5-Br-**5b** acetate, 83646-99-5; **5b** benzoate, 19614-35-8; **5c**, 98483-27-3; **5c** acetate, 98574-25-5; **5d**, 98483-28-4; **6a**, 23613-75-4; **6b**, 98574-26-6; **6b** acetate, 98574-27-7; 5-Br-**6b** acetate, 83647-01-2; **6c**, 98483-29-5; **6d**, 98483-30-8; **7**, 98483-52-4; **8a**, 98483-31-9; **8a** benzoate, 98483-32-0; **8b**, 98483-33-1; **8b** acetate, 98483-34-2; **9b**, 98483-35-3; **9b** acetate, 98483-36-4; **10a**, 4019-92-5; **10b**, 98574-28-8; **10b** ketone, 98574-36-8; **11b**, 76225-57-5; **11c**, 98483-37-5; **11d**, 98483-38-6; **12b**, 98483-39-7; **12c**, 98483-40-0; **13b**, 76225-13-3; **14**, 76225-64-4; **15**, 56116-09-7; **16a**, 98483-41-1; α-**16b**, 98574-29-9; β-**16b**, 98574-30-2; **17a**, 98483-42-2; α-**17b**, 98574-31-3; β-**17b**, 98574-32-4; α-**18a**, 98483-43-3; β-**18a**, 98574-33-5; (2α,6α)-**18b**, 98574-34-6; (2β,6α)-**18b**, 98632-56-5; (2α,β)-**18b**, 98574-37-9; (2β,6β)-**18b**, 98574-38-0; α-**19a**, 98483-44-4; β-**19a**, 98574-35-7; α-**22a**, 98509-00-3; β-**22a**, 98483-45-5; α-**22b**, 98483-46-6; β-**22b**, 98483-47-7; α-**23a**, 98483-48-8; β-**23a**, 98483-49-9; **24**, 98483-50-2; **25**, 10232-46-9; **26**, 10232-57-2; **27**, 10232-54-9; **28**, 68875-97-8; **29**, 35130-89-3; **30**, 15247-10-6; **31**, 98483-51-3; **33**, 10072-75-0; MeBr, 74-83-9; EtBr, 74-96-4; PrBr, 106-94-5; BuBr, 109-65-9; MeI, 74-88-4; EtI, 75-03-6; PrI, 107-08-4; 1,4-dibromo-1,4-*seco*-2,3-bisnor-5α-androst-17β-ol acetate, 23015-70-5.

# Dopamine Receptor Agonist Activity of Some 5-(2-Aminoethyl)carbostyril† Derivatives

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The potency of β-adrenoreceptor agonists, e.g., isoproterenol, is strikingly increased by substitution of the meta catecholic hydroxyl group with the NH group of a carbostyril system. To explore the possibility that comparable potency enhancement might occur upon similar modification of the catechol ring of dopamine, a series of 5-(2-aminoethyl)carbostyril derivatives was prepared and examined for D-1 and D-2 dopamine receptor-stimulating activity. Only the parent compound, 5-(2-aminoethyl)-8-hydroxycarbostyril (**2**), produced measurable activation of dopamine-sensitive adenylate cyclase (29% at a concentration of 10 μM). Some of the compounds, however, did produce significant activity in tests, namely displacement of [$^3$H]spiroperidol binding from bovine pituitary homogenate and an isolated perfused rabbit ear artery preparation, that measure interaction with D-2 receptors. Potency of the carbostyrils was enhanced by 8-hydroxylation and by appropriate substitution of the amino group of the ethylamine side chain. The most potent member of the series was 8-hydroxy-5-[2-[[2-(4-hydroxyphenyl)ethyl]-*n*-propylamino]ethyl]carbostyril (**16b**). This compound was about 3 times more effective than dopamine in the D-2 receptor tests. Clearly, the results of this study indicate that potency of dopamine receptor agonists is not increased by carbostyril replacement of the *m*-hydroxyl as is noted with the β-adrenergic receptor agonists.

Structure–activity relationship (SAR) studies among dopamine (DA) receptor agonists are ambiguous regarding the significance of the catechol system for binding to, and activation of, DA receptors. Both hydroxyl groups apparently are important for stimulation of the D-1[1] or $DA_1$[2-4] subpopulations of DA receptors that are involved in activation of DA-sensitive adenylate cyclase and initiation of smooth muscle relaxation, respectively. There are notable exceptions to this generalization, however. Thus, some 2-aminotetralins that bear only a single hydroxyl group in a position meta to the embedded ethylamine side chain, depending to a large extent on the nature of substitution on the basic nitrogen, retain a marked degree of D-1 agonist activity. Although selective noncatecholic $DA_1$ receptor agonists have not been identified, stimulation of this receptor subtype is also dependent upon the pattern of substitution of the nitrogen.[6] Clearly, the catecholic system is not required for activation of the D-2 (not associated, or negatively linked with cyclic-AMP)[1] and the $DA_2$ (located on sympathetic nerve endings and subserving inhibition of norepinephrine release) receptors.[2-4] Thus, the monohydroxylated tyramine derivatives RU 24213 [*N*-*n*-propyl-*N*-(2-phenylethyl)tyramine] and RU 24926 [*N*-*n*-propyl-*N*-[2-(4-hydroxyphenyl)ethyl]tyramine] are selective D-2 receptor agonists.[7,8] Among the many other noncatecholic DA relatives that are capable of stimulating D-2 or $DA_2$ receptors,[9] the octahydropyrazolo[3,4-*g*]-quinoline LY 141865,[10-12] piribedil [1-[3,4-(methylenedioxy)benzyl]-4-(2-pyrimidyl)piperazine] and related compounds,[15] 4-[2-(dipropylamino)ethyl]indole,[16] and various

† *Chemical Abstracts* nomenclature is 5-(2-aminoethyl)-2-(1*H*)-quinolone; however, in this paper the more common carbostyril naming is employed.

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§ Department of Pharmacology.

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(2) Goldberg, L. I.; Kohli, J. D. *Commun. Psychopharmacol.* **1979**, *3*, 447.
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(8) Euvrard, C.; Ferland, L.; DiPaolo, T.; Beaulieu, M.; Labrie, F.; Oberlander, C.; Raynaud, J. P.; Boissier, J. R. *Neuropharmacol.* **1980**, *19*, 379.
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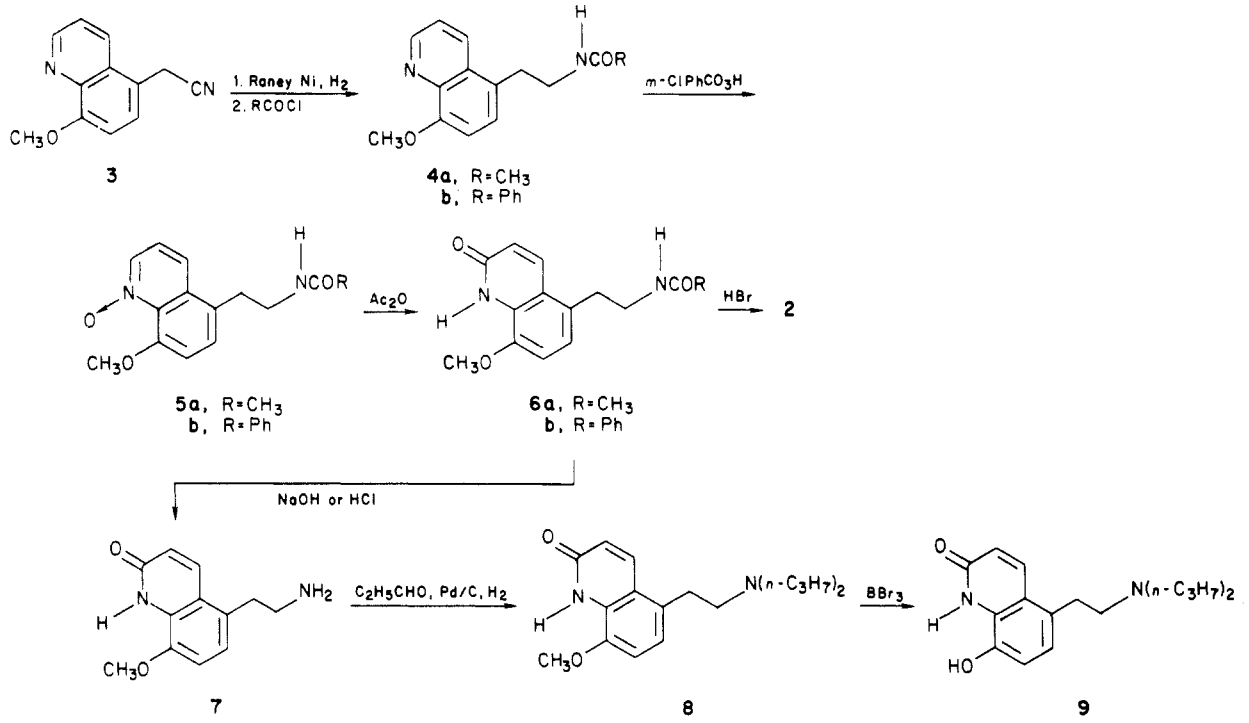
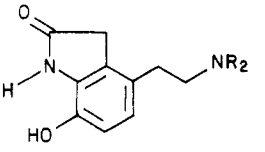
**Scheme I**

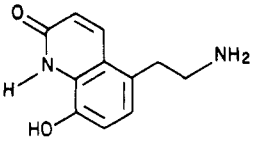



bicyclic and tricyclic ergoline structures[17] represent notable examples. Many ergotlike compounds seem to be selective agonists of the $DA_2$ receptors;[18] however, in a presently unresolved difference in the classification of DA receptor subtypes, some of these compounds are also capable of stimulating DA-sensitive adenylate cyclase, a D-1 receptor response (cf. ref 19 and 20).

As a generalization, however, the presence of a hydroxyl group, or a moiety that can imitate this functionality, in a position meta to the ethylamine side chain is considered to constitute the dopaminergic pharmacophore.[15] This SAR is reminiscent of that in the β-adrenoreceptor agonist series. Here, the prototype is the catechol isoproterenol, and studies with its monohydroxy derivatives suggest the hydroxyl group meta to the ethanolamine side chain plays the more significant role in β-adrenoreceptor activation. Thus, the 3-hydroxy analogue of isoproterenol is a more potent β-adrenergic receptor agonist than is the 4-isomer.[21,22] Interestingly, this *m*-hydroxyl group that is more significant for β-adrenoreceptor agonist activity can be replaced by a variety of phenolic hydroxyl simulating groups with retention or enhancement of activity and, in general, increased selectivity for the $\beta_2$ vs. $\beta_1$ subtype of these receptors.[23] Somewhat surprisingly, similar replacement of the more significant hydroxyl group in the position meta to the ethylamine side chain in various classes of DA receptor agonists has received little attention. One report[24] has described such replacement of the *m*-hydroxyl group of DA and its *N,N*-di-*n*-propyl derivative with an indolone system. These 4-(aminoalkyl)-7-hydroxy-2-(3*H*)-indolones (**1**) demonstrated potent pre-



**1a**, R=H
**b**, R=*n*-Pr



**2**

synaptic ($DA_2$) DA receptor agonist activity. In the series of β-adrenoreceptor agonists, the most effective hydroxyl replacement group is the NH of a carbostyril derivative. Indeed, such replacement has led to compounds with greatly enhanced $\beta_2$ vs. $\beta_1$ adrenergic receptor selectivity and extraordinarily increased potency.[23,25] In order to determine if a similar subtype selectivity and increase in efficacy accompanied identical replacement of the *m*-hydroxyl of DA, synthesis and pharmacological evaluation of 5-(2-aminoethyl)-8-hydroxycarbostyril (**2**) and several derivatives were undertaken.

**Chemistry.** The general procedure for the synthesis of **2**, as well as several N-substituted and 8-methoxy derivatives, is illustrated in Scheme I.

The required starting material for this sequence, i.e., 5-(cyanomethyl)-8-methoxyquinoline (**3**), was prepared from commercially available 8-hydroxyquinoline via

(16) Cannon, J. G.; Suarez-Gutierrez, C.; Lee, T.; Long, J. P.; Costall, B.; Fortune, D. H.; Naylor, R. J. *J. Med. Chem.* **1979**, *22*, 341.
(17) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481.
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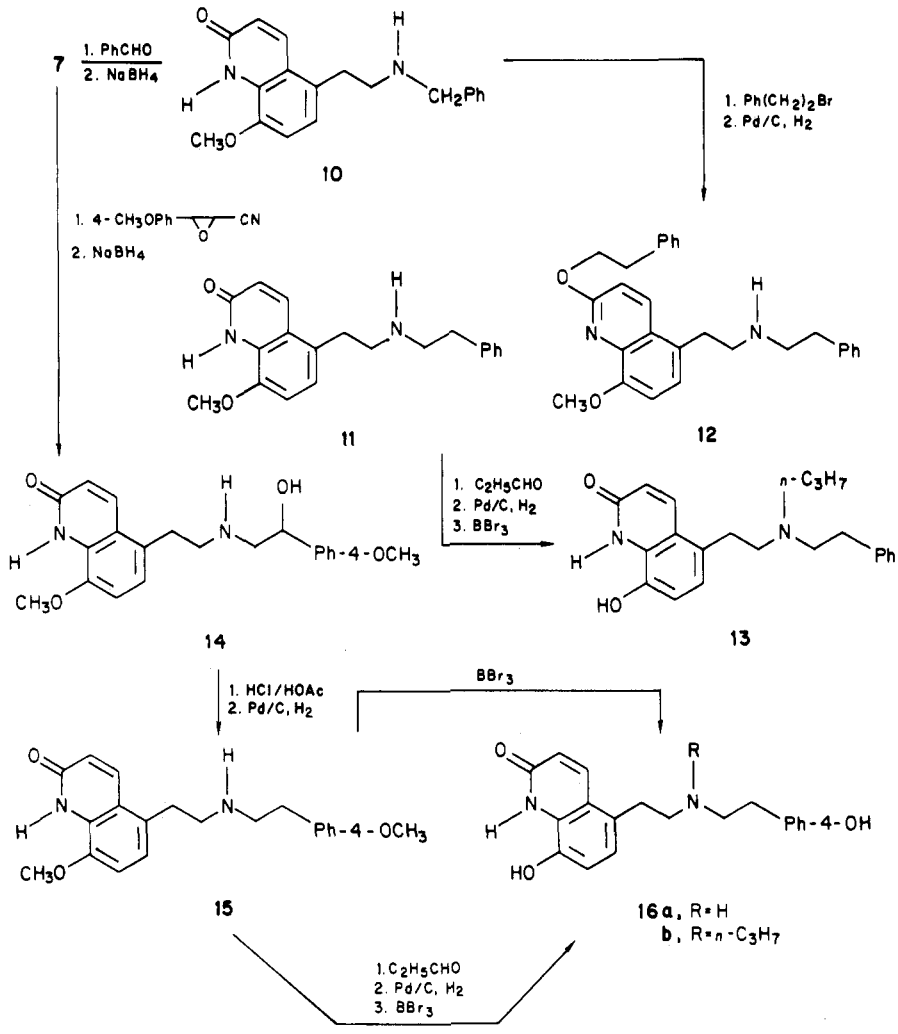
(25) Yoshizaki, S.; Tanimura, K.; Tamada, S.; Yabuuchi, Y.; Nakagawa, K. *J. Med. Chem.* **1976**, *19*, 1138.

**Scheme II**




chloromethylation[26] followed by cyano replacement of the halogen[27] and methylation of the phenolic hydroxyl. Catalytic hydrogenation of the nitrile followed by acylation of the resulting amine afforded the amides **4**. *m*-Chloroperbenzoic acid oxidation of the amides **4** afforded the quinoline *N*-oxides **5** which were rearranged to the corresponding carbostyrils **6** by a conventional Polonovski reaction.[28] Treatment of **6a** with hydrobromic acid resulted in cleavage of the methyl ether and hydrolysis of the amide (presumably during the processing of the reaction) to afford **2**. The benzamide **6b** was hydrolyzed under either basic or preferably acidic conditions to give **7**. Reductive alkylation of **7** with propionaldehyde afforded **8**, which upon methoxy scission with $BBr_3$ gave **9**, the *N*,*N*-di-*n*-propyl derivative of **2**.

For the preparation of a series of N-substituted derivatives of **2**, the sequence outlined in Scheme II was employed. 5-(2-Aminoethyl)-8-methoxycarbostyril (**7**) was utilized as starting material. This was reductively benzylated to give **10**, which upon alkylation with phenethyl bromide followed by hydrogenolysis produced a mixture of N- (**11**) and O,N-phenethylated (**12**) products that was separated by chromatography. Reductive propylation of **11**, followed by methoxy cleavage afforded **13**. Several *N*-(4-hydroxyphenethyl)-substituted derivatives of **2** also originated synthetically from **7**. As illustrated in Scheme II, **7** was treated with the appropriate epicyanohydrin to give the (4-methoxyphenyl)ethanolamine **14**. Hydrogenolysis of the benzylic alcohol was effected under acidic conditions to afford the 4-methoxyphenethyl derivative **15**, which was converted to **16a** by $BBr_3$-induced cleavage of the methoxy groups and to **16b** by reductive propylation followed by similar cleavage of the methoxy groups.

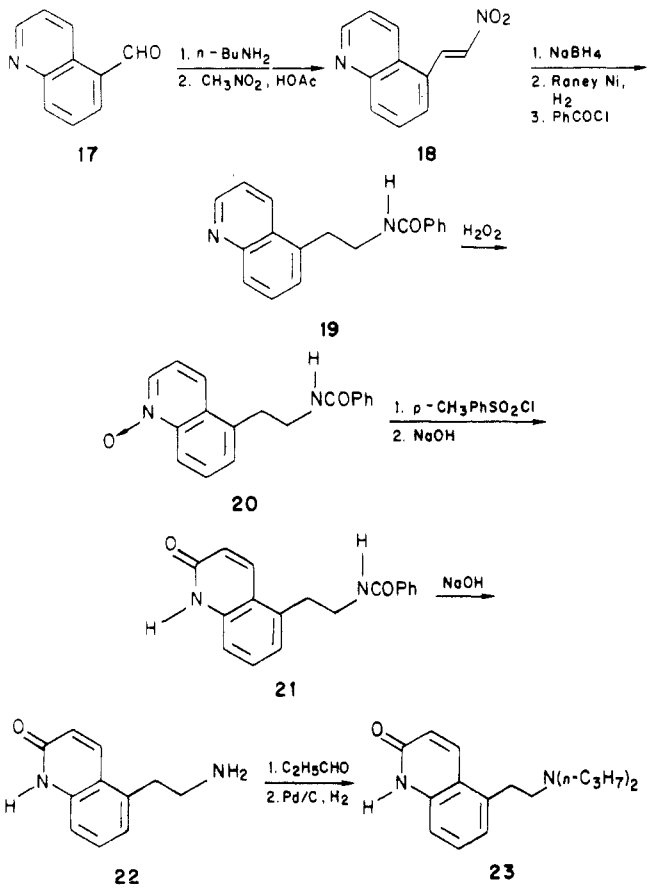
The preparation of several 5-(aminoalkyl)carbostyrils lacking the 8-hydroxyl substituent of **2** was accomplished as outlined in Scheme III. Quinoline-5-carboxaldehyde (**17**)[29] was prepared from quinoline-5-carboxylic acid[30] by a modification of the literature[29] procedure involving reduction of the acid to the alcohol followed by $MnO_2$ oxidation to the aldehyde.

Condensation of **17** with nitromethane under conventional conditions[31] afforded the nitroethylene **18** which was reduced and benzoylated to produce **19**. Peroxide oxidation of **19** followed by a modified Polonovski reaction[28] gave **20** and **21**, respectively. Basic hydrolysis of the benzamide **21** yielded 5-(2-aminoethyl)carbostyril (**22**) which was reductively propylated to **23**.

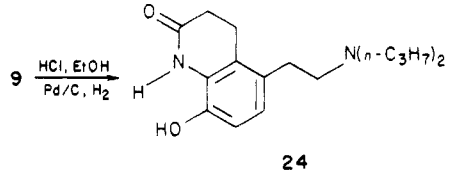
One dihydrocarbostyril **24**, a ring homologue of the dopaminergic (aminoalkyl)indolone **1b**, was prepared by

(26) Burckhalter, J. H.; Leib, R. I. *J. Org. Chem.* **1961**, *26*, 4078.
(27) Warner, V. D.; Sayne, J. N.; Mirth, D. B.; Turesky, S. S.; Soloway, B. *J. Med. Chem.* **1976**, *19*, 167.
(28) Katritzky, A. R.; Lagowski, J. N. "Chemistry of Heterocyclic N-Oxides"; Academic Press: New York, 1971; pp 279, 362.
(29) Cook, A. H.; Heilbron, I. M.; Steger, L. *J. Chem. Soc.* **1943**, 413.
(30) Bradford, L.; Elliott, T. J.; Rowe, F. M. *J. Chem. Soc.* **1947**, 437.
(31) Nagawa, M.; Koremura, M.; Hattori, Z. Jap. Patent (to Sankyo Co., Ltd.) 4485, March 30, 1961; *Chem. Abstr.* **1964**, *61*, 6997g.

**Scheme III**




catalytic hydrogenation[32] of the corresponding carbostyril **9**.

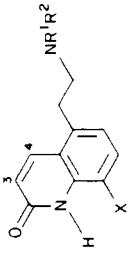



## Results and Discussion

5-(2-Aminoethyl)-8-hydroxycarbostyril (**2**) and various derivatives in which the substituents at position 8 and on the basic nitrogen of the side chain are altered were examined in several tests for dopaminergic activity. These pharmacological tests included ones that measure the ability of the compounds to stimulate or inhibit rat caudate adenylate cyclase (a D-1 DA receptor response[1]) and to inhibit specific [$^3$H]spiroperidol binding to bovine anterior pituitary homogenate (probably indicative of binding to primarily the D-2 subpopulation of DA receptors[33]) and DA agonistlike activity in the isolated, perfused rabbit ear artery[34,35] (attributed to activation of presynaptic DA receptors, probably of the $DA_2$ type[24]).

As can be seen from the data presented in Table I, only the 8-hydroxylated primary aminocarbostyril **2** showed any D-1 DA receptor agonist activity as measured in the test for stimulation of adenylate cyclase, and even this effect

Table I. Dopaminergic Actions of 5-(2-Aminoethyl)carbostyrils




| no. | X | R$^1$ | R$^2$ | adenylate cyclase, rat caudate[a] % stimn at 10 μM[b] | adenylate cyclase, rat caudate[a] % inhibn at 10 μM[b] | [$^3$H]spiroperidol binding, bovine pituitary[a] % displacement at 10 μM[b] | [$^3$H]spiroperidol binding, bovine pituitary[a] $K_{Bind}$,[b] μM | rabbit ear artery test: $ED_{50}$ + std error, nM[a,c] |
|---|---|---|---|---|---|---|---|---|
| **2** | HO | H | H | 27 (2) | 1 (2) | 56 (5) | 4.04 (0.32) | 140 + 37 ($K_B$ = 6 nM)[d] |
| **7** | $CH_3O$ | H | H | 3 (4) | 1 (2) | 9 (14) | *e* | *e* |
| **8** | $CH_3O$ | *n*-$C_3H_7$ | *n*-$C_3H_7$ | 3 (5) | 0 (0) | 6 (11) | *e* | *e* |
| **9** | HO | *n*-$C_3H_7$ | *n*-$C_3H_7$ | 1 (1) | 0 (0) | 19 (13) | *e* | 493 + 32 |
| **11** | $CH_3O$ | H | $(CH_2)_2Ph$ | 0[f] | 0[f] | 9 (14) | *e* | *e* |
| **13** | HO | *n*-$C_3H_7$ | $(CH_2)_2Ph$ | 0 (0) | 6 (2) | 72 (32) | 2.02 (2.17) | 128 + 58 |
| **16a** | HO | H | $(CH_2)_2Ph$-4-OH | 2 (4) | 6 (12) | 42 (3) | *e* | 136 + 26 ($K_B$ = 38 nM)[d] |
| **16b** | HO | *n*-$C_3H_7$ | $(CH_2)_2Ph$-4-OH | 0 (0) | 0 (0) | 78 (13) | 0.77 (1.04) | 12.3 + 0.4[g] |
| **22** | H | H | H | 1 (2) | 5 (5) | 21 (5) | *e* | *e* |
| **23** | H | *n*-$C_3H_7$ | *n*-$C_3H_7$ | 4 (5) | 0 (0) | 30 (39) | 15.1 (32.1) | *e* |
| **24**[h] | HO | *n*-$C_3H_7$ | *n*-$C_3H_7$ | 1 (2) | 0 (0) | 40 (0) | 14.5 (7.76) | 252 + 70 ($K_B$ = 14 nM)[d] |
| DA | 2-(3,4-dihydroxyphenyl)ethylamine | | | $EC_{50}$ = 3.5 μM | *e* | *e* | 2.35 | 37 + 6 ($K_B$ = 10.5 nM)[d] |
| ADTN | 2-amino-6,7-dihydroxytetralin | | | $EC_{50}$ = 1.3 μM | *e* | *e* | 0.21 | 4.6 + 0.8 ($K_B$ = 10.5 nM)[d] |

[a] See the Experimental Section for description of test procedure and calculation of indicated values. [b] Values are the mean of two to four experiments in which each value was determined in triplicate samples. The number in parentheses is the variation of values from which the mean was determined. [c] $N$ = 4, unless otherwise indicated. [d] $K_B$ vs. (*S*)-sulpiride. [e] Value not determined. [f] Tested in only one experiment. [g] $N$ = 5. [h] 3,4-Dihydro derivative.

(32) Nakagawa, K.; Yoshizaki, S.; Tanimura, K.; Tamada, S. U.S. Patent (to Otsuka Pharm. Co.) 3 975 391, Aug 17, 1976.
(33) Frey, E. A.; Cote, T. E.; Grewe, C. W.; Kebabian, J. W. *Endocrinology* **1982**, *110*, 1897.
(34) Hieble, J. P.; Pendleton, R. G. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *309*, 217.
(35) Flaim, K. E.; Gessner, G. W.; Crooke, S. T.; Sarau, H. M.; Weinstock, J. *Life Sci.* **1985**, *36*, 1427.

was weak. In the displacement of [$^3$H]spiroperidol binding test for D-2 receptor affinity **2** was significantly effective; it had about half the affinity of DA.

The 8-methoxy compound **7** and the N-substituted derivatives **8** and **11** essentially lost both D-1 and D-2 DA receptor affinity. Removal of the 8-hydroxyl substituent from **2**, i.e., to afford **22**, resulted in a marked decrease in dopaminergic activity. Similar removal of the 8-hydroxyl group from the N,N-dipropylated congener **9**, i.e., to give **23**, however, did not have a similar effect. Thus, **9** and **23** have comparable potencies in displacing [$^3$H]spiroperidol from its binding sites and indeed **23** was about one-seventh as potent as DA in inhibiting adrenergic neurotransmission in the isolated, perfused rabbit ear artery test.

Substitution of the side-chain nitrogen of 5-(2-aminoethyl)-8-hydroxycarbostyril (**2**) had a significant effect on the activity of these compounds in D-2 DA receptor tests, i.e., in displacement of [$^3$H]spiroperidol binding and in the rabbit ear artery paradigm. Although the N,N-di-*n*-propylated derivative **9** was less effective than its primary amine counterpart **2**, the *N*-*n*-propyl-*N*-phenethyl-substituted derivative **13** and even the N-*p*-hydroxyphenethylated secondary amine **16a** were approximately equipotent with the prototype **2** of the series. The *N*-*n*-propyl-*N*-*p*-hydroxyphenethyl derivative **16b** was clearly the most potent 5-(2-aminoethyl)-8-hydroxycarbostyril studied; it was about 3 times more potent than DA and about one-third to one-fourth as potent as ADTN in both of the D-2 DA receptor tests.

The *N*,*N*-di-*n*-propyldihydrocarbostyril **24**, like the related carbostyril **9**, neither stimulated nor blocked DA-sensitive adenylate cyclase; however, it was more effective than its carbostyril counterpart in displacing [$^3$H]-spiroperidol from bovine pituitary homogenate and it was about twice as potent as **9** in the rabbit ear artery test. It is interesting to note that this dihydrocarbostyril is 140 times less potent than its lower homologue, i.e., 7-hydroxy-4-[2-(di-*n*-propylamino)ethyl]-2(3*H*)-indoline (SK&F 89124) which has an $EC_{50}$ of 1.8 ± 0.3 nM in the latter test.[24]

Thus, our study of a series of compounds in which the catecholic hydroxyl group that is meta to the ethylamine side chain of DA is replaced by the hydroxyl-imitating NH group of a carbostyril indicates that such modification results in DA analogues having little or no activity on the D-1 subpopulation of DA receptors. Only the primary amine **2** had measurable activity in the test for stimulation of DA-sensitive adenylate cyclase (D-1 receptor activation). Some of the carbostyril derivatives, however, retained or, in one case (i.e. **16b**), had enhanced affinity for the D-2 subtype of DA receptor. These observations, coupled with the marked dependence of potency in tests for D-2 receptor activity on the nature of substitution of the side-chain nitrogen is in substantial accord with previously described DA-related compounds.[7-16,24] Clearly, replacement of the *m*-hydroxyl of DA with a carbostyril NH group does not cause the striking potency enhancement observed upon similar modification of β-adrenoreceptor agonists.[23] In fact, significantly greater D-2 receptor potency enhancement is observed in compounds in which the *m*-hydroxyl of DA is simulated by the NH group of an indolone system.[24]

## Experimental Section

Melting points were determined in open capillary tubes in a Thomas-Hoover Uni-Melt apparatus; they were not corrected. Elemental analyses were performed by the Analytical, Physical and Structural Chemistry Department of Smith Kline & French Laboratories. Where analyses are reported by symbols of the elements, results were within 0.4% of the calculated value unless indicated otherwise. Although IR, NMR, and mass spectral data are not reported, these spectra were obtained for all compounds described in this section and were evaluated as consistent with the indicated structures. IR and NMR spectra supported assignment of hydration for indicated compounds. IR spectra were obtained on a Perkin-Elmer 727 IR spectrophotometer. NMR spectra were obtained in a Hitachi Perkin-Elmer R-24 spectrometer ($Me_4Si$). Mass spectra were determined on a Hitachi Perkin-Elmer-6E spectrometer. TLCs were carried out on Analtech Uniplates, silica gel GF, 250 μm.

**Chemistry. 5-(Cyanomethyl)-8-methoxyquinoline (3).** To a stirred solution of 10.8 g (60 mmol) of 5-(cyanomethyl)-8-hydroxyquinoline (prepared from 8-hydroxyquinoline via chloromethylation[26] followed by replacement of the chloro substituent with cyanide[27]) in 100 mL of DMF was added, in portions over a period of 20 min, 3.13 g (65 mmol) of a 50% dispersion of NaH in mineral oil. After the addition was completed, the solution was stirred at 50 °C for 2.5 h. Next, the solution was cooled to 25 °C, and 10.3 g (70 mmol) of MeI in 10 mL of DMF was added dropwise over a period of 10 min. The solution was stirred at 50 °C for 30 min, and then it was poured onto 85 mL of ice water. The mixture was extracted with EtOAc. After being washed with $H_2O$, the extracts were dried ($MgSO_4$, decolorizing C) and concentrated to give a semisolid. This material was washed with hexane to give 5.1 g (44%) of pale pink crystals, mp 153–155 °C, after recrystallization from MeCN–$Et_2O$. Anal. ($C_{12}H_{10}N_2O$) C, H, N.

**5-(2-Acetamidoethyl)-8-methoxyquinoline (4a).** A mixture of 14.5 g (73 mmol) of **3** and about 4 g of Raney Ni in 300 mL of a saturated solution of $NH_3$ in MeOH was hydrogenated at 25 °C and an initial pressure of 50 psi of $H_2$ for 3 h. The mixture was filtered and concentrated. After the residue was stripped twice with toluene, it was dissolved in 100 mL of acetic anhydride. The solution was allowed to stand at 25 °C for 10 min, and then it was concentrated in vacuo. The residue was stripped with $H_2O$ three times, and then it was dissolved in $CHCl_3$. After the $CHCl_3$ solution was dried ($MgSO_4$) and concentrated, the residual solid was recrystallized from $Me_2CO$–$Et_2O$ to give 12.2 g (63%) of colorless crystals, mp 155–156 °C. Anal. ($C_{14}H_{16}N_2O_2 \cdot 0.25H_2O$) C, H, N.

**5-(2-Benzamidoethyl)-8-methoxyquinoline (4b).** A suspension of 4.76 g (24 mmol) of **3** and about 2 g of Raney Ni in 50 mL of concentrated aqueous $NH_3$ and 100 mL of MeOH was hydrogenated at 25 °C and an initial $H_2$ pressure of 60 psi for 3 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The residue was dissolved in $CHCl_3$. After the resulting solution was dried ($MgSO_4$), it was treated with 2.43 g (24 mmol) of triethylamine and 3.37 g (24 mmol) of benzoyl chloride. The solution was stirred at 25 °C for 30 min, and then it was diluted with ice water. The mixture was made alkaline with aqueous $NH_3$. After the layers were separated, the aqueous phase was extracted with $CH_2Cl_2$. The combined organic extracts were washed with $H_2O$, dried ($MgSO_4$), and concentrated to give 6.34 g (86%) of nearly colorless crystals, mp 171.5–173 °C, after recrystallization from MeCN. Anal. ($C_{19}H_{18}N_2O$) C, H, N.

**5-(2-Acetamidoethyl)-8-methoxyquinoline *N*-Oxide (5a).** A solution of 12.2 g (49.2 mmol) of **4a** and 15.5 g (72 mmol) of 80% *m*-chloroperbenzoic acid in 200 mL of $CHCl_3$ was stirred at 25 °C for 16 h. The solution was filtered through a 5-cm layer of neutral alumina (activity grade III). Concentration of the filtrate gave a crystalline residue that was recrystallized from $Me_2CO$–$Et_2O$ to afford 6.5 g (51%) of colorless crystals, mp 147–148 °C. Anal. ($C_{14}H_{16}N_2O_3 \cdot 0375H_2O$) C, H, N.

**5-(2-Benzamidoethyl)-8-methoxyquinoline *N*-Oxide (5b).** A solution of 1.33 g (4.34 mmol) of **4b** and 1.46 g (8.44 mol) of *m*-chloroperbenzoic acid in 15 mL of $CHCl_3$ was stirred at 25 °C for 16 h. After the solution was diluted with 45 mL of $CH_2Cl_2$, it was extracted with an equal amount of a saturated aqueous solution of $NaHCO_3$. The organic phase was then washed with $H_2O$, dried ($MgSO_4$), and concentrated to give a semisolid residue. Trituration of the residue with warm EtOAc afforded 0.57 g (41%) of pale yellow crystals, mp 160–162 °C, after recrystallization from $Me_2CO$; TLC (silica; 90:10:2 $CH_2Cl_2$–MeOH–concentrated aqueous $NH_3$) gave a single spot, $R_f$ 0.6. Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

**5-(2-Acetamidoethyl)-8-methoxycarbostyril (6a).** A solution of 4.0 g (15.4 mmol) of **5a** and 50 mL of acetic anhydride was heated at 100 °C for 30 min. The solution was concentrated in

vacuo to give a viscous residue that was stirred with $H_2O$ for 30 min and then concentrated. A solution of the residue in $CH_2Cl_2$ was passed through a 20-cm column of neutral alumina (activity grade III), eluting with a mixture of 50% $CHCl_3$–hexane, followed by $CHCl_3$ and finally 10% MeOH in $CHCl_3$. Concentration of the eluates afforded 1.5 g (38%) of colorless crystals, mp 168–169 °C, after recrystallization from $Me_2CO$. Anal. ($C_{14}H_{16}N_2O_3 \cdot 0.25H_2O$) C, H, N.

**5-(2-Benzamidoethyl)-8-methoxycarbostyril (6b).** A mixture of 3.13 g (9.4 mmol) of **5b** in 47 mL of THF was treated with 6.6 mL (46.9 mmol) of triethylamine, followed by 9.4 mL (96 mmol) of acetic anhydride. After being stirred at 25 °C for 20 h, the resulting solution was stirred while 90 mL of 2.5 N NaOH was added with cooling. Stirring was continued at 25 °C for 30 min. The mixture was then brought to pH 6 by addition of 2.5 N HCl to give 2.48 g (82%) of a tan solid, mp 208–210 °C, after recrystallization from $Me_2CO$. Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

**5-(2-Aminoethyl)-8-hydroxycarbostyril Hydrobromide (2·HBr).** A solution of 0.2 g (0.62 mmol) of **6b** in 5 mL of 48% HBr was refluxed for 16 h. After the solution was concentrated, the resulting residue was stripped with MeOH and toluene to give a tan solid. Recrystallization from MeOH–$Et_2O$ afforded 0.148 g (84%) of off-white crystals, mp 338–341 °C. Anal. ($C_{11}H_{12}N_2O_2 \cdot 0.25H_2O$) C, H, N.

A similar result was obtained when the acetamide **6a** was subjected to similar HBr treatment.

**5-(2-Aminoethyl)-8-methoxycarbostyril (7). Method A.** A solution of 4.5 g (14 mmol) of **6b** in 100 mL of MeOH and 100 mL of 2.5 N NaOH was stirred at reflux for 24 h. The solution was acidified with concentrated HCl, and then it was extracted with EtOAc. After the aqueous phase was made alkaline with concentrated aqueous $NH_3$, it was continuously extracted with $CHCl_3$. The organic solution was dried ($MgSO_4$) and concentrated to give 2.4 g (80%) of **7** as a viscous liquid; TLC (silica; 70:30:3 $CH_2Cl_2$–MeOH–concentrated aqueous $NH_3$) gave a single spot, $R_f$ 0.5.

**Method B.** A solution of 1.41 g (3.54 mmol) of **6b** in 25 mL of concentrated HCl was stirred and refluxed for 3 h, and then it was concentrated in vacuo. The residue was stripped with MeOH–toluene, and then it was suspended in 5 mL of 7.5 N $NH_4OH$ and 200 mL of $CH_2Cl_2$. The layers were separated, and the aqueous phase was extracted twice with 25-mL portions of $CH_2Cl_2$. The combined organic extracts were dried ($MgSO_4$) and concentrated to leave a yellow amorphous residue. This residue was dissolved in MeOH. The solution was acidified with HCl and concentrated. The resulting amorphous solid was suspended in 20 mL of $H_2O$ to which 2 mL of 2 N HCl had been added. The aqueous mixture was extracted three times with $CH_2Cl_2$, and then it was concentrated in vacuo. The residue was stripped twice with MeOH–toluene, and then 5 mL of EtOH was added. Crystals [0.41 g (45%); mp 250–258 °C], after being washed with cold EtOH and $Et_2O$, were collected. Anal. ($C_{12}H_{14}N_2O_2 \cdot 2.25H_2O$) C, N; H: calcd, 6.32; found, 5.57.

**5-[2-(Di-*n*-propylamino)ethyl]-8-methoxycarbostyril (8).** A mixture of 2.4 g (11.0 mmol) of **7** (prepared by method A), 14 mL of propanal, and 1.5 g of 10% Pd/C in 200 mL of HOAc was hydrogenated at 25 °C and an initial pressure of 50 psi of $H_2$ for 2 h. The mixture was filtered, and the filtrate was concentrated. The residue was suspended in 100 mL of $H_2O$ and made alkaline with concentrated aqueous $NH_3$. The mixture was extracted with EtOAc. After being dried ($MgSO_4$), the extract was concentrated to give an oily residue. A solution of this residue in 50% $CHCl_3$–hexane was chromatographed on a silica column. Elution was carried out sequentially with 50% $CHCl_3$–hexane, $CHCl_3$, and 10% MeOH in $CHCl_3$, monitoring individual fractions by TLC [silica; 80:20 $CHCl_3$–MeOH]. Fractions having a single spot at $R_f$ 0.8 were combined and concentrated to leave an oily product. To a solution of this material in MeOH was added excess fumaric acid. Subsequent addition of EtOAc and $Et_2O$ gave a crystalline product of the *hydrogen fumarate* [4.3 g (92%); mp 161.5–162 °C] after recrystallization from MeOH–EtOAc–$Et_2O$. Anal. ($C_{18}H_{26}N_2O_2 \cdot C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

**5-[2-(Di-*n*-propylamino)ethyl]-8-hydroxycarbostyril (9).** To a stirred solution of 2.7 g (8.94 mmol) of **8** in 50 mL of $CHCl_3$ was added dropwise 20 mL of a solution containing 1 g of $BBr_3$ in 2.5 mL of $CH_2Cl_2$. Stirring was continued at 25 °C for 30 min, and then the solution was heated at reflux for 10 min. After the stirred solution was cooled to 0–5 °C, 10 mL of MeOH was added dropwise. The solution was concentrated under reduced pressure and the residue was suspended in $H_2O$. The aqueous phase was then adjusted to pH 8 by addition of aqueous $NH_3$. The mixture was extracted exhaustively with EtOAc. After the extracts were dried and concentrated, the residual solid was recrystallized from $H_2O$ to give 1.7 g (66%) of colorless crystals, mp 228–230 °C. Anal. ($C_{17}H_{24}N_2O_2$) C, H, N.

**5-[2-(Benzylamino)ethyl]-8-methoxycarbostyril (10).** A solution of 12.0 g (51.5 mmol) of **7**, prepared by method A, and 13.4 mL (131.8 mmol) of benzaldehyde in 200 mL of toluene was refluxed azeotropically for 2 h. The solution was concentrated to leave an oily residue that was dissolved in MeOH. To the stirred methanolic solution at 0–5 °C was added, in portions, 7.0 g (185.2 mmol) of $NaBH_4$. Stirring was continued for 30 min at 0 °C; then the solution was poured onto 200 mL of ice water, and concentrated aqueous $NH_3$ was added to pH 10. The mixture was extracted with $CHCl_3$. After the extracts were dried ($MgSO_4$), they were concentrated to leave an oily residue. A solution of this oil in MeOH was made acidic with HCl. Upon addition of EtOAc and $Et_2O$, 11.1 g (91%) of a crystalline *hydrochloride*, mp 266–268 °C, after recrystallization from MeOH–EtOAc–$Et_2O$, was collected. Anal. ($C_{19}H_{20}N_2O_2 \cdot HCl \cdot H_2O$) C, H, N.

**8-Methoxy-5-[2-[(2-phenylethyl)amino]ethyl]carbostyril (11) and 8-Methoxy-2-[(2-phenylethyl)oxy]-5-[2-[(2-phenylethyl)amino]ethyl]carbostyril (12).** A stirred mixture of 12.0 g (38.9 mmol) of **10**, 15 mL (0.11 mol) of 2-phenylethyl bromide, and 50.0 g (0.36 mol) of $K_2CO_3$ in 100 mL of DMF was refluxed for 30 min. The resulting solution was poured onto 1 L of ice water, and the mixture was extracted with EtOAc. The extracts were washed with $H_2O$, dried ($MgSO_4$), and concentrated to give an oily residue; TLC (silica; 90:10 $CHCl_3$–MeOH) showed two major spots at $R_f$ 0.5 and 0.6. A solution of the oil in 100 mL of MeOH was acidified with 12 N HCl, 3.0 g of 10% Pd/C was added, and the mixture was hydrogenated for 30 min at 25 °C at an initial pressure of 50 psi of $H_2$. After the mixture was filtered, the filtrate was concentrated and the residue was suspended in 2 N $NH_4OH$. The mixture was extracted with EtOAc. The extract was dried ($MgSO_4$) and concentrated to leave a residue that afforded 2.5 g (20%) of crystals, mp 92–93 °C, after recrystallization from $Et_2O$. IR and NMR were consistent for **11**; TLC (silica; 90:10 $CHCl_3$–MeOH) indicated a single spot with $R_f$ 0.5. Anal. ($C_{20}H_{22}N_2O_2$) C, H, N.

The mother liquors from the preceding recrystallization were concentrated to leave an oily residue. This oil was chromatographed on a silica column eluting with 30:70 hexane–EtOAc followed by EtOAc. Fractions of eluate were monitored by the TLC system described for the mixture. All fractions with $R_f$ 0.6 were combined and concentrated to leave an oily residue. This was dissolved in MeOH, the solution was made acidic with HCl, and EtOAc and $Et_2O$ were added to give 3.5 g (21%) of **12**·2HCl, mp 142–144 °C, after recrystallization from MeOH–EtOAc. Anal. ($C_{28}H_{30}N_2O \cdot 2HCl$) C, H, N.

**8-Hydroxy-5-[2-[(2-phenylethyl)-*n*-propylamino]ethyl]carbostyril (13).** A mixture of 2.5 g (7.76 mmol) of **11**, 2.5 mL (34.7 mmol) of propanal, and 2.0 g of 10% Pd/C in 100 mL of HOAc was hydrogenated for 30 min at 25 °C at an initial pressure of 50 psi of $H_2$. The mixture was filtered. The filtrate was concentrated, and the residue was suspended in $H_2O$. After the mixture was made alkaline with concentrated aqueous $NH_3$, it was extracted with EtOAc. The extracts were washed with $H_2O$, dried ($MgSO_4$), and concentrated to leave an oily product. To a stirred solution of this material (2.2 g, 6.04 mmol) in 100 mL of $CH_2Cl_2$ was added dropwise 20 mL of a 1 M solution of $BBr_3$ in $CH_2Cl_2$. The reaction mixture was stirred at reflux for 1 h, and then it was cooled to 5 °C and 20 mL of MeOH was added dropwise. After the solution was concentrated, to the residual oil was added 100 mL of $H_2O$. The mixture was made alkaline with aqueous $NH_3$ and extracted with EtOAc. The organic extracts were dried and concentrated. Trituration of the residue with hexane afforded 1.3 g (62%) of crystals, mp 183–184 °C, after recrystallization from MeOH–$H_2O$. Anal. ($C_{22}H_{26}N_2O_2$) C, H, N.

**5-[2-[[2-(4-Methoxyphenyl)-2-hydroxyethyl]amino]ethyl]-8-methoxycarbostyril (14).** A mixture of 7.3 mL (60.2

mmol) of 4-methoxybenzaldehyde, 4.2 mL of chloroacetonitrile, 25 mL of 10 N NaOH, and 0.15 g of benzyltrimethylammonium chloride was stirred at 25 °C for 30 min. The layers were separated, and the organic layer was washed with $H_2O$, dried, and concentrated to give 8.1 g (77%) of crude (4-methoxyphenyl)-epicyanohydrin. This product was refluxed with 50 mL of $H_2O$ and 0.06 g of concentrated $H_2SO_4$ for 30 min. A solution of 8.1 g (37.2 mmol) of 7, prepared by method A, in 40 mL of $H_2O$ was added to the refluxing solution. The resulting solution was immediately poured into 100 mL of ice water to give 11.2 g of a crystalline intermediate cyano alcohol: TLC (silica; 90:10 $CHCl_3$–MeOH) single spot, $R_f$ 0.3; mp 135–136 °C. This intermediate (11.0 g, 28 mmol) was suspended in 300 mL of EtOH, and 28 g (0.74 mol) of $NaBH_4$ was added *cautiously* in small portions. The resulting mixture was stirred at 25 °C for 24 h, and then it was diluted with 200 mL of 10% aqueous HOAc. After being made alkaline with concentrated aqueous $NH_3$, the mixture was extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated to give 5.3 (50%) of colorless crystals, mp 157–162 °C, after trituration with EtOAc. This product was carried to the next step without further purification.

**5-[2-[[2-(4-Methoxyphenyl)ethyl]amino]ethyl]-8-methoxycarbostyril (15).** A mixture of 10.0 g (27.2 mmol) of **14**, 100 mL of HOAc, 50 mL of 12 N HCl, and 7.0 g of Pd/C was hydrogenated for 30 min at 25 °C and an initial $H_2$ pressure of 50 psi. The mixture was filtered, and the filtrate was concentrated in vacuo. The residue was suspended in $H_2O$ and made alkaline with concentrated aqueous $NH_3$. The mixture was extracted with EtOAc. The extracts were dried ($MgSO_4$) and concentrated to give a crystalline residue [7.0 g (73%); mp 89–91 °C] after recrystallization from EtOAc–$Et_2O$. Anal. ($C_{21}H_{24}N_2O_3$) C, H, N.

**8-Hydroxy-5-[2-[[2-(4-hydroxyphenyl)ethyl]amino]ethyl]carbostyril (16a).** To a stirred solution of 0.55 g (1.56 mmol) of **15** in 50 mL of $CH_2Cl_2$ was added dropwise 15 mL of a solution containing 1 g of $BBr_3$ in 2.5 mL of $CH_2Cl_2$. The reaction mixture was stirred at 25 °C for 30 min, and then it was heated at reflux for 1 h. After it was cooled to 5 °C, 15 mL of MeOH was added dropwise. The solution was evaporated, and the residue was twice taken into 25 mL of MeOH and concentrated. The residual solid *hydrobromide* was recrystallized from MeOH–EtOAc to give 0.158 g (25%) of off-white crystals, mp 248–250 °C. Anal. ($C_{19}H_{20}N_2O_3 \cdot HBr \cdot 0.75H_2O$) C, H, N.

**8-Hydroxy-5-[2-[[2-(4-hydroxyphenyl)ethyl]-*n*-propylamino]ethyl]carbostyril (16b).** A mixture of 1.0 g (2.84 mmol) of **15**, 3.0 mL (42 mmol) of propanal, and 1 g of 10% Pd/C in 100 mL of HOAc was hydrogenated at 25 °C and an initial pressure of 50 psi of $H_2$ for 30 min. The mixture was filtered, and the filtrate was evaporated. The residue was suspended in 50 mL of $H_2O$, and 10 mL of concentrated aqueous $NH_3$ was added. After the mixture was extracted with EtOAc, the extracts were dried ($MgSO_4$) and concentrated to give 0.95 g of an oily product. To a stirred solution of this product in 50 mL of $CH_2Cl_2$ was added dropwise 15 mL of a solution containing 1 g of $BBr_3$ in 2.5 mL of $CH_2Cl_2$. After the solution was refluxed for 1 h, it was processed as described for **16a** to give 0.21 g (23%) of a crystalline product, mp 176–178 °C, after recrystallization from $H_2O$–MeOH. Anal. ($C_{22}H_{26}N_2O_3$) C, H, N.

A crystalline *hydrogen fumarate* was prepared by addition of excess fumaric acid to a methanolic solution of **16b**, followed by precipitation with $Et_2O$. It melted at 139–141 °C after recrystallization from MeOH–EtOAc–$Et_2O$. Anal. ($C_{22}H_{26}N_2O_3 \cdot C_4H_4O_4 \cdot 0.75H_2O$) C, H, N.

**Quinoline-5-carboxaldehyde (17).** This material was prepared by a modification of the procedure that has been reported previously.[29] Quinoline-5-carboxylic acid[30] (43.9 g, 0.254 mol) was dissolved in 1 L of EtOH, and HCl gas was bubbled through the solution for 3.5 h. The resulting suspension was stirred at reflux for 20 h to produce a brown solution. Following concentration of the solution, to the residue was added 250 mL of ice water. The mixture was made alkaline with $NH_3$ and extracted with EtOAc. After the extract was dried, it was concentrated to leave 35.9 g of ethyl ester; TLC (silica; 50:50 EtOAc–hexane) showed a single spot, $R_f$ = 0.8. A solution of this ester (35.9 g, 0.179 mol) in 500 mL of $Et_2O$ was added dropwise to a stirred suspension of 8.19 g (0.215 mol) of $LiAlH_4$ in 500 mL of $Et_2O$ at −50 °C over a period of 30 min. After addition was completed, the mixture was allowed to warm to 0 °C, and stirring was continued for 1.5 h. To the stirred mixture was added dropwise, and with *caution*, in sequence 8.2 mL of $H_2O$, 12.3 mL of 2.5 N NaOH, and 18.4 mL of $H_2O$. The mixture was filtered. The filter cake was stirred with boiling EtOH and filtered. The ethanolic and ethereal filtrates were combined and concentrated to give 30.2 g of solid carbinol. This product was stirred with 150 g of activated $MnO_2$ in 300 mL of $CHCl_3$ for 3 h. The mixture was filtered, and the filter cake was stirred for 10 min with boiling EtOH and filtered. Concentration of the combined organic extracts gave 17.7 g (63%) of crystals, mp 95.5–96.5 °C (lit.[29] mp 95.5–96.5 °C).

**5-(2-Nitroethenyl)quinoline (18).**[31] A solution of 17.7 g (0.113 mol) of **17** and 150 mL of *n*-butylamine in 200 mL of toluene was refluxed azeotropically for 1 h. After the solution was concentrated in vacuo, the residue was dissolved in 80 mL of nitromethane and 250 mL of HOAc, and the solution was refluxed for 30 min. The solution was cooled to 15 °C to give 15.0 g (52%) of a crystalline product, mp 149–151 °C (lit.[31] mp 163 °C).

**5-(2-Benzamidoethyl)quinoline (19).** To a stirred suspension of 14.0 g (53.8 mmol) of **18** in 250 mL of MeOH at −10 °C was added, in portions, 7.2 g (0.19 mol) of $NaBH_4$. The mixture was stirred at 25 °C for 30 min, and then it was poured into 1 L of 2.5 N HCl. The solution was made alkaline with concentrated aqueous $NH_3$. The resulting mixture was extracted with $CHCl_3$, and the extracts were dried ($MgSO_4$) and concentrated to give 10.7 g of an oily residue; TLC (silica; 50:50 EtOAc–hexane) gave a single spot, $R_f$ 0.6. A mixture of this oil, about 4 g of Raney Ni, and 100 mL of MeOH was hydrogenated at 25 °C for 1 h at an initial $H_2$ pressure of 50 psi. The mixture was filtered and concentrated, and the residue was dissolved in 200 mL of $CHCl_3$. To this stirred solution at 25 °C was added 8.1 mL (5.88 g, 58.2 mmol) of triethylamine and 6.8 mL (58.2 mmol) of benzoyl chloride. The solution was immediately poured into 200 mL of ice water. The mixture was made alkaline with concentrated aqueous $NH_3$. The layers were separated. The aqueous phase was extracted with 100 mL of $CHCl_3$, and the organic solutions were combined. After the organic solution was dried ($MgSO_4$), it was concentrated to leave an oily residue. This material was chromatographed on an alumina column, eluting successively with 50:50 EtOAc–hexane and 70:30 EtOAc–hexane. All fractions were subjected to TLC analysis (silica; 20:80 MeOH–$CHCl_3$), and those showing a single spot at $R_f$ 0.6 were combined and concentrated to give 9.04 g (61%) of a liquid product.

A solution of this liquid in 2-propanol was acidified with HCl. Recrystallization of the resulting solid from 2-propanol afforded a crystalline *hydrochloride*, mp 192–193 °C. Anal. ($C_{18}H_{16}N_2O \cdot HCl \cdot H_2O$) C, H, N.

**5-(2-Benzamidoethyl)quinoline *N*-Oxide (20).** A solution 8.5 g (30.8 mmol) of **19**, 20.0 mL of 30% $H_2O_2$, and 100 mL of HOAc was stirred and refluxed for 1 h. The solution was poured into 200 mL of ice water, and the mixture was made alkaline with 2 N $NaHCO_3$. Following extraction of the resulting mixture with $CHCl_3$, the extracts were dried ($MgSO_4$) and concentrated to give 4.1 g (45%) of a crystalline product, mp 164–167 °C, after recrystallization from THF–EtOAc–$Et_2O$. Anal. ($C_{18}H_{16}N_2O_2 \cdot H_2O$) C, H, N.

**5-(2-Benzamidoethyl)carbostyril (21).** A solution of 4.1 g (14.0 mmol) of **20** and 3.2 g (16.8 mmol) of *p*-toluenesulfonyl chloride in 100 mL of $CHCl_3$ was stirred at reflux for 1 h. After the solution was cooled to 0 °C, it was adjusted to pH 7 by addition of 2 N $NaHCO_3$. $CHCl_3$ was evaporated in vacuo. To the resulting mixture were added 50 mL of 10 N NaOH and 60 mL of MeOH. After this mixture was refluxed for 1 h, it was cooled to 25 °C and made acidic with 11 N HCl. The solution was adjusted to pH 8 with aqueous $NH_3$, and the solid was filtered to give 1.83 g (44%) of crystals, mp 224–226 °C, after recrystallization from $Me_2CO$–$Et_2O$; TLC (silica; 10:90 MeOH–$CHCl_3$) gave a single spot, $R_f$ 0.6. Anal. ($C_{18}H_{16}N_2O_2 \cdot 2.5H_2O$) C, H, N.

**5-(2-Aminoethyl)carbostyril (22).** A stirred mixture of 1.83 g (6.25 mmol) of **21**, 50 mL of 10 N NaOH, 20 mL of $H_2O$, and 60 mL of MeOH was heated under reflux for 20 h. The mixture was poured into 200 mL of ice water, made acidic with 11 N HCl, and extracted with EtOAc. The aqueous phase was made basic with concentrated aqueous $NH_3$ and extracted continuously with $CHCl_3$. The extracts were dried ($MgSO_4$) and concentrated to afford 1.1 g (94%) of colorless crystals, mp 156–159 °C, after

recrystallization from $H_2O$. Anal. ($C_{11}H_{12}N_2O \cdot 1.125H_2O$) C, H, N.

**5-[2-(Di-*n*-propylamino)ethyl]carbostyril (23).** A mixture of 0.95 g (5.1 mmol) of **22**, 3.0 mL (2.42 g, 41.6 mmol) of propanal, and 1.0 g of 10% Pd/C was hydrogenated at 25 °C for 2 h at an initial $H_2$ pressure of 50 psi. The mixture was filtered, and the filtrate was evaporated. The resulting residue was diluted with 50 mL of $H_2O$, and the mixture was made alkaline with concentrated aqueous $NH_3$ and extracted with EtOAc. After the extracts were dried and concentrated, the resulting oil was chromatographed on a silica column. The column was eluted sequentially with 50:50 hexane–EtOAc, EtOAc, and 10:90 MeOH–EtOAc. Concentration of the combined eluates gave 0.51 g (50%) of crystalline product, mp 133–135 °C, after recrystallization from hexane. Anal. ($C_{17}H_{24}N_2O$) C, H, N.

**3,4-Dihydro-8-hydroxy-5-[2-(di-*n*-propylamino)ethyl]carbostyril Hydrochloride (24).** A mixture of 279 mg (0.97 mmol) of **9** and 100 mL of EtOH was made acidic with HCl, and 2.79 g of 10% Pd/C was added. The mixture was hydrogenated for 8 h at 25 °C and an initial pressure of 60 psi of $H_2$. The mixture was filtered, and the filtrate was concentrated in vacuo. The resulting solid was triturated with MeCN to give 143 mg (45%) of colorless crystals: mp 145 °C dec; TLC (silica; 90:10:2 $CHCl_2$–MeOH–concentrated aqueous $NH_3$) single spot, $R_f$ 0.6. Anal. ($C_{17}H_{26}N_2O_2 \cdot HCl$) C, H, N. $M_r$ ($C_{17}H_{27}N_2O_2$) calcd, 291.206; found, 291.207.

**Pharmacology. Stimulation or Inhibition of Dopamine-Sensitive Adenylate Cyclase.**[34] Freshly dissected caudate nuclei from rat brain were homogenized (20 mg/mL) and preincubated on ice for 30 min in 50 mM Tris–maleate, pH 7.4, containing 2 mM of EGTA. A 50-μL aliquot of the homogenate was added to 250 μL of 80 mM Tris–maleate, pH 7.4, 2 mM $MgSO_4$, 0.2 mM EGTA, 5 mM aminophylline, 0.05% sodium metabisulfite, and test compound. [$^{14}$C]-ATP was added to give a concentration of 0.625 mM, and incubation was allowed to proceed for 3 min at 30 °C. The reaction was terminated by placing the tubes in boiling $H_2O$ for 3 min, and 600 μL of $H_2O$ was added. The [$^{14}$C]-c-AMP produced was isolated by chromatography on alumina and Dowex columns, and radioactivity was measured by liquid scintillation spectrometry. c-AMP activity was determined in the absence (basal) and presence (100% stimulation) of 50 μM dopamine. The stimulation induced by test compounds was compared to that of dopamine and basal activity. Stimulations equal to or greater than 25% above basal activity were considered significant, and the compound was tested more extensively to obtain an $EC_{50}$, i.e., the concentration required to produce 50% of the maximum stimulation attainable with the test compound.

Activity of compounds as antagonists was measured as the percent decrease of the 100% response to 50 μM dopamine.

**Competition for [$^3$H]Spiroperidol in Bovine Anterior Pituitary.**[34] Homogenized and washed membrane preparations from bovine anterior pituitary were incubated for 20 min at 37 °C in 50 mM Tris-HCl, pH 7.4, containing 10 mM $MgSO_4$, 2 mM EDTA, and 0.1% ascorbate. The membrane-bound radioactivity was trapped by rapid filtration over glass fiber (GF/C) filters. In each experiment the amount of [$^3$H]spiroperidol bound was determined in the absence (total) and presence (nonspecific) of $10^{-6}$ M (+)-butaclamol. The difference represents specific [$^3$H]spiroperidol binding. The ability of each compound to compete with [$^3$H]spiroperidol (approximately 0.25 nM) was tested at concentrations of $10^{-5}$ and $10^{-7}$ M. Compounds displacing [$^3$H]spiroperidol by 50% or more were tested further to obtain an $IC_{50}$. The $K_{Bind}$ of a compound equals $(IC_{50})/(1 + L/K_D)$ where $L$ is the concentration of [$^3$H]spiroperidol and $K_D$ is the dissociation constant for spiroperidol (0.3 nM).

**Isolated Perfused Rabbit Ear Artery Test.**[35,36] This test was conducted as described previously.[35,36] The concentration-dependent inhibition of the constrictor response of the rabbit ear artery to brief intermittent periods of nerve stimulation was measured. The $EC_{50}$ is the concentration of drug required to produce 50% inhibition of the neuroeffector response (constriction) to nerve stimulation. Dissociation constants ($K_B$) for (*S*)-sulpiride, a selective $DA_2$ receptor antagonist, were determined according to the method of Furchgott.[37]

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**Registry No.** **2**, 94592-62-8; **2**·HBr, 98421-17-1; **3**, 94592-57-1; **4a**, 94592-58-2; **4b**, 94592-63-9; **5a**, 94592-59-3; **5b**, 94592-64-0; **6a**, 94592-60-6; **6b**, 94592-65-1; **7**, 94592-66-2; **8**, 94592-67-3; **8**·fumarate, 98421-18-2; **9**, 94592-69-5; **10**, 94938-81-5; **10**·HCl, 98421-19-3; **11**, 94592-72-0; **12**, 98421-20-6; **12**·2HCl, 98421-21-7; **13**, 94938-82-6; **14**, 94592-39-9; **15**, 94592-40-2; **16a**, 98421-23-9; **16a**·HBr, 94592-43-5; **16b**, 94592-42-4; **16b**·fumarate, 98421-24-0; **17**, 22934-41-4; **18**, 1080-96-2; **19**, 98421-29-5; **19**·HCl, 98421-30-8; **20**, 98421-31-9; **21**, 98421-32-0; **22**, 98421-33-1; **23**, 98421-34-2; **24**, 98421-35-3; **24** (free base), 98421-36-4; 5-(cyanomethyl)-8-hydroxyquinoline, 57434-83-0; 5-(2-aminoethyl)-8-methoxyquinoline, 98421-16-0; propanal, 123-38-6; benzaldehyde, 100-52-7; 5-[2-(benzoylamino)ethyl]-8-methoxycarbostyril, 94592-65-1; 2-phenylethyl bromide, 103-63-9; 8-methoxy-5-[2-[*N*-(2-phenylethyl)-*N*-(benzyl)amino]ethyl]carbostyril, 94592-71-9; 8-methoxy-2-[(2-phenylethyl)oxy]-5-[2-[*N*-(2-phenylethyl)-*N*-(benzyl)amino]ethyl]carbostyril, 98421-37-5; 8-methoxy-5-[2-[(2-phenylethyl)-*n*-propylamino]ethyl]carbostyril, 94592-75-3; 4-methoxybenzaldehyde, 123-11-5; chloroacetonitrile, 107-14-2; (4-methoxyphenyl)epicyanohydrin, 81860-68-6; 5-[2-[[2-(4-methoxyphenyl)-2-hydroxy-1-cyanoethyl]amino]ethyl]-8-methoxycarbostyril, 98421-22-8; 8-methoxy-5-[2-[[2-(4-hydroxyphenyl)ethyl]-*n*-propylamino]ethyl]carbostyril, 94592-41-3; quinoline-5-carboxylic acid, 7250-53-5; ethyl 5-quinolinecarboxylate, 98421-25-1; 5-quinolinemethanol, 16178-42-0; *n*-butylamine, 109-73-9; 5-(*n*-butyliminomethyl)quinoline, 98421-26-2; nitromethane, 75-52-5; 5-(2-aminoethenyl)quinoline, 98421-27-3; 5-(2-aminoethyl)quinoline, 98421-28-4.

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