# 2,5-Dimethoxy Congeners of (+)- and (-)-3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine

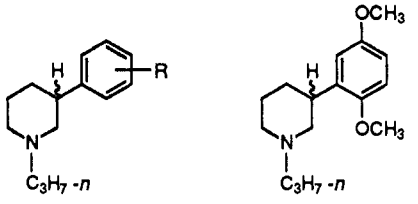
Joseph G. Cannon,*,† Karen S. Kirschbaum,† Victor E. D. Amoo,† Alan K. Johnson,‡ and John Paul Long‡

*Division of Medicinal and Natural Products Chemistry, College of Pharmacy, and Department of Pharmacology, College of Medicine, The University of Iowa, Iowa City, Iowa 52242*

*Received February 3, 1993*

*p*-Dimethoxyaryl analogs of certain potent catechol-derived dopaminergic agonists show dopaminergic properties for which no structure–activity relationship has yet been defined. (*S*)-3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine (1, *S*-"3-PPP") is a dopaminergic autoreceptor agonist, and at high doses it also exhibits postsynaptic antagonism. (*R*)-1 is a postsynaptic agonist. In a continuation of studies of effects of the *p*-dimethoxy moiety at dopamine receptors, synthesis and resolution of the 2,5-dimethoxy analog 3 of 3-PPP was undertaken. The two enantiomers and the racemic modification showed cardiovascular effects consistent with actions at DA-2 receptors. The potency of all three compounds was much lower than that of 3-PPP, although they displayed approximately the same duration of action. Absolute configuration does not seem to be a major determinant of these compounds' ability to interact with DA-2 receptors.

(*S*)-3-(3-Hydroxyphenyl)-*N*-*n*-propylpiperidine (1, "3-PPP") is a selective dopaminergic autoreceptor agonist;[1,2] at the same dose level it also blocks certain postsynaptic dopaminergic receptor sites, and thus it exhibits a bifunctional mode of dopaminergic attenuation. Clark *et al.*[3] reported that (*S*)-1 is a partial agonist at D-2 receptor sites, but it does not appear to interact at D-1 receptors. In contrast, (*R*)-1 at low doses stimulates postsynaptic dopaminergic receptor sites, and at high doses it stimulates presynaptically.[1,2] The (*RS*)-catechol derivative 2 is a potent postsynaptic dopaminergic agonist, but it lacks presynaptic effects.[4]



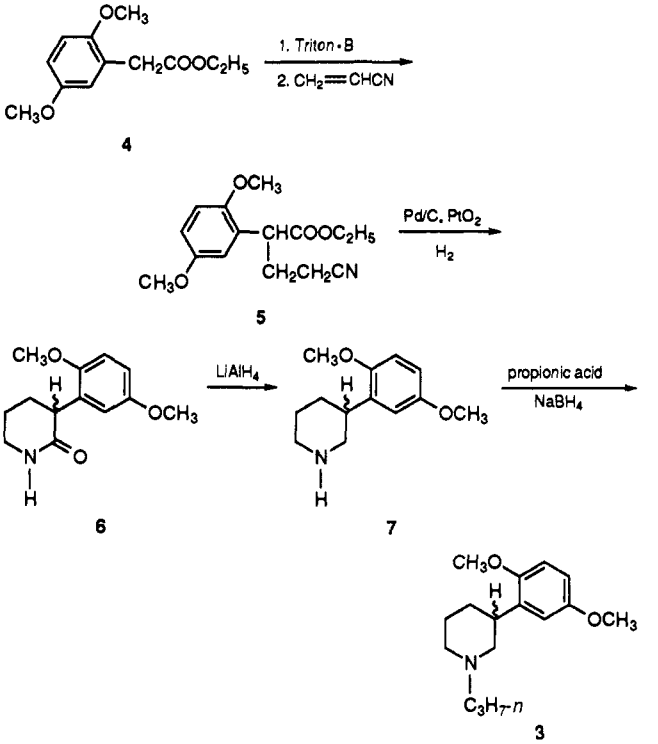
1: R = 3-OH
2: R = 3,4-di-OH

The *p*-dimethoxy moiety has been incorporated into a variety of aromatic ring systems, catechol derivatives of which elicit dopaminergic agonist action: β-phenethylamine, 2-aminotetralin, 2-aminoindan, and linearly and angularly octahydrobenzoquinolines. Some of the *p*-dimethoxy derivatives showed dopaminergic agonist effects;[5-7] some showed effects at $\alpha_1$ adrenoceptors;[8] and some were inert in all assays for activity at catecholamine neurotransmitter receptors.[7] No consistent nor predictable pharmacological effect was produced by replacement of the catechol moiety by *p*-dimethoxy. To seek further insight into pharmacological properties of the *p*-dimethoxy moiety, preparation of the 3-PPP analog 3 was undertaken. Due to the striking qualitative and quantitative pharmacological differences between the enantiomers of 3-PPP, (*R*)- and (*S*)-3 were prepared.

## Chemistry

The racemic target compound 3 was prepared as illustrated in Scheme I. The reductive cyclization reaction

**Scheme I.** Preparation of (*RS*)-3-(2,5-Dimethoxyphenyl)-*N*-*n*-propylpiperidine

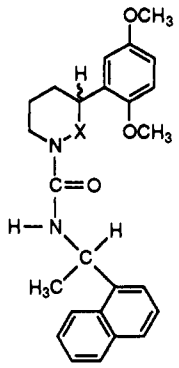


(5 → 6) could be achieved in one step only in the presence of two catalysts, platinum oxide and palladium on charcoal. Attempts to resolve (±)-3 by formation and recrystallization of diastereomeric salts failed. Resolution of the racemic lactam intermediate 6 by a method of Pirkle *et al.*[9] involving formation of diastereomeric ureas with (*R*)-1-(1-naphthyl)ethyl isocyanate was not successful.

The diastereomeric ureas 8 formed in good yields, and they were separable by chromatographic methods. However, the chiral center of the piperidone ring is optically labile under the basic conditions necessary to effect cleavage of the urea derivative, and only the racemic lactam 6 could be isolated. Alternatively, the secondary amine 7 was derivatized with (*R*)-1-(1-naphthyl)ethyl isocyanate to provide the diastereomeric urea derivatives 9 and 10 in good yield; these were separable by chromatographic methods. The optically active secondary amines, (+)-7

† Division of Medicinal and Natural Products Chemistry, College of Pharmacy.
‡ Department of Pharmacology, College of Medicine.

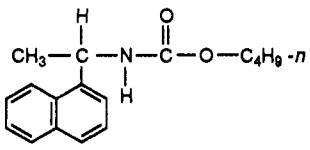
0022-2623/93/1836-2416$04.00/0 



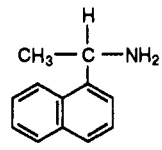
8: X = C=O
9, 10: X = $CH_2$

and (−)-7, were liberated by a method of Schoenenberger and Brossi:[10] thermolysis of the urea derivative in refluxing higher boiling alcohol in the presence of base. To verify the optical integrity of the secondary amines (+)-7 and (−)-7, they were reconverted into the urea derivatives by treatment with the chiral isocyanate. Thin-layer chromatographic analysis of each of the resulting urea products revealed only one spot, providing evidence that racemization of the secondary amines had not occurred during the thermal cleavage of the urea derivatives.

Thermal decomposition of urea derivatives with at least one N–H group involves intramolecular proton transfer from one nitrogen to the other to form an amine and an isocyanate.[11] In the presence of base (sodium 1-butoxide) the resulting isocyanate is immediately scavenged, forming an *N*-butylcarbamate derivative 11, and driving the reaction to completion. In the present work, 1-naphth-1-ylethylamine (12) was isolated as a byproduct of the thermolysis reaction. It was speculated that this compound resulted from hydrolysis of the carbamate 11. While the formation of the naphthylethylamine derivative 12 did not interfere with the thermal decomposition reaction, the presence of a second amine compound in the crude reaction mixture necessitated chromatographic isolation and purification of the target amine 7.



11



12

Spectral (IR, NMR, MS) data on all intermediates and final compounds were consistent with the proposed structures.

## Pharmacology

**Results and Discussion.** All three target compounds [(±)-3, (+)-3, and (−)-3] and (*R*)-(+)-3-PPP (1) induced bradycardia and hypotension in the rat, apparently by interacting at $DA_2$ receptors on sympathetic nerve terminals. In separate experiments, sulpiride (100 μg/kg) and haloperidol (50 μg/kg) were used to inhibit $DA_2$ receptors, thus to antagonize $DA_2$ agonist properties of the test compounds. The above doses of sulpiride and haloperidol resulted in approximately 80% antagonism of the neuronal inhibition induced by (±)-3, (+)-3, (−)-3, and (+)-3-PPP (1). Results are shown in Table I. The methoxy analogs were less active than the reference compound ["3-PPP" (1)], but they demonstrated approximately the same duration of action. Absolute configuration does not appear to be a major determinant of ability of the *p*-dimethoxy congeners to interact with $DA_2$ receptors. Again, the unpredictable effect of the *p*-dimethoxy moiety on dopaminergic activity is demonstrated.

**Table I.** Cardiovascular Responses of 2,5-Dimethoxy 3-PPP Congeners in Anesthetized Rats (Mean Values ± SD)

| compd no. dose, μg/kg | arterial pressure decrease, mmHg[a] | heart rate decrease, beats/min[a] | duration, min |
|---|---|---|---|
| (*R*) − (+) − 3 − PPP (1) | | | |
| 10 | 5 ± 2 | 13 ± 8 | 6 ± 3 |
| 30 | 16 ± 6 | 37 ± 13 | 10 ± 3 |
| 100 | 23 ± 8 | 44 ± 17 | 14 ± 6 |
| (±) − 3 | | | |
| 300 | 10 ± 3 | 17 ± 6 | 5 ± 2 |
| 1000 | 17 ± 5 | 35 ± 12 | 8 ± 3 |
| 3000 | 23 ± 7 | 45 ± 14 | 13 ± 7 |
| (−) − 3 | | | |
| 300 | 15 ± 4 | 10 ± 3 | 2 ± 2 |
| 1000 | 22 ± 8 | 40 ± 14 | 5 ± 4 |
| 3000 | 27 ± 12 | 45 ± 15 | 10 ± 5 |
| (+) − 3 | | | |
| 300 | NA | NA | |
| 1000 | 25[b] | 30[b] | 18[b] |

[a] Cardiovascular responses were >80% inhibited by pretreatment with sulpiride (100 μg/kg) or with haloperidol (50 μg/kg). [b] Insufficient sample for statistical treatment.

## Experimental Section

**Pharmacology. Methods. Heart Rate and Mean Arterial Pressure in Anesthetized Rats.** Sprague–Dawley rats were anesthetized following ip administration of urethane (900 mg/kg). After induction of anesthesia the right femoral vein was cannulated for administration of chemicals, and arterial pressure was monitored from the femoral artery using a Statham P23AA arterial transducer and recorded using a Beckman R-611 recorder. Heart rate was followed using a Beckman 9857 B cardiotachometer coupler which was triggered from arterial pulse. Three rats were used for each compound. Test compounds were administered intravenously. Cumulative doses, varying by 0.48 $\log_{10}$ intervals, were administered after cardiovascular responses to preceding doses had stabilized for at least 5 min. In separate experiments, sulpiride or haloperidol, $DA_2$ receptor antagonists, were administered intravenously in doses of 100 and 50 μg/kg, respectively, 5 min prior to administration of the test compound. The duration of hypotension and bradycardia were recorded.

**Chemistry.** Melting points were determined in open capillaries using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. NMR spectra were recorded on Varian Associates EM60, Bruker-IBM NR-80, or Bruker-IBM WM-360 spectrometers, using $Me_4Si$ as the internal standard. Mass spectra were recorded with a Ribermag R-10-10C mass spectrometer. Optical rotations were recorded with a Perkin-Elmer Model 141 digital polarimeter. Preparative chromatography was done either with a Chromatotron apparatus (Harrison Research) using kieselgel 60PF254 (EM Science) as the stationary phase or by flash chromatography using 150A, 35–75 μm silica gel. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Where analyses are indicated by the symbols of the elements, analytical results were within ±0.4% of the theoretical values.

**Ethyl (2,5-Dimethoxyphenyl)acetate (4).** A mixture of 15.0 g (0.0765 mol) of (2,5-dimethoxyphenyl)acetic acid, 150 mL of freshly distilled EtOH, and 2.5 mL of concentrated $H_2SO_4$ was heated under reflux for 5 h. The cooled solution was neutralized with 10% $Na_2CO_3$, and the resulting mixture was extracted with $CHCl_3$. The extract was washed several times with $H_2O$, dried ($Na_2SO_4$), and filtered. Volatiles were removed from the filtrate under reduced pressure to afford a pale yellow oil which was distilled (Kugelrohr), 160 °C, 2.6 mmHg) to afford 15.3 g (89%) of a clear oil which was shown by TLC analysis ($SiO_2$, hexanes/EtOAc, 4:1) to be homogeneous. NMR data were consistent with

those reported by Kong and Loach[12] for this compound. An analytical sample was distilled, bp 118–119 °C (1.2 mmHg). Anal. ($C_{12}H_{16}O_4$) C, H. $H_2O$ (Karl Fischer) 0.55%.

**(±)-Ethyl (2-Cyanoethyl)(2,5-dimethoxyphenyl)acetate (5).** A 200-mL round-bottom flask equipped with a dropping funnel and a reflux condenser was charged with 10 g (0.0471 mol) of **4**, 100 mL of freshly distilled benzene, and 0.30 g (0.0018 mol) of benzyltrimethylammonium hydroxide (*Triton B*). The resulting mixture was stirred for 10 min at room temperature, and then 5.0 g (0.0942 mol) of acrylonitrile was added dropwise to the cooled (ice–water), stirred mixture. The reaction mixture was stirred at room temperature for 6 h and then was neutralized with 2 N HCl. The resulting mixture was extracted with $Et_2O$. The extract was washed several times with $H_2O$, dried ($Na_2SO_4$), and filtered. Volatiles were removed from the filtrate under reduced pressure, and the resulting oily residue was flash chromatographed (hexanes/EtOAc, 4:1). The eluate was evaporated under reduced pressure to afford a residue which was distilled (Kugelrohr, 190 °C, 1.8 mmHg) to give 11.9 g (91%) of a pale yellow oil. An analytical sample was crystallized from EtOH/$H_2O$ (1:5) to give white needles, mp 48–50 °C. Anal. ($C_{15}H_{19}NO_4$) C, H, N. $H_2O$ (Karl Fischer) 0.11%.

**(±)-3-(2,5-Dimethoxyphenyl)piperidin-2-one (6).** A mixture of 1.08 g (0.0039 mol) of **5**, 0.166 g of 5% Pd/C, and 0.400 g of $PtO_2$ in 100 mL of saturated ethanolic $NH_3$ was hydrogenated at ambient temperature at an initial pressure of 40 psig for 12 h or until $H_2$ uptake ceased. The reduction mixture was warmed to 50 °C and filtered through a Celite pad, and the Celite was washed with warm EtOH. The combined filtrate and washings were evaporated under reduced pressure to afford an opaque oily residue. Treatment of this with 50 mL of $Et_2O$ gave a white solid which was shown by TLC analysis ($SiO_2$, hexanes/EtOH, 4:1) to be homogeneous. Recrystallization from EtOAc afforded 0.624 g (68%) of a white, matted solid, mp 154–155 °C. MS: *m/z* 235 ($M^+$). Anal. ($C_{13}H_{17}NO_3$) C, H, N. $H_2O$ (Karl Fischer) 0.86%.

**(±)-3-(2,5-Dimethoxyphenyl)piperidine Hydrobromide (7).** A slurry of 1.45 g (0.0617 mol) of **6** in 100 mL of $Et_2O$ was heated under reflux for 18 h with 0.75 g (0.0194 mol) of $LiAlH_4$. The excess $LiAlH_4$ was destroyed by dropwise addition of aqueous sodium potassium tartrate (0.9 g/mL) to the chilled (0 °C), stirred reaction mixture over 0.75 h, or until $H_2$ evolution ceased. The insoluble salts were removed by filtration, and the filtrate was washed with $H_2O$ and dried ($Na_2SO_4$). Volatiles were removed under reduced pressure, and the residual gold oil was chromatographed on $SiO_2$ and eluted with $CHCl_3$/MeOH/concentrated $NH_4OH$ (6:1:0.04) to afford 1.048 g (84%) of pure **7** as a clear oil. For elemental analysis a small amount of this material was treated with ethereal HBr and the resulting solid was recrystallized from 2-PrCH/hexanes to give off-white crystals, mp 169.5–170.5 °C. MS: CI ($NH_3$) *m/z* 222 ($M^+ + H$). Anal. ($C_{12}H_{20}BrNO_2$) C, H, N. $H_2O$ (Karl Fischer) 0.17%.

**(±)-3-(2,5-Dimethoxyphenyl)-*N*-*n*-propylpiperidine Hydrobromide [(±)-3].** The reductive alkylation method of Marchini *et al.*[13] was used. To a stirred solution of 0.256 g (0.00116 mol) of **7** in 2.85 mL (38.2 mmol) of dry propionic acid and 3.5 mL of benzene at 50–55 °C, under $N_2$, was added 0.2 g (0.0053 mol) of $NaBH_4$. After 10 h at 50–55 °C, 25 mL of $H_2O$ was added to the reaction mixture, and then it was treated with excess solid $Na_2CO_3$. The resulting mixture was extracted with four 10-mL portions of $CHCl_3$. The combined extracts were washed with $H_2O$ until they were neutral (pH paper) and dried ($Na_2SO_4$). Volatiles were removed under reduced pressure to afford 0.244 g (80%) of a clear oil. A solution of this in a small volume of $Et_2O$ was treated with ethereal HBr to afford a solid which was recrystallized from 2-PrOH/hexanes to afford 0.244 g (71%) of white, matted crystals, mp 109–110.5 °C. Anal. ($C_{15}H_{26}BrNO_2$) C, H, N, Br. $H_2O$ (Karl Fischer) 2.74%.

**(*R*)-1-[(1-Naphthylethyl)carbamoyl]-(−)-3-(2,5-dimethoxyphenyl)piperidine (9) and (*R*)-1-[(1-Naphthylethyl)carbamoyl]-(+)-3-(2,5-dimethoxyphenyl)piperidine (10).** A solution of 1.0 g (0.0045 mol) of the free base of (±)-**7** and 0.888 g (0.0045 mol) of (*R*)-1-naphth-1-ylethyl isocyanate in 20 mL of $CH_2Cl_2$ was stirred at room temperature for 1 h. Evaporation of the reaction mixture afforded an oily residue which was flash chromatographed and eluted with hexanes/EtOAc (4:1) to yield 1.73 g (92%) of the diastereomeric urea product mixture (**9** and **10**) as a viscous oil. MS: CI ($NH_3$) *m/z* 418 ($M^+$).

**Chromatographic Separation of Diastereomeric Ureas 9 and 10.** The isomeric mixture was chromatographed on preparative plates (Analtech, silica gel, 80 mg per 4-mm plate). The plates were subjected to multiple developments (hexanes/EtOAc 1:1) until the mixture separated into two bands. The higher and lower $R_f$ value bands were scraped away separately and were extracted from the silica with MeOH in a Sohxlet apparatus. The middle portion of the separated band area was collected and, after the diastereomeric ureas were extracted with MeOH in a Sohxlet apparatus, was recycled through the chromatographic separation procedure. The first eluate (**9**) was recovered in 58% yield (≥98% ee), while the second eluate (**10**) was recovered in 76% yield (≥98% ee). [Integration of the benzylic proton signals at 3.06 and 2.97 ppm and/or inspection of the methoxy peaks at 3.66 and 3.71 or 3.56 ppm in the proton NMR (360.13 MHz) spectra provided % ee determinations for **9** and **10**, respectively]. Alternately, the diastereomers were separated in a series of flash chromatographic column separations. The initial column separation ($SiO_2$, 120 × 40 mm; hexanes/EtOAc/MeOH/2-PrOH, 500:250:0.83:0.9) using 2 g of the diastereomeric mixture afforded 1 g each of enriched fractions of the first and second eluates. These fractions were evaporated to dryness, and after a second chromatographic run using the same column, solvent system, and conditions, they afforded 10–15% (≥90% ee) total isolated yield of each isomer. Enriched fractions were recovered and pooled, and the volatiles were removed under reduced pressure to afford an oil which was recycled through the chromatographic procedure to afford additional quantities of stereochemically pure materials. The yield of each isomer after two chromatographic separations was 0.15 g (8%).

**(−)-3-(2,5-Dimethoxyphenyl)piperidine [(−)-7] by Thermal Decomposition of 9 in the Presence of Base.** Na (55 mg, 2.4 mg atom) was dissolved in 1 mL of 1-BuOH, and this solution was added to a stirred solution of 350 mg (0.839 mmol) of **9** in 10 mL of 1-BuOH. The resulting mixture was heated under reflux until TLC analysis ($SiO_2$, hexanes/EtOAc, 1:1) showed the absence of starting material. The reaction mixture was then evaporated under reduced pressure, acidified with 2N HCl, and washed once with $Et_2O$, and this extract was reserved as extract A. The aqueous layer was basified with 10% NaOH, and the resulting mixture was extracted with $CHCl_3$. The $CHCl_3$ extract was washed several times with $H_2O$, evaporated under reduced pressure, and the resulting pale yellow oil was chromatographed on $SiO_2$ and eluted with $CHCl_3$/MeOH/concentrated $NH_4OH$ (6:1:0.04) to afford two compounds: 0.167 g (90%) of (−)-**7**, $[\alpha]^{20}_D = -18.48°$ ($c$ = 0.167, MeOH). MS: *m/z* 222 ($M^+ + H$). $R_f$ value (silica, $CHCl_3$/MeOH/concentrated $NH_4OH$, 6:1:0.04) and NMR spectrum of (−)-**7** were identical to those for (±)-**7**, and 0.071 g (45%) of (*R*)-(+)-(1-naphthyl)ethylamine (**12**), identified by its NMR spectrum which was identical with that of the authentic compound.[14] MS: *m/z* 171 ($M^+$). $[\alpha]^{20}_D = +54°$ ($c$ = 0.013, MeOH); lit[9] $[\alpha]^{20}_D = +59°$ ($c$ = 5, MeOH).

Extract A was evaporated to leave an oily residue which, after subsequent purification with the Chromatotron radial TLC apparatus (hexanes/EtOAc, 4:1), afforded 0.09 g (36%) of *N*-(*n*-butoxycarbonyl)-1-(1-naphthyl)ethylamine (**11**), mp 89 °C. This compound was identified by comparison of its spectral (NMR, IR, MS) data with those of an authentic sample (*vide infra*).

**(+)-3-(2,5-Dimethoxyphenyl)piperidine [(+)-7] by Thermal Decomposition of 10 in the Presence of Base.** The reaction was performed as described for (−)-**7**. Thus, 0.242 g (0.00579 mol) of **10** afforded 0.118 g (87%) of (+)-**7**, $[\alpha]^{20}_D = +18.04°$ ($c$ = 0.092, MeOH). $R_f$ value ($SiO_2$, $CHCl_3$/MeOH/concentrated $NH_4OH$, 6:1:0.04) and NMR spectrum of (+)-**6** were identical with those of (±)-**7**.

**(*R*)-(−)-*N*-(*n*-Butoxycarbonyl)-1-naphth-1-ylethylamine (11).** (*R*)-1-Naphth-1-ylethyl isocyanate (320 mg, 1.622 mg atom) was added to a solution of 40 mg (1, 74 mg atom) of Na in 10 mL of 1-BuOH and the resulting mixture was heated under reflux for 10 min. The cooled reaction mixture was acidified with 2 N HCl and extracted with $Et_2O$, and the pooled extracts were washed twice with $H_2O$. After drying ($Na_2SO_4$), the $Et_2O$ was evaporated to leave a white solid which was shown by TLC analysis (silica, hexanes/EtOAc, 2:1) to be homogeneous. Re-

crystallization from hexanes afforded 192 mg (89%) of white matted crystals, mp 89 °C. MS: $m/z$ 271 ($M^+$).

**(−)-3-(2,5-Dimethoxyphenyl)-*N*-*n*-propylpiperidine Bifumarate [(−)-3].** To a stirred solution of 2.10 mL (28.1 mmol) of dry propionic acid in 5 mL of benzene at 20–25 °C, under $N_2$, was added 154 mg (4.05 mmol) of $NaBH_4$. This mixture was stirred for 5 h at room temperature, then 170 mg (0.769 mmol) of (−)-7 was added, and the stirred reaction mixture was heated at 80 °C for 8.5 h. $H_2O$ (25 mL) was added to the cooled reaction mixture, and this mixture was taken to pH 8 (pH paper) with solid $Na_2CO_3$. The resulting mixture was extracted with four 20-mL portions of $CHCl_3$, and the pooled extracts were washed with $H_2O$ until the washings were neutral to pH paper. After drying ($Na_2SO_4$), volatiles were removed under reduced pressure to afford 0.155 g (77%) of an oil whose $R_f$ value and spectral (NMR, MS) data were identical with those of the free base of (±)-3. $[\alpha]^{20}_D = -1.43°$ ($c = 0.048$, MeOH). The free base of (−)-2 in 1 mL of anhydrous $Et_2O$ was added to 75 mL of a saturated solution of fumaric acid in anhydrous $Et_2O$ under $N_2$. After several hours at ambient temperature white needles began to appear, and after several days, these were collected and dried under reduced pressure. Recrystallization from EtOH/$Et_2O$ gave 16.2 mg (4%) of long white needles, mp 95 °C. MS: CI ($NH_3$) $m/z$ 264 ($M^+ + H$).

**(+)-3-(2,5-Dimethoxyphenyl)-*N*-*n*-propylpiperidine [(+)-3].** To a stirred solution of 100 mg (0.452 mmol) of (+)-7 in 1.1 mL (14.7 mmol) of propionic acid and 5 mL of benzene at 50–55 °C, under $N_2$, was added 7 mg (2.07 mmol) of $NaBH_4$. After 3 h, 15 mL of $H_2O$ was added and the reaction mixture was treated with excess $Na_2CO_3$. The resulting mixture was extracted several times with $CHCl_3$, and the combined extracts were washed three times with $H_2O$ and dried over $Na_2SO_4$. Volatiles were removed under reduced pressure to afford 87.4 mg (74%) of a gold oil which showed an $R_f$ value and spectral (MS, NMR) data identical with those of the free base of (±)-3. $[\alpha]^{20}_D = +1.51°$ ($c = 0.012$, MeOH). Attempts to prepare crystalline salts of this material were unsuccessful.

**Acknowledgment.** This work was supported in part by N.I.H. Grant HLB-14,388-20.

## References

(1) Wikström, H.; Sanchez, D.; Lindberg, P.; Hacksell, U.; Arvidsson, L.-E.; Johansson, A. M.; Thorberg, S.-O.; Nilsson, J. L. G.; Svensson, K.; Hjorth, S.; Clark, D.; Carlsson, A. Resolved 3-(3-Hydroxyphenyl)-N-*n*-propylpiperidine and Its Analogues: Central Dopamine Receptor Activity. *J. Med. Chem.* **1984**, *27*, 1030–1036.

(2) Hjorth, S.; Carlsson, A.; Wikström, H.; Lindberg, P.; Sanchez, D.; Hacksell, U.; Arvidsson, L. E.; Svensson, U.; Nilsson, J. L. G. 3-PPP, A New Centrally Acting DA-Receptor Agonist with Selectivity for Autoreceptors. *Life Sci.* **1981**, *28*, 1225–1238.

(3) Clark, D.; Hjorth, S.; Carlsson, A. Dopamine Receptor Agonists: Mechanisms Underlying Autoreceptor Selectivity II. Theoretical Considerations. *J. Neural. Transm.* **1985**, *62*, 171–207.

(4) Hacksell, U.; Arvidsson, L.-E.; Svensson, U.; Nilsson, J. L. G.; Sanchez, D.; Wikström, H.; Lindberg, P.; Hjorth, S.; Carlsson, A. 3-Phenylpiperidines. Central Dopamine-Autoreceptor Stimulating Activity. *J. Med. Chem.* **1981**, *24*, 1475–1482.

(5) Arneric, S. P.; Long, J. P.; William, M.; Goodale, D. B.; Mott, J.; Lakoski, J. M.; Gebhardt, G. E. RDS-127 (2-di-*n*-Propylamino-4,7-Dimethoxyindane): Central Effects of a New Dopamine Receptor Agonist. *J. Pharmacol. Exp. Ther.* **1983**, *224*, 161–170.

(6) Sindelar, R. D.; Mott, J.; Barfknecht, C. F.; Arneric, S. P.; Flynn, J. R.; Long, J. P.; Bhatnagar, R. K. 2-Amino-4,7-dimethoxyindan Derivatives: Synthesis and Assessment of Dopaminergic and Cardiovascular Actions. *J. Med. Chem.* **1982**, *25*, 858–864.

(7) Cannon, J. G.; Amoo, V. E. D.; Long, J. P.; Bhatnagar, R. K.; Flynn, J. R. *p*-Dimethoxy-Substituted trans-Octahydrobenzo[*f*]- and [*g*]-quinolines: Synthesis and Assessment of Dopaminergic Agonist Effects. *J. Med. Chem.* **1986**, *29*, 2529–2534.

(8) De Marinis, R. M.; Shah, D. H.; Hall, R. F.; Hieble, J. P.; Pendleton, R. G. α-Adrenergic Agents. 2. Synthesis and $\alpha_1$-Agonist Activity of 2-Aminotetralins. *J. Med. Chem.* **1982**, *25*, 136–141.

(9) Pirkle, W. H.; Robertson, M. R.; Hyun, M. H. A Liquid Chromatographic Method for Resolving Chiral Lactams as Their Diastereomeric Ureide Derivatives. *J. Org. Chem.* **1984**, *49*, 2433–2437.

(10) Schoenenberger, B.; Brossi, A. Fragmentation of Optically Active (1-Phenylethyl)- and (1-Naphthylethyl) Ureas in Refluxing Alcohols: Easy Preparation of Optically Active Amines of High Optical Purity. *Helv. Chim. Acta* **1986**, *69*, 1486.

(11) Shaw, W. H. R.; Walker, D. G. Kinetic Studies of Thiourea Derivatives. IV. The Methylated Thioureas. Conclusions. *J. Am. Chem. Soc.* **1958**, *80*, 5337–5342.

(12) Kong, J. L. Y.; Loach, P. A. Syntheses of Covalently Linked Porphyrin-Quinone Complexes. *J. Heterocycl. Chem.* **1980**, *17*, 737–744.

(13) Marchini, P.; Liso, G.; Reho, A.; Liberatore, F.; Moracci, F. M. Sodium Borohydride-Carboxylic Acid Systems. Useful Reagents for the Alkylation of Amines. *J. Org. Chem.* **1975**, *40*, 3453–3456.

(14) Pouchert, C. J. *Aldrich Chemical Library of NMR Spectra*, 2nd ed.; Aldrich Chemical: Milwaukee, 1983; p 1103.