of the partial agonist **10** were determined against carbachol as described above for antagonists on the ileum. The compounds were allowed to equilibrate with the tissue for 30 min.

Muscarinic and Antimuscarinic Activity in Intact Mice. Male Swiss-Webster mice (24-32 g) were injected intraperitoneally. All experiments were carried out at 20.5 ± 1.0 °C. Threshold doses for salivation were estimated by the up-and-down method.[34] The presence or absence of salivation was determined by lightly pressing the mouth of the animal to an absorbent paper tissue. Effects on core body temperature were measured with a digital thermometer with the probe inserted about 25 mm in the rectum. The compounds were administered to groups of six mice at five to six dose levels and measurements were made every 20 min for 3 h. The difference between post- and pretreatment temperature were calculated and dose-response curves were constructed from the maximal hypothermic response. ED_{50} values were estimated by fitting a logistic function to the dose-response curves.[35] The tail-flick assay[36] was used to estimate effects on nociceptive thresholds. The compounds were administered to groups of ten mice at three to four dose levels. A cut-off time of 15 s was employed. Those animals that had posttreatment reaction times greater than the control mean reaction time plus 3 SD were considered as having significantly increased reaction times. ED_{50} values were estimated by probit analysis.

Antagonism of oxotremorine-induced tremor was studied by ip administration of antagonists to groups of six or more mice, while six control animals remained untreated. Twenty minutes after drug administration, the ED_{50} value of oxotremorine, injected iv, was estimated by the up-and-down method with intermittent spontaneous (grade 2) tremor[37] as the end point. The ED_{50} value of oxotremorine was plotted against the dose of antagonist used for premedication. That dose of antagonist that doubled the ED_{50} value of oxotremorine was estimated by linear regression analysis.

Acute Toxicity in Mice. LD_{50} values were estimated by the up-and-down method.[34] Compounds were administered intraperitoneally, and mortality counts were taken at 30 min.

Acknowledgment. This work was supported by USPHS Grants MH17691 and GM37816. The excellent secretarial assistance of Holly Batal is gratefully acknowledged.

Registry No. **3**, 18327-34-9; **4**, 112483-23-5; **4**·$^3/_2$oxalate, 112483-27-9; **5**, 112483-24-6; **6**, 112483-19-9; **6**·$^3/_2$oxalate, 112483-20-2; **7**, 112483-25-7; **8**, 71970-74-6; **8**·$^3/_2$oxalate, 71970-75-7; **9**, 112483-26-8; **10**, 112483-21-3; **10**·oxalate, 112483-22-4; MeNHEt, 624-78-2; $HNEt_2$, 109-89-7; $HNMe_2$, 124-40-3; azetidine, 503-29-7.

(34) Dixon, W. J. *J. Am. Stat. Assoc.* **1965**, *60*, 967.
(35) Ringdahl, B.; Jenden, D. J. *J. Pharmacol. Exp. Ther.* **1987**, *240*, 370.
(36) D'Amour, F. E.; Smith, D. L. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74.
(37) Cho, A. K.; Jenden, D. J. *Int. J. Neuropharmacol.* **1964**, *3*, 27.

6- and 8-Hydroxy-3,4-dihydro-3-(dipropylamino)-2*H*-1-benzopyrans. Dopamine Agonists with Autoreceptor Selectivity

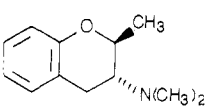
Lawrence D. Wise,*† Horace A. DeWald,† Elma S. Hawkins,† Donna M. Reynolds,† Thomas G. Heffner,‡ Leonard T. Meltzer,‡ and Thomas A. Pugsley‡

Departments of Chemistry and Pharmacology, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48105. *Received July 10, 1987*

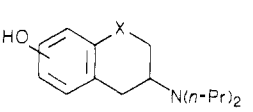
The dopamine agonist profiles of 3,4-dihydro-3-(3-dipropylamino)-2*H*-1-benzopyran-6- and -8-ol (**4** and **5**, respectively) were examined. Both **4** and **5** exhibited greater relative affinity for receptors labeled with the dopamine agonist ligand [^{3}H]propylnorapomorphine than for those labeled with the dopamine antagonist ligand [^{3}H]haloperidol. Both compounds attenuated the stimulation of brain dopamine synthesis caused by γ-butyrolactone (GBL) and decreased the firing rate of substantia nigra dopamine neurons in rats. This profile of activity, together with the ability of the dopamine antagonist haloperidol to reverse the inhibition of dopamine neuronal firing, indicate that both compounds are brain dopamine agonists.

Several years ago the preclinical and clinical profiles of *trans*-3,4-dihydro-2-methyl-3-(dimethylamino)-2*H*-1-benzopyran (CI-686) (**1**) were examined.[1,2] Although **1** displayed both stimulating and blocking effects on behaviours known to depend on brain dopamine (DA) in experimental animals, these effects did not appear to be mediated by direct actions at brain DA receptors. Since this time, there has been a rapid development of compounds that are potent and selective agonists or antagonists at DA receptors.[3,4] For example, several hydroxy-substituted aminotetralins related to **1** have been described as DA agonists.[5] In accordance with the model of McDermed et al., DA agonist activity is maximized when such compounds contain a hydroxyl group at a meta position on the aromatic ring of the incorporated phenethylamine DA pharmacophore and a dipropyl-substituted amino moiety (i.e., 5-or 7-hydroxy analogues **2** and **3**, respectively).[6]

Because of the structural similarity between **1** and these aminotetralins, we examined the pharmacological profiles



1



2: 5-OH; X = CH_2
3: 7-OH; X = CH_2
4: 6-OH; X = O
5: 8-OH; X = O

of analogues of **1**, namely the 6- and 8-hydroxy-3,4-dihydro-3-(dipropylamino)-2*H*-1-benzopyrans, **4** and **5**, respectively, that incorporate critical features for DA agonist

† Department of Chemistry.
‡ Department of Pharmacology.

(1) Stanley, M.; Rotrosen, J.; Sculerati, N.; Gershon, S.; Kuhn, C.; Cohen, B. M. *Psychopharmacology (Berlin)* **1979**, *66*, 23.
(2) Georgotas, A.; Gerbino, L.; Jordan, B.; McCarthy, M.; Gershon, S.; Kleinberg, D.; Lautin, A.; Stanley, M.; Rotrosen, J. *Psychopharmacology (Berlin)* **1981**, *73*, 292.
(3) Cannon, J. G. *Prog. Drug. Res.* **1985**, *29*, 303-414.
(4) Hillister, L. E. *Med. Actual.* **1985**, *22*, 551.
(5) See, for example: McDermed, J. D.; McKenzie, G. M.; Freeman, H. S. *J. Med. Chem.* **1976**, *19*, 547. Tedesco, J. L.; Seeman, P.; McDermed, J. D. *Mol. Pharmacol.* **1979**, *16*, 369.
(6) McDermed, J.; Freeman, H.; Ferris, R. *Catecholamines: Basic and Clinical Frontiers*; Usdin, E., Kopin, I., Barchas, J., Eds.; Pergamon: New York, 1979; p 568.

0022-2623/88/1831-0688$01.50/0

Scheme I

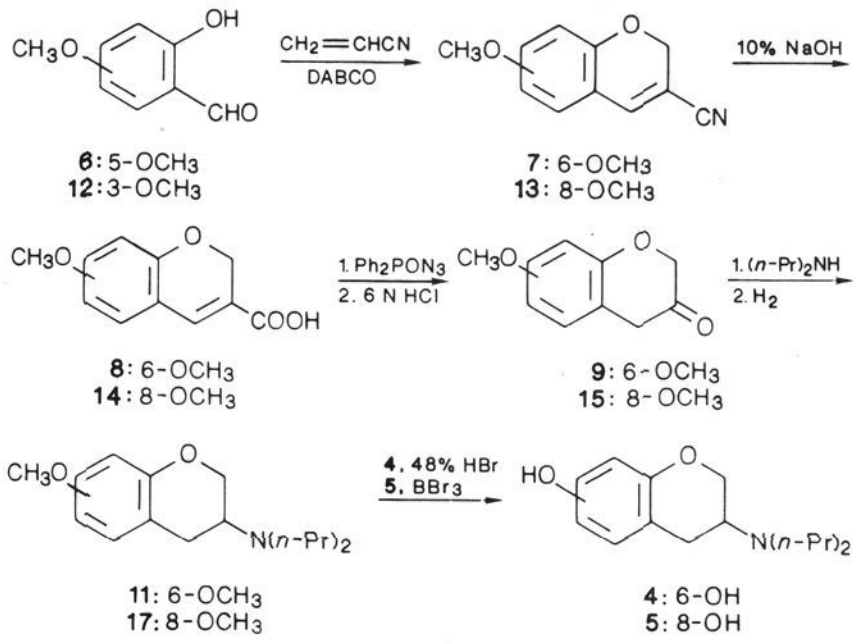


Table I. Effects of **4**, **5**, and Reference Agent on Rat Striatal DA Receptors

compound	^{3}H-HPD[a,b] IC_{50}, nM	^{3}H-NPA[b,c] IC_{50}, nM	DOPA accumulation:[d] ED_{50}, mg/kg ip
4	800	13.3	0.85
5	10	0.32	0.05
apomorphine	27	2.60	0.04[e]

[a] [^{3}H]Halopridol. [b] IC_{50} values were determined from four or five concentrations by a nonlinear regression analysis. [c] [^{3}H]*N*-Propylnorapomorphine. [d] Shown are the doses giving half-maximal reversal of the γ-butyrolactone-induced increase in DOPA formation in rat striatum. [e] Value taken from ref 19.

activity as proposed by the McDermed model. Target compound **4** may be visualized as incorporating the β-conformer of the DA pharmacophore while **5** embodies the α-conformer.

Chemistry

The syntheses of target compounds **4** and **5** are outlined in Scheme I. The requisite 6- and 8-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-ones, **9** and **15**, respectively, were prepared by the general method of Gupta et al.[7] and Rene and Royer.[8] Briefly, treatment of the appropriately substituted salicylaldehydes **6** and **12** with acrylonitrile and 1,4-diazabicyclo[2.2.2]octane (Dabco) afforded nitriles **7** and **13**, which in turn were hydrolyzed to 3-carboxylic acids **8** and **14**. Ketones **9** and **15** were obtained via a Curtius rearrangement of **8** and **14** utilizing diphenyl phosphorazidate.[9]

Reaction of **9** and **15** with dipropylamine in the presence of glacial acetic acid in pentan-1-ol gave the substituted 3-(dipropylamino)benzopyrans **10** and **16**, which were catalytically hydrogenated to the corresponding 3,4-dihydrobenzopyrans **11** and **17**. Finally, demethylation of **11** and **17** yielded the 6- and 8-hydroxy-substituted targets, **4** and **5**, respectively. Several methods of demethylation were examined; 48% hydrobromic acid appeared optimal for **11** while boron tribromide was employed for **17**.

Results and Discussion

The in vitro affinities of **4** and **5** for DA receptors were determined with use of the DA agonist ligand [^{3}H]*N*-propylnorapomorphine (^{3}H-NPA) and the DA antagonist ligand [^{3}H]haloperidol (^{3}H-HPD).[10,11] Both **4** and **5**, like most known DA agonists (e.g., apomorphine), exhibited a greater affinity for DA agonist labeled receptors than for DA antagonist labeled sites (Table I). As expected of DA agonists, **4** and **5** decreased DA synthesis in the corpus striatum (a major brain DA projection area) of rats pretreated with γ-butyrolactone (GBL) with ED_{50} values of 0.85 and 0.05 mg/kg ip, respectively.[12] In comparison, apomorphine displayed an ED_{50} of 0.04 mg/kg ip. At 2.5 mg/kg ip, **4** and **5** also inhibited the firing activity of substantia nigra DA neurons, an effect indicative of DA autoreceptor agonist activity.[13] The complete cessation of DA neuron firing produced by **4** and **5** and the reversal of these effects by the DA receptor antagonist haloperidol (Figure 1) demonstrated the direct agonist actions of these compounds at brain DA receptors.

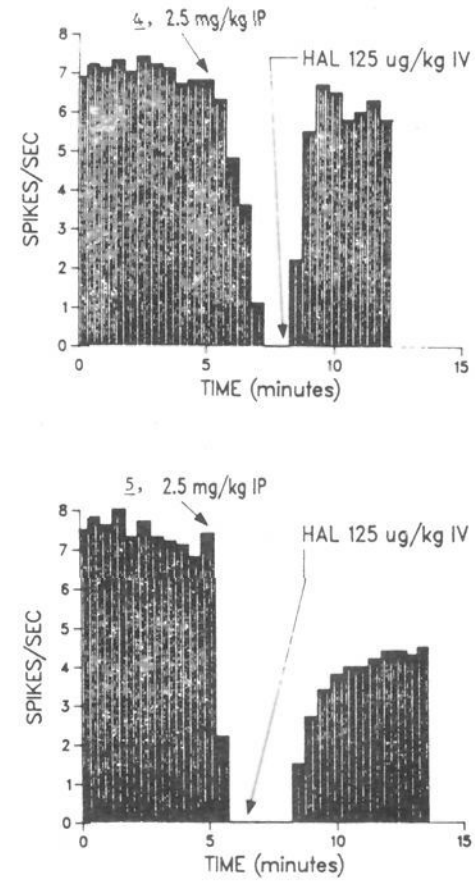


Figure 1. Histograms depicting the typical response of **4** and **5** on the firing rate of substantia nigra dopamine neurons. Complete inhibition of firing activity was observed with both compounds for all neurons tested ($N = 5$/compound).

Table II. Comparative Potency of **4** and **5** in Rats for Behavioral Effects Mediated by Pre- and Postsynaptic Brain DA Receptors

	ED_{50} (95% CI), mg/kg sc		
compound	inhibn of locomotor activity[a]	reversal of reserpine-induced depression[b]	post-/presynaptic effects[c]
4	0.17 (0.010)	13.44 (1.74)	79
5	0.013 (0.001)	3.95 (0.36)	304
apomorphine	0.021 (0.001)	0.096 (0.004)	5

[a] ED_{50} values were generated from four doses; 5–12 animals were used per dose. [b] ED_{50} values were generated from three doses; 5–10 animals were used per dose. [c] Ratio of ED_{50} values for inhibition of locomotor activity to reversal of reserpine-induced depression.

(7) Gupta, R. C.; Pratap, R.; Prasad, C. R.; Anand, N. *Indian J. Chem., Sect. B* **1982**, *21B*, 334.
(8) Rene, L.; Royer, R. *Eur. J. Med. Chem.* **1975**, *10*, 72.
(9) Capson, T. L.; Poulter, C. D. *Tetrahedron Lett.* **1984**, *25*, 3515.
(10) Seeman, P.; Ulpian, C.; Grigoriadis, D.; Pri-Bar, I.; Buchman, O. *Biochem. Pharmacol.* **1985**, *34*, 151.
(11) Burt, D. R.; Creese, I.; Snyder, S. H. *Mol. Pharmacol.* **1976**, *12*, 800.
(12) Walters, J. R.; Roth, R. H. *Biochem. Pharmacol.* **1976**, *25*, 649.
(13) Bunney, B. S.; Walter, J. R.; Roth, R. H.; Aghajanian, G. K. *J. Pharmacol. Exp. Ther.* **1973**, *185*, 560.

Both 4 and 5 also produced behavioral effects indicative of brain DA autoreceptor agonists. As shown in Table II, 4 and 5 inhibited spontaneous exploratory locomotor activity in mice dosed sc.[14] This effect suggested that 4 and 5 are brain DA autoreceptor agonists. In order to assess the relative potency at pre- and postsynaptic DA receptors, 4 and 5 were evaluated in both normal and reserpine-treated rats. While locomotor inhibition in rats is considered to reflect agonist effects at presynaptic DA autoreceptors, reversal of locomotor inhibition in rats treated with reserpine (a DA-depleting agent that induces supersensitivity of postsynaptic DA receptors) is a sensitive indicator of agonist activity at postsynaptic DA receptors in the brain.[15] Unlike apomorphine, which exhibited similar potency in both models, 4 and 5 inhibited locomotion in normal rats at much lower doses (79- and 304-fold, respectively) than those which reversed reserpine-induced depression. This suggests that in contrast to DA agonists such as apomorphine 4 and 5 are relatively selective DA autoreceptor agonists.

In summary, the present biochemical and electrophysiological results indicate that 4 and 5 are potent agonists at brain DA receptors. Furthermore, the behavioral effects on locomotion in naive and reserpine-treated rats suggest that these compounds do have selectivity for autoreceptor sites. In accordance with previous findings, 5, which contains the DA pharmacophore in an α-conformation, was more potent than 4 which exists in the β-conformation.[16]

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet MX-1 FT spectrometer. The proton NMR spectra were obtained on an IBM WP100SY NMR spectrometer (100 MHz) or a Varian XL200 NMR spectrometer (200 MHz) and were consistent with the proposed structures. The mass spectra were recorded on a Finnigan 4500 mass spectrometer or a VG Analytical 7070E/HF mass spectrometer. Where analyses are indicated by the symbols of the elements, the results are within 0.4% of the theoretical values. TLC was carried out with 0.25-mm silica gel 60 F254 (E. Merck) glass plates. GLC was carried out with a Shimadzu GC Mini 2 gas chromatograph equipped with FID. Unless otherwise noted, starting materials were obtained from Aldrich Chemical Co. and were used without further purification.

3-Cyano-6-methoxy-2*H*-1-benzopyran (7). A mixture of 45 g (0.3 mol) of 2-hydroxy-5-methoxybenzaldehyde, 80 g (1.5 mol) of acrylonitrile, and 7.5 g (0.07 mol) of 1,4-diazabicyclo[2.2.2]octane (Dabco) was refluxed for 20 h. The reaction mixture was diluted with ether and washed with 1 N sodium hydroxide and then with 1 N hydrochloric acid. The organic phase was dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo. The residue was recrystallized from methanol to afford 56 g (100%) of 7: mp 64–65 °C; ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3 H, OCH_3), 4.8 (s, 2 H, OCH_2), 6.86–6.9 (m, 3 H, Ar H, CH), 7.5 (s, 1 H, Ar H). Anal. ($C_{11}H_9NO_2$) C, H, N.

3-Cyano-8-methoxy-2*H*-1-benzopyran (13). By the procedure described for 7, 45 g (0.3 mol) of 2-hydroxy-3-methoxybenzaldehyde was converted to 56 g (100%) of 13: mp 101–102 °C; ^{1}H NMR (DMSO-d_6) δ 3.77 (s, 3 H, OCH_3), 4.85 (d, 2 H, OCH_2), 6.85–7.11 (m, 3 H, Ar H), 7.58–7.60 (t, 1 H, Ar H). Anal. ($C_{11}H_9NO_2$) C, H, N.

3-Carboxy-6-methoxy-2*H*-1-benzopyran (8). A mixture of 37 g (0.20 mol) of 7 and 600 mL of 10% sodium hydroxide was refluxed for 6 h. The mixture was acidified with concentrated hydrochloric acid. The resulting precipitate was collected and dried to yield 28 g (74%) of 8: mp 184–186 °C; ^{1}H NMR (DMSO-d_6) δ 3.7 (s, 3 H, OCH_3), 4.9 (d, 2 H, CH_2), 6.5–7.0 (m, 3 H, Ar H, CH), 7.3 (s, 1 H, Ar H). Anal. ($C_{11}H_{10}O_4$) C, H.

3-Carboxy-8-methoxy-2*H*-1-benzopyran (14). A 46.7-g (0.25 mol) sample of 13 was converted to 46 g (89%) of 14, mp 220 °C dec, by the method described for 8: ^{1}H NMR (DMSO-d_6) δ 3.8 (s, 3 H, OCH_3), 4.9 (s, 2 H, OCH_2), 6.9–7.0 (m, 3 H, Ar H, CH), 7.4 (1 H, d, Ar H). Anal. ($C_{11}H_{10}O_4$) C, H.

6-Methoxy-3,4-dihydro-2*H*-1-benzopyran-3-one (9). To 10 g (0.05 mol) of 8 in 8 mL of triethylamine and 100 mL of dichloromethane was added 14 g (0.05 mol) of diphenyl phosphorazidate in 40 mL of toluene dropwise while the mixture was heated slowly to distill the dichloromethane. At 60 °C, an additional 100 mL of toluene was added. The reaction mixture was heated with stirring for 1.5 h at 80–85 °C; 80 mL of 6 N hydrochloric acid was added, and the mixture was refluxed for 2 h. The layers were separated, and the organic extracts were washed with saturated sodium bicarbonate and dried over magnesium sulfate. Evaporation of the solvent afforded 9.5 g of a yellow oil. A small sample was distilled for analytical purposes. For all synthetic uses, the crude product was used without purification in the subsequent step: ^{1}H NMR ($CDCl_3$) δ 3.6 (s, 2 H, CH_2), 3.8 (s, 3 H, OCH_3), 4.4 (s, 2 H, CH_2), 6.7 (s, 1 H, Ar H), 6.75–6.8 (m, 1 H, Ar H), 6.9–7.0 (d, 1 H, Ar H). Anal. ($C_{10}H_{10}O_3$) C, H.

8-Methoxy-3,4-dihydro-2*H*-1-benzopyran-3-one (15). By the procedure described for 9, 10 g (0.05 mol) of 14 was reacted to afford 10 g of 15 as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.6 (s, 2 H, CH_2), 3.9 (s, 3 H, OCH_3), 4.4 (s, 2 H, OCH_2), 6.7 (d, 1 H, Ar H), 6.8 (d, 1 H, ArH), 7.0 (t, 1 H, Ar H). Anal. ($C_{10}H_{10}O_3$) C, H.

6-Methoxy-3,4-dihydro-3-(dipropylamino)-2*H*-1-benzopyran Hydrobromide (11). A mixture of 9.0 g (0.05 mol) of 9, 10 mL of dipropylamine, and 0.5 mL of glacial acetic acid in 75 mL of pentan-1-ol was refluxed for 4 h with use of a Dean–Stark water trap. The solvent was removed in vacuo. The residue was taken up in ethyl acetate and filtered through a bed of silica gel. Evaporation of the solvent afforded 12.4 g of 6-methoxy-3-(dipropylamino)-2*H*-1-benzopyran (10) as a dark viscous oil. A solution of 11 g (0.042 mol) of 10 in 100 mL of methanol was hydrogenated over 0.5 g of 10% platinum on carbon at an initial pressure of 50 psi. After the reaction mixture had taken up the requisite amount of hydrogen, the catalyst was removed by filtration, and the filtrate was evaporated. There was deposited 11 g (96%) of 11 as an oil. Treatment of the oil in toluene with hydrobromic acid in acetic acid afforded an analytical sample of 11 as the hydrobromide: mp 110–114 °C; ^{1}H NMR (DMSO-d_6) δ 1.0 (t, 6 H, CH_3), 2.1 (m, 4 H, CH_2), 3.1 (m, 4 H, CH_2), 3.3 (t, 2 H, CH_2), 3.7 (s, 3 H, OCH_3), 4.2 (m, 1 H, CH), 4.6 (m, 2 H, OCH_2), 6.7 (m, 3 H, Ar H). Anal. ($C_{16}H_{25}NO_2$·HBr) C, H, N.

8-Methoxy-3,4-dihydro-3-(dipropylamino)-2*H*-1-benzopyran (17). By the method described above, 9.0 g (0.05 mol) of 15 was reacted to give 9.5 g of 8-methoxy-3-(dipropylamino)-2*H*-1-benzopyran (16) as a dark viscous oil. Hydrogenation over 10% platinum on carbon yielded 9.4 g (82%) of 1m as an oil: MS, m/z 263 (M^+); ^{1}H NMR (DMSO-d_6) δ 0.9 (t, 6 H, CH_3), 1.45 (m, 4 H, CH_2), 2.5 (t, 4 H, CH_2), 3.0 (d, 2 H, CH_2), 3.9 (m overlapping s, CH and OCH_3), 4.4 (m, 2 H, CH_2O), 6.6–6.9 (m, 3 H, Ar H).

3,4-Dihydro-3-(dipropylamino)-2*H*-1-benzopyran-6-ol Hydrobromide (4). A mixture of 11 g (0.04 mol) of 11 in 200 mL of 48% hydrobromic acid was refluxed for 2 h. The solution was filtered, and the filtrate was evaporated in vacuo. The residual oil was dissolved in a solution of anhydrous hydrogen bromide–glacial acetic acid and evaporated. The residue was crystallized from ethyl acetate to afford 3.7 g (28%) of 4: mp 171–174 °C; ^{1}H NMR (D_2O) δ 0.85 (t, 6 H, CH_3), 1.5 (m, 4 H, CH_2), 2.5 (m, 4 H, CH_2), 2.85 (m, 2 H, CH_2), 3.15 (m, 2 H, CH_2), 3.8 (m, 1 H, CH), 6.5 (m, 2 H, Ar H), 6.7 (d, 1 H, Ar H). Anal. ($C_{15}H_{23}NO_2$·HBr) C, H, N.

3,4-Dihydro-3-(dipropylamino)-2*H*-1-benzopyran-8-ol Hydrobromide (5). To a stirred solution of 9.3 g (0.034 mol) of 17 in 300 mL of chloroform was added 10 g (0.04 mol) of boron tribromide in 30 mL of chloroform at −20 to −30 °C. After stirring at −20 °C for 1 h, the mixture was allowed to warm slowly to room temperature and was poured into ice water containing excess ammonium hydroxide. The layers were separated, and the organic extracts were dried over magnesium sulfate and evaporated in vacuo. The residual oil was treated with anhydrous hydrobromic

(14) Coughenour, L. L.; McLean, J. R.; Parker, R. B. *Pharmacol., Biochem. Behav.* **1977**, *12*, 800.
(15) Anden, N.-E.; Strombom, U.; Svensson, T. H. *Psychopharmacology (Berlin)* **1973**, *29*, 289.
(16) Cannon, J. G. *Prog. Drug Res.* **1985**, *29*, 306.

acid in glacial acetic acid. Trituration with ethyl acetate afforded 11.2 g (99%) of **5**: mp 150–155 °C; ^{1}H NMR (D_2O) δ 1.0 (t, 6 H, CH_3), 1.8 (m, 4 H, CH_2), 3.5 (m, 6 H, CH_2), 4.0 (m, 1 H, CH), 4.6 (m, 2 H, CH_2), 6.8 (m, 3 H, Ar H). Anal. ($C_{15}H_{23}NO_2$·HBr) C, H, N, Br.

Pharmacological Methods. DA Receptor Binding Assays. The affinities of compounds for brain DA receptors were determined by standard receptor binding assays.[10,11]

Effects on DA Synthesis.[12] Compounds to be tested were administered 1 h before sacrifice, and γ-butyrolactone (750 mg/kg ip) and NSD 1015 (100 mg/kg ip) were administered 30 min and 25 min, respectively, before sacrifice. Brain levels of dihydroxyphenylalanine (DOPA) were analyzed by HPLC with electrochemical detection.[17] Mean DOPA values in the vehicle-treated group were 1.26 ± 0.012 μg/g of tissue ± SEM.

Effects on Firing Rate of Substantia Nigral DA Neurons.[13] By use of standard extracellular recording techniques, the action potential of zona compacta DA cells was recorded in chloral hydrate anesthetized rats. DA cells were identified by waveform and firing pattern, and recording sites were verified histologically. Drugs were administered ip via an indwelling catheter. Base-line firing rate was calculated by averaging during the 2 min prior to drug injection. Drug effects were determined by averaging the response during the 1-min period of maximal activity.

Inhibition of spontaneous locomotor activity[14] was carried out according to methods described previously.[18]

Effects on Spontaneous Locomotion in Reserpinized Rat vs Normal Rat.[16] Drugs were administered sc to normal rats and to rats treated with 5 mg/kg of reserpine 24 h prior to testing. The effect on locomotor activity was measured immediately after as described above.

Acknowledgment. We thank J. N. Wiley, A. E. Williams, and L. L. Coughenour for biological testing. We are also indebted to Dr. F. M. Hershenson for valuable discussions.

Registry No. **4**, 112460-73-8; **5**, 112460-74-9; **6**, 673-22-3; **7**, 57543-71-2; **8**, 57543-62-1; **9**, 76322-25-3; **10**, 112460-75-0; **11**, 112460-76-1; **12**, 700-44-7; **13**, 57543-69-8; **14**, 57543-59-6; **15**, 91520-00-2; **16**, 112460-77-2; **17**, 110927-06-5; Ph_2PON_3, 4129-17-3.

(17) Myers, S.; Pugsley, T. A. *Brain Res.* **1986**, *375*, 193.

(18) Wise, L. D.; Butler, D. E.; DeWald, H. A.; Lustgarten, D.; Coughenour, L. L.; Downs, D. A.; Heffner, T. G.; Pugsley, T. A. *J. Med. Chem.* **1986**, *29*, 1628.

(19) Feenstra, M. G. P.; Summers, C.; Goedemoed, J. H.; de Vries, J. B.; Rollema, H.; Horn, A. S. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1983**, *324*, 108.