89556-63-8; **12**, 1201-38-3; **13**, 89556-65-0; **14**, 72648-95-4; **15**, 89556-66-1; **16**, 13620-78-5; **17**, 89556-67-2; **18**, 89556-68-3; $EtNO_2$, 79-24-3; EtBr, 74-96-4.

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Synthesis of a Novel Series of (Aryloxy)propanolamines: New Selective β_2-Blocking Agents

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A new family of β-blocking drugs is described. The originality of the new molecules lies in their functionalized hydrophobic folded structure, the basic part of which contains a benzocyclobutene ring. Excellent β_2-blocker selectivity has been obtained with some of these compounds. Interestingly, this selectivity was not modified toward β_1-blocker activity by introduction of the usual β_1 inducer groups.

β-Adrenoceptor blocking drugs have proved to be the most important advance in the pharmacotherapy of serious and widespread cardiovascular diseases.[1] They also have much to offer as therapy for some other serious clinical disorders.[2] However, β-blockers are far from being devoid of toxic or adverse effects.[3] These properties explain the constant efforts made to find new selective drugs.

Motivations other than therapeutic ones also explain the number of works presently devoted to the development of new β antagonists. Indeed, the different clinical events mentioned above are related to whether or not the drugs are selective for β_1 and β_2 adrenoceptors, as well as to whether or not they possess membrane-stabilizing qualities and/or intrinsic sympathomimetic activities. Knowledge of the behavior of the adrenergic system, as well as the

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