as the molar concentration of compound that gives half maximal stimulation of cyclic AMP production over the concentration range tested.

Spiroperidol binding was determined by a modification of the method of Fujita and Saito.[53] Male Charles River rats are decapitated. Caudates are dissected at 0 °C, frozen on dry ice, and stored at −80 °C. Frozen homogenates are homogenized in 50 volumes of 50 mM Tris-HCl buffer, pH 7.4, at 25 °C with a Polytron homogenizer (setting number 7 for 15 s) and centrifuged at 50000*g* for 15 min. The pellet is rehomogenized in 50 volumes of fresh buffer and again centrifuged. The resulting pellet is homogenized to 100 volumes of pH 7.4 Tris-HCl buffer containing 0.1% ascorbic acid, 5 mM ethylenediaminetetraacetic acid, and 10 μM pargyline. After being incubated at 37 °C for 15 min, the homogenate is cooled to 0 °C. To assay incubation vessels (in triplicate) there is added 0.2 mL of [^{3}H]spiroperidol (final concentration is about 0.2 nM) and 0.8 mL of buffer (control) or buffer with test compound (samples), or buffer with 1 μM (+)-butaclamol (nonspecific), or buffer, compound, and 1 μM (+)-butaclamol (compound specific). The homogenate (1 mL) is added to the assay vessels and the mixture is incubated at 37 °C for 30 min. After being held at 0 °C for 15–30 min, 4.5 mL of cold Tris-HCl buffer is added to the samples, the mixture is filtered through a Whatman GF/B filter, and the filter cake is washed with cold Tris-HCl buffer (3 × 4.5 mL). The filters and retained material are transferred to scintillation vials, 10 mL of Aquasol 2 is added, the mixture is shaken vigorously for 30 min, and the radioactivity is counted. The IC_{50} is the concentration of compound that produces 50% inhibition of specific spiroperidol binding.

Rotation in rats with lesions in the substantia nigra was determined as previously described.[10] The RD_{500} is defined as the dose calculated to produce 500 bodily rotations during a 2-h test period.

Renal vasodilator activity[15] was measured in anesthetized dogs surgically prepared for electromagnetic measurement of renal blood flow. Blood pressure was measured from the carotid artery. Drugs were infused into a antecubital vein. Renal vascular resistance (RVR) was calculated as the ratio of mean arterial blood pressure to mean blood flow. Cumulative dose–response data were obtained by infusing the compound at progressively increasing (generally threefold) concentrations. The ED_{15} ↓ RVR is the average maximum cumulative dose that decreases RVR by 15%.

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, bond angles, and observed and calculated structure factors (11 pages). Ordering information is given on any current masthead page.

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Synthesis of 2-(Alkylamino)-5,6- and -6,7-dihydroxy-3,4-dihydroquinazolines and Evaluation as Potential Dopamine Agonists[1]

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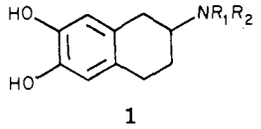
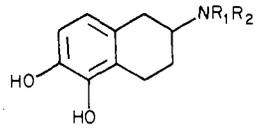
Based upon the known dopaminergic properties of 2-aminodihydroxy-1,2,3,4-tetrahydronaphthalenes (ADTN's), heterocyclic congeners were prepared. Several 2-(alkylamino)-5,6- and -6,7-dihydroxy-3,4-dihydroquinazolines were synthesized and tested for a dopamine-like vasodilatory action in the canine renal artery. The 6,7-disubstituted series had a weak antagonist effect against dopamine. Neither 5,6- nor 6,7-dihydroxy substitution gave dopamine agonists. Measured pK_a values confirmed the expectation that the dihydroquinazolines were more basic than dopamine, one possible reason for the lack of dopamine-like action.

The interesting pharmacological profile of the 2-(alkylamino)-6,7- and -5,6-dihydroxy-1,2,3,4-tetrahydronaphthlenes (ADTN's; **1** and **2**), particularly as dopaminergic agents, has led us to prepare heterocyclic congeners of these compounds. Encouraged by the biological activity of the previously reported 2-(alkylamino)-3,4-dihydroquinazolines,[3] as well as by the action of 2-[(3,4-dihydroxyphenyl)amino]imidazoline (DPI) as an α-adrenergic and dopamine agonist at selected sites,[4] it seemed worthwhile to employ the dihydroquinazoline ring system as the parent nucleus for this study. Since the activity of the tetrahydronaphthalenes varies with both the N-substitution[5] as well as the location of the hydroxy groups,[6] it was concluded that the target compounds should be representative of these structural modifications, with the



1



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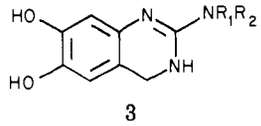

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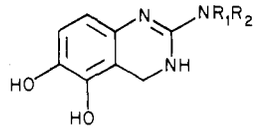

4

	R_1	R_2
a	H	H
b	H	CH_3
c	CH_3	CH_3
d	*n*-C_3H_7	*n*-C_3H_7

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(1) Taken, in part from the Ph.D. Thesis of John A. Grosso, Purdue University, 1980.
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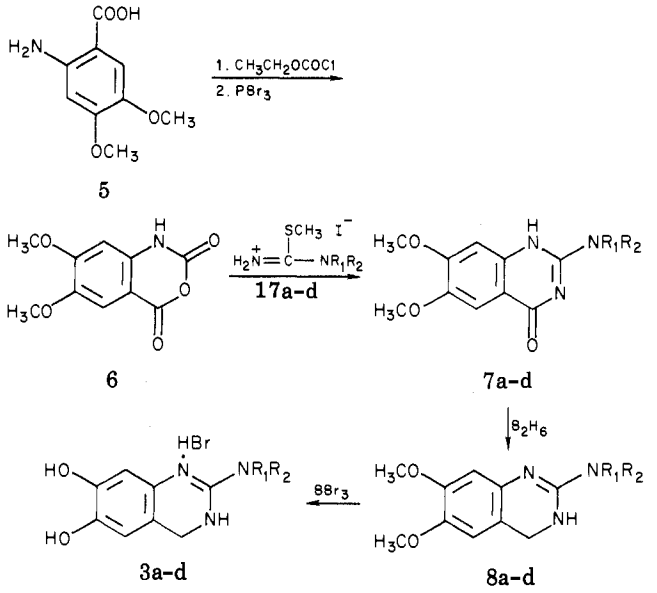
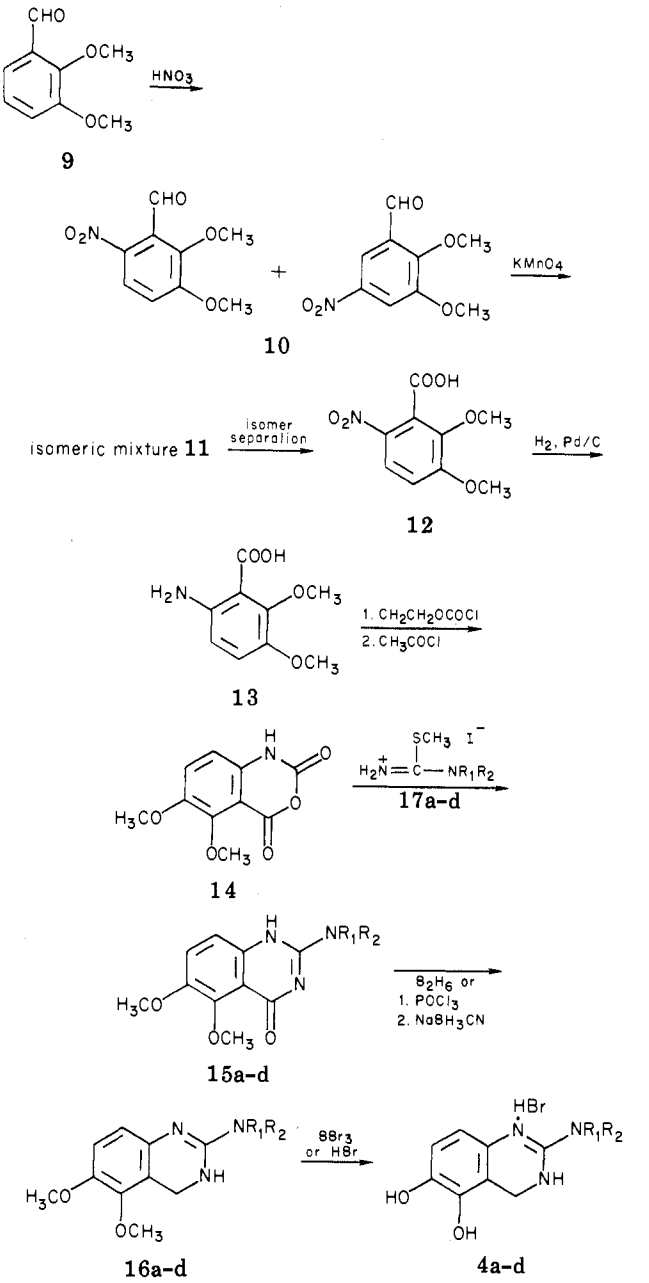
Scheme I



Scheme II



anticipation of observing a similar spectrum of activity. Therefore, the corresponding 6,7-dihydroxy (**3**) and 5,6-dihydroxy (**4**) series were prepared with amino (**a**), *N*-methylamino (**b**), *N,N*-dimethylamino (**c**), and *N,N*-di-*n*-propylamino (**d**) substitutions.

Chemistry. A convergent scheme was employed in the preparation of the target compounds. The key step involved the reaction of an isothiourea bearing the appropriate alkyl substitution with an isatoic anhydride containing the desired oxygen substitution.

6,7-Dihydroxy Series. The methyl ester of 3,4-dimethoxybenzoic acid was nitrated,[7] followed by basic hydrolysis, to afford 3,4-dimethoxy-6-nitrobenzoic acid. Catalytic hydrogenation led to the corresponding amino acid (**5**) in an overall yield of 85%. As shown in Scheme I, preparation of the carbamate by treatment of **5** with ethyl chloroformate,[8] followed by phosphorous tribromide,[9] gave 4,5-dimethoxyisatoic anhydride (**6**) in an 83% yield. The cyclization could be effected using acetyl chloride,[8] although yields were consistently less than 25%.

The convergent step was carried out using a modification of the method described by Coppola, Hardtman, and Pfister.[10] It was discovered, however, that the reported vigorous conditions for cyclization were not necessary in this study. Instead, the isatoic anhydride was combined with sodium carbonate and the appropriate *S*-methylisothiourea hydriodide (**17a–d**) in acetonitrile or dioxane and heated at reflux. Yields were generally excellent, with the exception of the *N,N*-dipropyl derivative (**7d**), which was prepared in a 25% yield. In that case, methyl 3,4-dimethoxythioanthranilate was identified as the major byproduct, evidently produced by a previously reported pathway.[11]

The reduction of quinazolin-4(1*H*)-ones to 3,4-dihydroquinazolines has been accomplished using lithium aluminum hydride.[12] However, even after vigorous reaction conditions, this method was not successful for the reduction of the 2-(alkylamino)-6,7-dimethoxy-4(1*H*)-quinazolinones. In contrast, diborane led to the smooth reduction of **7a–d** in satisfactory yields under mild conditions. The resulting 2-(alkylamino)-6,7-dimethoxy-3,4-dihydroquinazolines were not isolated but were treated directly with boron tribromide to give the target compounds (**3a–d**) in yields varying between 50 and 95%.

5,6-Dihydroxy Series. The preparation of these compounds is outlined in Scheme II. The synthesis of 2,3-dimethoxy-6-nitrobenzaldehyde has been reported.[13] The procedure, however, calls for the separation of the isomeric 5- and 6-nitro aldehydes by condensation with *p*-toluidine, fractional recrystallization of the resulting imine, and subsequent regeneration of the aldehydes by acidic hy-

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drolysis. In an effort to avoid this circuitous procedure, it was reasoned that the corresponding isomeric nitrobenzoic acids could be separated on the basis of their differing acidities. Thus, 2,3-dimethoxybenzaldehyde (**9**) was treated with nitric acid, and the resulting isomer mixture (**10**) was subjected to oxidation with potassium permanganate. The unwanted isomer was removed by acidification to pH 2.75 and filtration. Further acidification gave the desired 2,3-dimethoxy-6-nitrobenzoic acid (**12**). The nitro acid was catalytically hydrogenated to 6-amino-2,3-dimethoxybenzoic acid (**13**) in quantitative yield. Preparation of the carbamate, followed by treatment with acetyl chloride, provided 5,6-dimethoxyisatoic anhydride (**14**) in a yield of 89%.

The convergent step was carried out in an analogous manner to that of the 6,7-dihydroxy series. In this case, however, the *N,N*-di-*n*-propyl derivative (**15d**) required purification by column chromatography. The yields of the 2-(alkylamino)-5,6-dimethoxy-4(1*H*)-quinazolinones were generally somewhat lower than in the 6,7-dihydroxy series. Reduction of the primary amino derivative (**15a**) was accomplished with diborane. However, the remaining compounds in this series proved resistant to this method and to reduction by many other hydride reducing agents. Subsequent investigation revealed that the major products of the hydride reductions of **15b–d** were the 5-*O*-demethylated 2-(alkylamino)-5-hydroxy-6-methoxy-4(1*H*)-quinazolinones.

Direct reduction was abandoned in favor of a route which converted the quinazolinone into an intermediate which was more easily reduced. Rahman et al.[14] have recently reported that simple amides could be converted to the corresponding imino chlorides with phosphorous oxychloride or phosphorous pentachloride and subsequently reduced to the amine with sodium borohydride. Thus, the quinazolinones (**15a–d**) were first converted to their imino chlorides by treatment with phosphorous oxychloride, followed immediately by reduction with sodium cyanoborohydride. While the yield of the primary amino derivative (**16a**) was a modest 54%, the yields of the *N*-methyl (**16b**), *N,N*-dimethyl (**16c**), and *N,N*-di-*n*-propyl (**16d**) derivatives were virtually quantitative. The dimethyl ethers were cleaved with either boron tribromide or 48% hydrobromic acid to give **4a–d** in yields of 80 to 95%.

***S*-Methylisothiourea Hydriodides.** The *S*-methylisothiourea hydriodides were prepared using a modification of the procedure described by Braun[15] via alkylation of the corresponding thioureas with methyl iodide. In turn, the thioureas were obtained commercially in the case of the amino and dimethylamino derivatives or prepared by the method of Hartmann and Reuther.[16]

Results

None of the compounds in either series, tested up to a dose of 3000 nmol injected intraarterially, produced vasodilation in the renal artery characteristic of dopaminergic agents. However, administration of a dose of 3000 nmol of the primary amino (**3a**), *N*-methylamino (**3b**), and *N,N*-di-*n*-propylamino (**3d**) derivatives attenuated by 50% the vasodilation produced by a 47-nmol dose of dopamine. The *N,N*-dimethylamino derivative (**3c**) in two experiments showed no activity and in two experiments showed antagonist action. All the compounds in the 5,6-dihydroxy series (**4a–d**) possessed little or no antagonist activity.

The structure–antagonist activity of **3a–d** parallels the structure–agonist activity of ADTN's **1a–d**. That is, in the latter series the primary amino, *N*-methylamino, and *N,N*-di-*n*-propylamino derivatives have an agonist effect on the renal dopamine receptor, while the *N,N*-dimethylamino derivative is inactive. Compounds **4a–c** were not expected to be active in the renal artery, since the corresponding tetralin series (**2a–c**) is inert with respect to the renal dopamine receptor.

The lack of agonist activity for **3a–d** cannot readily be explained simply on the basis of geometry or available functionality. An inspection of molecular models of the ADTN's and the compounds of this report reveals a close similarity in shape and size, as well as a locational correspondence between the hydroxy and amino functionalities. However, if the receptor requires a highly localized positive charge on the nitrogen, the quinazolines clearly will not fill this requirement, since the positive charge is spread by resonance over the four-atom guanidinium moiety. This explanation, however, fails to account for the notable catecholamine-like action of a number of phenylaminoimidazolines, such as clonidine or DPI.[4] It is apparent though that there is a significant difference between the pK_a's of the ADTN's and the quinazolines.

The pK_a of the ADTN's would be expected to be similar to that of dopamine, 9.84 for the ammonium ion. The pK_a of **3a–d** can be estimated by extrapolation of the pK_a values of the corresponding dimethyl ethers. The hydrochloride salt of **8a** was prepared and titrated according to the method described by Albert and Serjeant.[17] The pK_a was determined to be 11.1. If one compares the pK_a's of the dimethyl ethers of various catecholamine salts with the catecholamine salts themselves, it is found that the pK_a of the catecholamine salt is approximately 1 pK_a unit higher.[18] One might then estimate the pK_a of **3a** to be approximately 12.

It has been proposed[18] and recently supported[19] that amine basicity is a critical factor in activating the receptor. If receptor activation is a consequence of proton transfer once the activating agent is initially bound, it is clear that such a transfer would be much less likely for **3a–d** than for the ADTN's. One is led to speculate that steric factors (*N*-alkyl substitution) may govern the initial binding, while an electrostatic change within the complex leads to "activation" of the receptor.

Experimental Section

Melting points were determined in open glass capillaries using a Mel-Temp apparatus and are corrected. IR spectra were recorded on a Beckman IR-33 instrument. The three strongest absorptions (four in the case of two being equal) are reported in reciprocal centimeters. NMR spectra were recorded on a Varian EM-360 or FT-80. Chemical shifts are reported in parts per million with Me_4Si as the internal reference, except when the solvent was D_2O; in such cases DSS was used. The multiplicities are expressed as follows: s = singlet; d = doublet; t = triplet; q = quartet; sx = sextet; br = broad. Elemental analyses were performed by the Purdue Microanalytical Laboratory and were within ±0.4% of the calculated values.

6,7-Dimethoxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (6). To 480 mL of dry THF was added 24.1 g (0.122 mol) of 6-amino-3,4-dimethoxybenzoic acid (**5**). The acid was suspended by rapid

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stirring. To the suspension was added 39.7 g (0.366 mol) of ethyl chloroformate. This reaction mixture was stirred at reflux for 24 h. The solvent was removed on the rotary evaporator, yielding a solid residue. To this was added 405 mL of dry Et_2O and 32.9 g (0.121 mol) of PBr_3. The resulting suspension was stirred for 45 h at reflux. The product was recovered by suction filtration. The filter cake was washed with 200 mL of dry Et_2O and recrystallized from CH_3CN: yield 25.5 g (94%); mp 263–264 °C; IR (KBr) 1765, 1710, 1505 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6 1:1) δ 7.20 (s, 1, Ar H_5), 6.59 (s, 1, Ar H_8), 3.82 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 3.30 (s, 1, NH). Anal. ($C_{10}H_9NO_5$) C, H, N.

2-Amino-6,7-dimethoxy-4(1*H*)-quinazolinone (7a). Exactly 3.0 g (0.0132 mol) of (**6**), 2.88 g (0.0132 mol) of *S*-methylisothiourea hydriodide (**17a**), and 1.53 g (0.014 mol) of Na_2CO_3 were added to a solution of 48 mL of CH_3CN and 12 mL of H_2O. The resulting solution was stirred at reflux for 75 min. The reaction vessel was allowed to cool for 1 h to 25 °C. The suspension was suction filtered and the filter cake was washed with 80% CH_3CN (aq): yield 2.43 g (84%).

An analytical sample was recrystallized from Me_2SO/H_2O and dried under an aspirator vacuum for 24 h at 70 °C: mp 313–316 °C [lit.[20] mp 317–319 °C (from DMF)]; IR (KBr) 1605, 1480, 1265 cm^{-1}; NMR (Me_2SO-d_6) δ 7.32 (s, 1, Ar H_5), 6.75 (s, 1, Ar H_8), 6.29 (br, 1, N_1 H), 3.88 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 3.39 (br, 2, NH_2).

2-(Methylamino)-6,7-dimethoxy-4(1*H*)-quinazolinone (7b). To 80 mL of 80% CH_3CN (aq) was added 4.0 g (0.0178 mol) of 4,5-dimethoxyisatoic anhydride (**6**), 4.18 g (0.0178 mol) of *N,S*-dimethylisothiourea hydriodide (**17b**), and 2.06 g (0.0194 mol) of Na_2CO_3. The suspension was stirred while heating at reflux for 2 h. The mixture was let stand at 5 °C for 2 h. The precipitate was collected by suction filtration. The filter cake was washed with 10 mL of CH_3CN: yield 4.2 g (quantitative).

An analytical sample was recrystallized from Me_2SO/H_2O: mp 289–291 °C [lit.[20] mp 294–296 °C (from DMF)]; IR (KBr) 1610, 1485, 1225 cm^{-1}; NMR (Me_2SO-d_6) δ 7.41 (s, 1, Ar H_5), 7.0 (br, 1, N_1 H), 6.86 (s, 1, Ar H_8), 4.0 (br, 1, N*H*CH_3), 3.92 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 2.90 (d, 3, NHC*H*$_3$).

2-(Dimethylamino)-6,7-dimethoxy-4(1*H*)-quinazolinone (7c). To 80 mL of dry dioxane was added 4.37 g (0.013 mol) of *S,N,N*-trimethylisothiorea hydriodide (**17c**), followed by 2.10 g (0.020 mol) of Na_2CO_3. The suspension was heated until the isothiourea had dissolved. To this was added 4.0 g (0.018 mol) of 4,5-dimethoxyisotoic anhydride (**6**). The suspension was heated at reflux for 14 h. The reaction mixture was cooled to 25 °C, and the product was recovered by suction filtration. The filter cake was washed with 40 mL of dry dioxane and dried under aspirator vacuum at 70 °C for 24 h. An isolated yield of 5.5 g (>100%) was due to inorganic contaminants.

An analytical sample was recrystallized from Me_2SO/H_2O: mp 246–247 °C [lit.[20] mp 246–248 °C (from DMF/H_2O)]; IR (KBr) 1642, 1590, 1485 cm^{-1}; NMR (Me_2SO-d_6) δ 10.93 (br, 1 N_1 H), 7.26 (s, 1, Ar H_5), 6.75 (s, 1, Ar H_8), 3.84 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.05 [s, 6, $N(CH_3)_2$].

2-(Di-*n*-propylamino)-6,7-dimethoxy-4(1*H*)-quinazolinone (7d). To 100 mL of CH_3CN was added 6.71 g (0.022 mol) of *S*-methyl-*N,N*-di-*n*-propylisothiourea hydriodide (**17d**) and 2.35 g (0.027 mol) of Na_2CO_3, followed by 5.0 g (0.022 mol) of 4,5-dimethoxyisatoic anhydride (**6**). The suspension was stirred at reflux for 61 h. The reaction was cooled, and the solvent was removed on the rotary evaporator. The residue was suspended in 50 mL of H_2O, and the product was extracted into four 50-mL portions of $CHCl_3$. Following gravity filtration, the filtrate was evaporated to dryness on the rotary evaporator. The crude solid was suspended in 30 mL of HOAc/H_2O (1:1) and stirred for 15 min. Any insoluble material was removed by suction filtration. The filtrate was basified with pellets of NaOH. The precipitate was recovered by suction filtration and recrystallized three times from MeOH: yield 2.31 g (34%); mp 201–203 °C (lit.[20] 197–200 °C); IR (KBr) 1660, 1580, 1485 cm^{-1}; NMR (Me_2SO-d_6) δ 10.83 (s, 1, N_1 H), 7.25 (s, 1, Ar H_5), 6.70 (s, 1, Ar H_8), 3.84 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.44 (t, 4, 2-NCH_2), 1.57 (sx, 4, 2-CH_2), 0.87 (t, 6, 2-CH_3).

2-Amino-6,7-dimethoxy-3,4-dihydroquinazoline (8a). To 32 mL of 1 M BH_3/THF (Aldrich Chemical Co.) was added 1.77 g (0.008 mol) of 2-amino-6,7-dimethoxy-4(1*H*)-quinazolinone (**7a**), followed by 48 mL of dry THF. The turbid solution was stirred at 25 °C under N_2 for 72 h. The borate complex and excess reagent were hydrolyzed by the addition of 5.6 mL of 6 N HCl. The suspension was neutralized with 20 mL of 2 N NaOH, and the solvents were removed on the rotary evaporator. The residue was digested in 100 mL of hot $CHCl_3$ and suction filtered. The filtrate was concentrated by rotary evaporation to yield a viscous oil: yield 1.26 g (76%). This material was pure by TLC: NMR (Me_2SO-d_6) δ 6.49 (s, 1, Ar H_5), 6.36 (s, 1, Ar H_8), 4.35 (s, 2, Ar CH_2), 4.10 (s, 2 NH_2), 3.75 (s, 6, OCH_3); CIMS, *m/e* 208 [$(M + 1)^+$]. A sample of the HCl salt had mp 245–247 °C. The crude base and **8b–d** were used directly in the ether cleavage step without further purification.

2-(Methylamino)-6,7-dimethoxy-3,4-dihydroquinazoline (8b). To 39 mL of 1 M BH_3/THF was added 40 mL of dry dioxane, followed by 3.072 g (0.0131 mol) of 2-(methylamino)-6,7-dimethoxy-4(1*H*)-quinazolinone (**7b**). The suspension was stirred under N_2 at reflux for 18 h. The borate complex and excess reagent were hydrolyzed by the addition of 6.5 mL of 6 N HCl. The acidic suspension was made basic by adding 8.7 mL of 6 N NaOH. The solvent was removed on the rotary evaporator. The residue was triturated with three 10-mL portions of $CHCl_3$. The combined washings were concentrated to a brown oil on the rotary evaporator. The oil was dried under a vacuum of 0.5 torr at 25 °C for 24 h: yield 1.47 g (50%). The material was homogeneous by TLC: EIMS, *m/e* 219 [$(M - 2)^+$]; NMR (Me_2SO-d_6) δ 10.47 (s, 1, N_1 H), 8.54 (s, 1, N_3 H), 8.08 (d, 1, NH), 6.83 (s, 1, Ar H_5), 6.77 (s, 1, Ar H_8), 4.40 (s, 2, Ar CH_2), 3.73 (s, 3, OCH_3), 3.71 (s, 3, OCH_3). A sample of the HCl salt had mp 204–210 °C.

2-(Dimethylamino)-6,7-dimethoxy-3,4-dihydroquinazoline (8c). To 80 mL of 1 M BH_3/THF was added 4.98 g (0.020 mol) of 2-(dimethylamino)-6,7-dimethoxy-4(1*H*)-quinazolinone (**7c**). The suspension was stirred at reflux under N_2 for 6 h. The reaction was cooled externally in an ice/H_2O bath. The borate complex and excess reagent were hydrolyzed by the addition of 30 mL of 6 N HCl. The organic solvent was removed on the rotary evaporator. The acidic residue was basified with 40 mL of 6 N NaOH. The product was extracted with three 60-mL portions of $CHCl_3$. The combined extract was dried over $MgSO_4$ and gravity filtered. The filtrate was concentrated under vacuum to yield an amber oil. The oil was dried under high vacuum for 24 h: yield 1.40 g (35% from the anhydride). The material was homogeneous by TLC: EIMS, *m/e* 233 [$(M - 2)^+$]; NMR (Me_2SO-d_6) δ 10.23 (s, 1, N_1 H), 8.51 (s, 1, N_3 H), 7.02 (s, 1, Ar H_5), 6.86 (s, 1, Ar H_8), 4.38 (s, 2, Ar CH_2), 3.17 [s, 6, $N(CH_3)_2$]. The HCl salt had mp 217–220 °C.

2-(Di-*n*-propylamino)-6,7-dimethoxy-3,4-dihydroquinazoline (8d). To 13 mL of 1 M BH_3/THF was added 6.68 g (0.026 mol) of 2-(di-*n*-propylamino)-6,7-dimethoxy-4(1*H*)-quinazolinone (**7d**), followed by an additional 13 mL of dry THF. The solution was stirred at reflux under N_2 for 4 h. The reaction mixture was cooled externally in an ice/H_2O bath. The borate complex and excess reagent were hydrolyzed by the dropwise addition of 4.9 mL of 6 N HCl. The turbid solution was allowed to warm to 25 °C over 30 min while stirring under N_2. The volume of solution was reduced on the rotary evaporator. The acidic residue was neutralized with 6 mL of 6 N NaOH. An additional 10 mL of H_2O was added to the suspension. The product was extracted with three 15-mL portions of $CHCl_3$. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The resulting oil was dried under high vacuum for 36 h at 25 °C: yield 0.74 g (98%). This material was pure by TLC: NMR (Me_2SO-d_6) δ 10.34 (s, 1, N_1 H), 8.62 (s, 1, N_3 H), 7.26 (s, 1, Ar H_5), 6.87 (s, 1, Ar H_8), 4.37 (s, 2, Ar CH_2), 3.72 (s, 6, OCH_3), 3.48 (t, 4, 2 NCH_2), 1.56 (sx, 4, 2 CH_2), 0.90 (t, 6, CH_3). A sample of the HCl salt was recrystallized from EtOH–ether, mp 182–183 °C. Anal. ($C_{16}H_{26}N_3O_2Cl$) C, H, N.

General Conditions for Dimethyl Ether Cleavage. Typically, to 4 mmol of the dimethyl ether suspended in 48 mL of dry CH_2Cl_2 was added 16 mL of a 1 M solution of BBr_3 in CH_2Cl_2. The reaction mixture was stirred at 25 °C under N_2 for 12 h. The

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borate complex and excess reagent were destroyed by the dropwise addition of anhydrous MeOH while being cooled externally in an ice/H_2O bath. The product was collected by direct filtration of the reaction mixture or by the addition to the reaction mixture of a 10-fold volume excess of anhydrous Et_2O, followed by filtration. The solid was then dried under a vacuum of 0.5 torr at 25 °C for 24 h.

2-Amino-6,7-dihydroxy-3,4-dihydroquinazoline hydrobromide (3a): yield 0.97 g (93%). An analytical sample was recrystallized from absolute EtOH/EtOAc: mp 259–262 °C dec; IR (KBr) 1660, 1515, 1260 cm^{-1}; NMR (Me_2SO-d_6) δ 10.19 (s, 1, N_1 H), 8.12 (s, 1, N_3 H), 7.25 (s, 2 NH_2), 6.53 (s, 1, Ar H), 6.46 (s, 1, Ar H), 4.32 (s, 2, Ar CH_2), 3.7 (br, 2, 2 Ar OH). Anal. ($C_8H_{10}N_3O_2Br$) C, H, N.

2-(Methylamino)-6,7-dihydroxy-3,4-dihydroquinazoline hydrobromide (3b): yield 0.73 g (67%). An analytical sample was recrystallized from absolute MeOH: mp 295–300 °C dec; IR (KBr) 1655, 1515, 1260 cm^{-1}; NMR (Me_2SO-d_6) δ 9.98 (s, 1, N_1 H), 9.20 (s, 1, Ar OH), 8.83 (s, 1, Ar OH), 8.22 (s, 1, N_3 H), 7.56 (d, 1, N*H*CH_3), 6.55 (s, 2, 2 Ar, H), 4.31 (s, 2, Ar CH_2), 2.84 (d, 3, NHCH_3). Anal. ($C_9H_{12}N_3O_2Br$) C, H, N.

2-(Dimethylamino)-6,7-dihydroxy-3,4-dihydroquinazoline hydrobromide (3c): yield 0.58 g (51%). An analytical sample was recrystallized from absolute MeOH: mp 292–298 °C dec; IR (KBr) 1660, 1520, 1265 cm^{-1}; NMR (Me_2SO-d_6) δ 9.82 (s, 1, N_1 H), 8.24 (s, 1, N_3 H), 6.72 (s, 1, Ar H_5), 6.57 (s, 1, Ar H_8), 4.30 (s, 2, Ar CH_2), 3.4 (br, 2, 2 Ar OH), 3.07 [s, 6, $N(CH_3)_2$]. Anal. ($C_{10}H_{14}N_3O_2Br$) C, H, N.

2-(Di-*n*-propylamino)-6,7-dihydroxy-3,4-dihydroquinazoline hydrobromide (3d): yield 1.18 g (86%). An analytical sample was recrystallized from absolute MeOH: mp 193–195 °C; IR (KBr) 2325, 1640, 1525 cm^{-1}; NMR (Me_2SO-d_6) δ 9.70 (s, 1, N_1 H), 9.1 (br, 2, 2 Ar OH), 8.22 (s, 1 N_3 H), 6.78 (s, 1, Ar H_5), 6.59 (s, 1, Ar H_8), 4.28 (s, Ar CH_2), 3.40 (t, 4, 2-NCH_2), 1.59 (sx, 4, 2 CH_2), 0.88 (t, 6, 2 CH_3). Anal. ($C_{14}H_{22}N_3O_2Br$) C, H, N.

2,3-Dimethoxy-6-nitrobenzoic Acid (12). To 81.7 g (0.563 mol) of $KMnO_4$ dissolved in 2 L of 2% NaOH (aq) was added 108.0 g (0.512 mol) of the mixture of nitro aldehyde isomers (**10**) obtained in the nitration step. The suspension was stirred at 60 °C for 1.5 h. The MnO_2 precipitate was removed by filtration through a bed of Celite on a sintered glass funnel. The excess MnO_4^- was destroyed by the addition of MeOH. The additional MnO_2 precipitate was removed as described above. The filtrate was acidified to pH 2.75 with concentrated HCl, and the 5-nitro isomer was removed by suction filtration. The filtrate was further acidified until no more solid formed. This product was collected by filtration and recrystallized from EtOH/H_2O: yield 19.33 g (16%); mp 186–189 °C [lit.[13] mp 183 °C (from H_2O)]; IR (KBr) 1707, 1275, 1045 cm^{-1}; NMR (Me_2SO-d_6) δ 10.40 (s, 1, COOH), 8.15 (d, 1, Ar H_5), 7.40 (d, 1, Ar H_4), 4.03 (s, 3, OCH_3), 3.58 (s, 3, 2 OCH_3).

6-Amino-2,3-dimethoxybenzoic Acid (13). To 500 mL of absolute EtOH was added 20.9 g (0.0919 mol) of 2,3-dimethoxy-6-nitrobenzoic acid (**12**), followed by 0.650 g of 10% Pd/C. The mixture was shaken on a Parr apparatus at an initial H_2 pressure of 50 psig until the uptake of H_2 ceased (~2 h). The catalyst was removed by filtration through a bed of Celite on a sintered glass funnel under a blanket of N_2. The filtrate was evaporated to dryness, and the residue was dried under aspirator vacuum at 25 °C for 14 h: yield 18.2 g (quantitative). An analytical sample was recrystallized from absolute EtOH: mp 98.8–100 °C (lit.[20] mp 98–99 °C); IR (KBr) 1605, 1360, 1160 cm^{-1}; NMR (Me_2SO-d_6) δ 6.95 (d, 1, Ar H_4), 6.42 (d, 1, Ar H_5), 4.9 (br, 3, NH_2 and COOH), 3.70 (s, 3, OCH_3), 3.65 (s, 3, OCH_3).

5,6-Dimethoxy-2*H*-3,1-benzoxazine-2,4(1*H*)-dione (14). To 30.9 g (0.277 mol) of ethyl chloroformate was added 18.2 g (0.072 mol) of 6-amino-2,3-dimethoxybenzoic acid (**13**). The mixture was heated at reflux until all of the suspended solid went into solution (21 h). To this solution was added 108.5 g (1.38 mol) of acetyl chloride, dropwise. The reaction was heated at reflux until the evolution of HCl was no longer evident (4 h). The product was obtained by suction filtration. The filter cake was washed with 50 mL of CCl_4 and air-dried: yield 14.4 g (89%).

An analytical sample was recrystallized from absolute MeOH: mp 241–242 °C dec; IR (KBr) 1780, 1726, 1254 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6, 1:1) δ 11.58 (s, 1, NH), 7.43 (d, 1, Ar H_7), 6.99 (d, 1, Ar H_8), 3.97 (s, 3, OCH_3), 3.94 (s, 3, OCH_3). Anal. ($C_{10}H_9NO_5$) C, H, N.

2-Amino-5,6-dimethoxy-4(1*H*)-quinazolinone (15a). To a mixture of 80 mL of CH_3CN and 3.92 g (0.018 mol) of *S*-methylisothiourea hydriodide (**17a**) was added 1.91 g (0.018 mol) of Na_2CO_3 and 4.0 g (0.018 mol) of 5,6-dimethoxyisatoic anhydride (**14**). The suspension was stirred at reflux for 2.5 h. The solvent was removed on the rotary evaporator. The residue was suspended in 30 mL of H_2O and suction filtered. The filter cake was washed with three 10-mL portions of H_2O and dried under aspirator vacuum for 24 h at 70 °C: yield 2.81 g (71%).

An analytical sample was recrystallized from Me_2SO/H_2O: mp 200–202 °C; IR (KBr) 1640, 1480, 1275 cm^{-1}; NMR (Me_2SO-d_6) δ 10.76 (br, 1, N_1 H), 7.36 (d, 1, Ar H_7), 6.62 (d, 1, Ar H_8), 6.13 (br, 2, NH_2), 3.78 (s, 3, OCH_3), 3.71 (s, 3, OCH_3). Anal. ($C_{10}H_{11}N_3O_3$) C, H, N.

2-(Methylamino)-5,6-dimethoxy-4(1*H*)-quinazolinone (15b). A suspension of 6.16 g (0.0266 mol) of *N,S*-dimethylisothiourea hydriodide (**17b**), 2.81 g (0.0266 mol) of Na_2CO_3, and 5.98 g (0.0266 mol) of 5,6-dimethoxyisatoic anhydride (**14**) in 180 mL of CH_3CN was stirred at reflux for 2.75 h. The solvent was removed on the rotary evaporator. The residue was suspended in 15 mL of H_2O and suction filtered. The filter cake was washed with three 5-mL portions of H_2O and dried under aspirator vacuum at 70 °C for 24 h: yield 3.54 g (57%). An analytical sample was recrystallized from Me_2SO/H_2O: mp 199–202 °C; IR (KBr) 1665, 1620, 1480 cm^{-1}; NMR (Me_2SO-d_6) δ 10.76 (br, 1, N_1 H), 7.36 (d, 1, Ar H_7), 7.00 (d, 1, Ar H_8), 5.92 (br, 1, N*H*CH_3), 3.78 (s, 3, OCH_3), 3.71 (s, 3, OCH_3), 2.79 (d, 3, NHCH_3). Anal. ($C_{10}H_{13}N_3O_3$) C, H, N.

2-(Dimethylamino)-5,6-dimethoxy-4(1*H*)-quinazolinone (15c). To 100 mL of dry dioxane was added 4.38 g (0.0178 mol) of *S,N,N*-trimethylisothiourea hydriodide (**17c**), 2.03 g (0.0195 mol) of Na_2CO_3, and 4.00 g (0.0178 mol) of 5,6-dimethoxyisatoic anhydride (**14**). The suspension was stirred at reflux for 6 h. The product was obtained by filtration of the cooled reaction mixture. The filter cake was dried under aspirator vacuum at 70 °C for 24 h. The isolated yield of 5.3 g (>100%) was contaminated with inorganic impurities. An analytical sample was recrystallized from absolute MeOH: mp 234–235 °C dec; IR (KBr) 1650, 1595, 1470 cm^{-1}; NMR (Me_2SO-d_6) δ 7.45 (d, 1, Ar H_7), 7.12 (d, 1, Ar H_8), 3.83 (s, 3, OCH_3), 3.75 (s, 3, OCH_3), 3.05 [s, 6, $N(CH_3)_2$], N_1 H, not found. Anal. ($C_{12}N_{15}N_3O_3$) C, H, N.

2-(Di-*n*-propylamino)-5,6-dimethoxy-4(1*H*)-quinazolinone (15d). To 120 mL of dry dioxane was added 8.15 g (0.027 mol) of *S*-methyl-*N,N*-di-*n*-propylisothiourea hydriodide (**17d**) and 3.07 g (0.027 mol) of Na_2CO_3, followed by 6.00 g (0.027 mol) of 5,6-dimethoxyisatoic anhydride (**14**). The suspension was stirred at reflux for 12 h. The precipitated inorganic salts were removed by suction filtration. The filtrate was concentrated on a rotary evaporator. The resulting dark brown oil was chromatographed on a silica gel (70–270 mesh ASTM) column by elution with $CHCl_3/CH_3CN$ (7:3). The band fluorescing in long-wave UV was collected. The eluate was concentrated, and the residue was recrystallized from absolute EtOH: yield 2.11 g (27%); mp 137–138 °C; IR (KBr) 1630, 1570, 1465 cm^{-1}; NMR (Me_2SO-d_6) δ 11.50 (br, 1, N_1 H), 7.35 (d, 1, Ar H_7), 7.15 (d, 1, Ar H_8), 3.90 (s, 3, OCH_3), 3.86, (s, 3, OCH_3), 3.55 (t, 4, 2 NCH_2), 1.65 (sx, 4, 2-CH_2), 0.95 (t, 6, 2-CH_3). Anal. ($C_{16}H_{23}N_3O_3$) C, H, N.

2-Amino-5,6-dimethoxy-3,4-dihydroquinazoline (16a). To 12 mL of 1 M BH_3/THF was added 1.71 g (0.0077 mol) of 2-amino-5,6-dimethoxy-4(1*H*)-quinazolinone (**15a**), followed by an additional 10 mL of dry THF. The suspension was stirred under N_2 for 24 h at 25 °C. The borate complex was hydrolyzed by the addition of 3 mL of 6 N HCl and stirred under N_2 for 0.5 h. With stirring, the acidic solution was basified under N_2 with 4 mL of 6 N NaOH. The precipitate was collected by suction filtration and dried under aspirator vacuum at 50 °C for 24 h: yield 0.857 g (54%). This material was pure by TLC: CIMS, m/e 208 [(M + 1)$^+$]; NMR (Me_2SO-d_6) δ 6.68 (d, 1, Ar H_7), 6.30 (d, 1, Ar H_8), 6.0 (br, 3, N_3 H and NH_2), 4.39 (s, 2, Ar CH), 3.69 (s, 3, OCH_3), 3.66 (s, 3, OCH_3). A sample of the HCl salt had mp 307–310 °C dec. This product and **16b–d** were used without further purification in the ether cleavage steps.

2-(Methylamino)-5,6-dimethoxy-3,4-dihydroquinazoline (16b). To 60 mL of $POCl_3$ was added 2.05 g (0.0087 mol) of 2-(methylamino)-5,6-dimethoxy-4(1*H*)-quinazolinone (**15b**). The resulting solution was stirred at reflux under N_2 for 14 h. The excess reagent was removed on the rotary evaporator. The residue was dissolved in 50 mL of dry THF, and to this solution was added 2.74 g (0.0435 mol) of $NaBH_3CN$. The suspension was stirred at 25 °C under N_2 for 6 h. The organic solvent was removed on the rotary evaporator. The residue was suspended in 30 mL of 2 N NaOH, and the product was extracted with four 30-mL portions of EtOAc. The combined extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated under vacuum to give an oil, which was dried at 25 °C under a vacuum of 0.5 torr for 24 h: yield 1.92 g (quantitative) of material; pure by TLC; NMR ($CDCl_3$) δ 7.5 (br, 1, N_3 H), 6.73 (t, 2, Ar, H_7 and Ar H_8), 5.2 (br, 1, N*H*CH_3), 4.54 (s, 2, Ar CH_2), 3.85 (s, 6, 2 OCH_3), 2.85 (s, 3, CH_3). A sample of the HCl salt had mp 202–205 °C.

2-(Dimethylamino)-5,6-dimethoxy-3,4-dihydroquinazoline (16c). To 90 mL of $POCl_3$ was added 3.46 g (0.014 mol) of 2-(dimethylamino)-5,6-dimethoxy-4(1*H*)-quinazolinone (**15c**). The suspension was stirred at reflux under N_2 for 15 h and then cooled. The solvent was reduced under vacuum, and the residue was suspended in 70 mL of dry THF. To this mixture was added 3.77 g (0.060 mol) of $NaBH_3CN$. The reaction was stirred under N_2 at 25 °C for 6 h. The solvent was concentrated on the rotary evaporator, and the residue was added to 40 mL of 2 N NaOH. The product was extracted with four 40-mL porportions of EtOAc. The combined extracts were dried over $MgSO_4$ and filtered. The filtrate was concentrated to an oil, which was dried under high vacuum for 24 h at 25 °C: yield 2.82 g (72% from anhydride); pure by TLC; NMR (Me_2SO-d_6) δ 6.96 (t, 2, Ar H_7 and Ar H_8), 4.45 (s, 2, Ar CH_2), 3.80 (s, 6, 2 OCH_3), 3.05 [s, 6, $N(CH_3)_2$]; EIMS, m/e 233 [$(M - 2)^+$]. The HCl salt had mp 230–235 °C dec.

2-(Di-*n*-propylamino)-5,6-dimethoxy-3,4-dihydroquinazoline (16d). To 42 mL of $POCl_3$ was added 1.72 g (0.0056 mol) of 2-(di-*n*-propylamino)-5,6-dimethoxy-4(1*H*)-quinazolinone (**15d**). The solution was stirred at reflux for 3.5 h. The excess reagent was removed under vacuum, and the residue was dissolved in 35 mL of dry THF. To the solution was added 1.76 g (0.028 mol) of $NaBH_3CN$. The resulting suspension was stirred at 25 °C under N_2 for 4 h. The solvent was removed on the rotary evaporator. The residue was suspended in 25 mL of 2 N NaOH, and the product was extracted with four 25-mL portions of EtOAc. The combined extracts were dried over $MgSO_4$ and filtered. The filtrate was evaporated to an oil, which solidified while under high vacuum for 24 h at 25 °C: yield 1.64 g (quantitative); pure by TLC; NMR ($CDCl_3$) δ 7.00 (t, 2, Ar H_7 and Ar H_8), 6.65 (br, 1, N_3 H), 4.50 (s, 2, Ar CH_2), 3.90 (s, 6, 2 OCH_3), 3.42 (t, 4, NCH_2), 1.70 (sx, 4, CH_2), 1.00 (t, 6, CH_3).

2-Amino-5,6-dihydroxy-3,4-dihydroquinazoline hydrobromide (4a) was prepared following the general method described earlier: yield 0.89 g (86%). An analytical sample was recrystallized from absolute MeOH/anhydrous Et_2O: mp 268–270 °C; IR (KBr) 3405, 1675, 1495 cm^{-1}; NMR (Me_2SO-d_6) δ 10.05 (s, 1, N_1 H), 8.00 (s, 1, N_3 H), 7.15 (s, 2, NH_2), 6.66 (d, 1, Ar H_7), 6.24 (d, 1, Ar H_8), 4.38 (s, 2, Ar CH_2), 3.2 (br, 2, 2 Ar OH). Anal. ($C_8H_{10}N_3O_2Br$) C, H, N.

2-(Methylamino)-5,6-dihydroxy-3,4-dihydroquinazoline hydrobromide (4b): yield 1.04 g (95%); mp 295 °C dec; IR (KBr) 3200, 1625, 1490 cm^{-1}; NMR (Me_2SO-d_6) δ 9.99 (s, 1, N_1 H), 9.7 (br, 2, Ar OH), 8.22 (s, 1, N_3 H), 7.52 (d, 1, N*H*CH_3), 6.67 (d, 1, Ar H_7), 6.37 (d, 1, Ar H_8), 4.36 (s, 2, Ar CH_2), 2.85 (d, 3, NHC*H*$_3$). Anal. ($C_9H_{12}N_3O_2Br$) C, H, N.

2-(Dimethylamino)-5,6-dihydroxy-3,4-dihydroquinazoline hydrobromide (4c): yield 1.094 g (95%). An analytical sample was recrystallized from absolute MeOH/anhydrous Et_2O: mp 285 °C dec; IR (KBr) 3050, 1640, 1285 cm^{-1}; NMR (D_2O) δ 6.85 (d, 2, Ar H_7), 6.45 (d, 2, Ar H_8), 4.20 (s, 2, Ar CH_2), 3.05 [s, 6, $N(CH_3)_2$]. Anal. ($C_{10}H_{14}N_3O_2Br$) C, H, N.

2-(Di-*n*-propylamino)-5,6-dihydroxy-3,4-dihydroquinazoline Hydrobromide (4d). To 1.21 g (0.0041 mol) of the dimethyl ether (**16d**) was added 60 mL of 48% HBr. The suspension was stirred under N_2 at reflux for 4 h. The resulting solution was concentrated, and upon chilling in an ice/H_2O bath, crystallization occurred. The product was obtained by suction filtration. The filter cake was washed with three 20-mL portions of absolute EtOH. The filter cake was then suspended in 50 mL of absolute EtOH, and the alcohol was removed under vacuum to azeotrope residual traces of H_2O and HBr (this procedure was repeated ten times). The resulting tan solid was dried under a vacuum of 0.5 torr for 24 h at 25 °C: yield 1.31 g (93%); mp 95–98 °C; IR (KBr) 3070, 1620, 1490 cm^{-1}; NMR (D_2O) δ 6.80 (d, 1, Ar H_7), 6.53 (d, 1, Ar H_8), 4.41 (s, 2, Ar CH_2), 3.37 (t, 4, 2 NCH_2), 1.67 (sx, 4, 2 CH_2), 0.93 (t, 6, 2 CH_3). Anal. ($C_{14}H_{22}N_3O_2Br$) C, H, N.

***S*,*N*,*N*-Trimethylisothiourea Hydriodide (17c).** To 15.7 g (0.15 mol) of *N*,*N*-dimethylthiourea was added 10 mL of absolute EtOH. Through the top of a long water-cooled condenser was added 23.4 g (0.165 mol) of CH_3I. At the evolution of heat, the reaction vessel was cooled in an ice/H_2O bath. Shortly thereafter (~3 min), the liquid solidified. The solid was broken up in 50 mL of anhydrous Et_2O. The product was obtained by suction filtration and was washed with three 30-mL portions of anhydrous Et_2O: yield 36.9 g (quantitative); mp 98.5–99.5 °C; IR (KBr) 3050, 1620, 1580 cm^{-1}; NMR (Me_2SO-d_6) δ 8.8 (br, 2, NH_2), 3.30 [s, 6, $N(CH_3)_2$], 2.75 (s, 3, SCH_3). Anal. ($C_4H_{11}N_2SI$) C, H, N.

***S*-Methyl-*N*,*N*-di-*n*-propylthiourea Hydriodide (17d).** Following a similar procedure to the one above for **17c**, using *N*,*N*-dipropylthiourea, we obtained 21.4 g (quantitative) of **17d**: mp 137–139 °C; IR (KBr) 3030, 1614, 1572 cm^{-1}; NMR (Me_2SO-d_6) δ 8.9 (br, 2, NH_2), 3.60 (t, 4, 2 NCH_2), 2.78 (s, 3, SCH_3), 1.14 (sx, 4, 2 CH_2), 0.90 (t, 6, 2 CH_3). Anal. ($C_8H_{19}N_2SI$) C, H, N.

Pharmacology. Essentially following the method of McNay and Goldberg,[22] we anesthetized male mongrel dogs (20–25 kg) with sodium pentobarbital (30 mg/kg, intravenously). A tracheotomy was performed, and respiration was maintained with room air via a Harvard respirator.

In our studies on the dopamine vascular receptor, the right renal artery was exposed using a flank incision and retroperitoneal dissection. An electromagnetic flow probe was placed on the artery for measurement of blood flow, and a 25-gauge needle, bent at an 80° angle, was proximally inserted into the artery for subsequent drug administration. All studies on the dopamine vascular receptor were carried out after the infusion of phenoxybenzamine, 5 mg/kg ia. A dose–response curve to dopamine (11.75, 47, and 188 nmol/dog) was obtained, and increasing doses of the test agonist were administered, up to 3000 nmol. All drug dosages were injected in a fixed volume of 0.2 mL. Following this, the compounds were analyzed for antagonism of dopamine-induced renal vasodilation. A fixed dosage of dopamine, 47 nmol, was injected directly into the artery of each dog in a volume of 0.2 mL to produce vasodilation. Then a combination of dopamine plus the putative antagonist, contained in a volume of 0.4 mL, was given. The highest doses of antagonists studied were combined with equivasodilating doses of bradykinin to demonstrate specific antagonism.

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(22) J. L. McNay and L. I. Goldberg, *J. Pharmacol. Exp. Ther.*, 151, 23 (1966).