morhinorrhea, lack of feces production, hypoactivity, ptosis, coma, lethargy, and perianal staining. All survivors except one given 3650 mg/kg appeared normal at 7 days after dosing. This animal continued to have leg weakness and poor grooming. The 7-day median lethal dose ($LD_{50}$) of **27** was estimated to be 4550 mg/kg.

**Acknowledgment.** We thank Dr. William B. Lacefield for his interest and helpful discussions. Ron Lawson, Dick Kattau, and Ron Love provided invaluable technical assistance, and Dr. George Sandusky and his associates provided the toxicological data. Finally, we gratefully acknowledge Patsy Abbett for typing the manuscript.

**Registry No.** **8**, 39696-13-4; **10** (7-methyl), 98216-24-1; **11** (X = Cl), 98216-60-5; **12**, 30084-90-3; **12** (R = $(CH_2)_3I$), 102072-40-2; **13**·HCl, 98216-38-7; **13**, 98216-39-8; **14**, 102072-20-8; **14** (alcohol), 102072-39-9; **15**, 95104-51-1; **16**, 102072-21-9; **17**, 102072-22-0; **18**, 102072-42-4; **18**·HCl, 102072-23-1; **19**, 102072-43-5; **19**·HCl, 102072-24-2; **20**, 80170-20-3; **20**·HCl, 102072-25-3; **21**, 102072-44-6; **21**·HCl, 102072-26-4; **22**, 102072-45-7; **22**·HCl, 102072-27-5; **23**, 102072-46-8; **23**·HCl, 102072-28-6; **24**, 102072-47-9; **24**·HCl, 102072-29-7; **25**, 72459-49-5; **26**, 102072-30-0; **27**, 98216-44-5; **28**, 98216-67-2; **28**·HCl, 98216-36-5; **29**, 98216-68-3; **29**·HCl, 98216-37-6; **30**, 98216-64-9; **30**·HCl, 98216-32-1; **31**, 98216-65-0; **31**·HCl, 98216-33-2; **32**, 102072-48-0; **32**·HCl, 102072-31-1; **33**, 98216-34-3; **34**, 102072-49-1; **34**·HCl, 102072-32-2; **35**, 102072-50-4; **35**·HCl, 102072-33-3; **36**, 98216-63-8; **36**·HCl, 98216-31-0; **37**, 98242-50-3; **38**, 98216-29-6; **39**, 98216-30-9; **40**, 102072-34-4; **41**, 98216-47-8; **42**, 98216-50-3; **42**·HCl, 98216-49-0; **43**, 98216-42-3; **43**·HCl, 98216-41-2; **44**, 98216-48-9; **45**, 102072-51-5; **45**·HCl, 102072-35-5; **46**, 98216-61-6; **47**, 98242-51-4; **48**, 98216-54-7; **49**, 102072-52-6; **49**·HCl, 102072-36-6; **50**, 98216-55-8; **51**, 102072-37-7; **52**, 98216-58-1; **53**, 98216-45-6; **53**·HCl, 98216-43-4; **54**, 98216-69-4; **54**·HCl, 98216-46-7; **55**, 102072-38-8; 1-9*H*-fluorenecarboxylic acid, 6276-03-5; 1-(9*H*-fluoren-1-yl)ethanone, 36272-09-0; 9-methyl-9*H*-fluorene, 2523-37-7; fluorene, 86-73-7; 2-methyl-9*H*-fluorene, 1430-97-3; 2-ethyl-9*H*-fluorene, 1207-20-1; 2-(9*H*-fluoren-2-yl)-2-propanol, 54527-61-6; 2-isopropyl-9*H*-fluorene, 1687-92-9; 2-methylimidazole, 693-98-1; imidazole, 288-32-4; cyclopropyl bromide, 4333-56-6; 2-chloro-1-(9*H*-fluoren-2-yl)ethanone, 24040-34-4; 2-(2-naphthalenyl)ethanol, 1485-07-0; 2-[(methylsulfonyl)oxy]-1-(9*H*-fluoren-2-yl)ethane, 102072-41-3.

# Synthesis and Renal Vasodilator Activity of 2-Chlorodopamine and N-Substituted Derivatives

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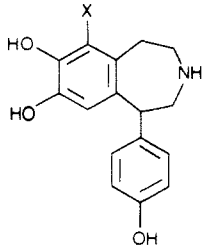
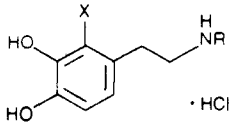
A four-step synthesis of 2-chlorodopamine (**2b**) is presented as well as methods for the syntheses of the *N*-methyl, ethyl, and *n*-propyl analogues (**2c–e**). Compounds **2b** and **2c** were essentially equipotent to dopamine for increasing renal blood flow in anesthetized dogs that had been treated with the α-adrenergic antagonist phenoxybenzamine. The increases in renal blood flow were blocked by the $DA_1$ antagonist (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine. Compounds **2d** and **2e** were significantly less potent than dopamine in the same model; the increases in renal blood flow were attenuated by propranolol and blocked by a combination of propranolol and (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine. The significance of an *o*-chloro substituent on dopamine analogues for the activation of the $DA_1$ receptor is briefly discussed.

There has been considerable interest in renal vascular $DA_1$ receptors[2] following the report that fenoldopam (**1a**) (SKF 82526), a renal vasodilator, is a specific dopamine agonist selective for the $DA_1$ receptor.[3] The importance of the chlorine on **1a** for its activity was demonstrated by replacement with either fluorine or hydrogen. The fluoro analogue (**1b**) had the pharmacological profile of a partial agonist, while the hydrogen analogue (**1c**) was inactive as a renal vasodilator.[4] 2-Fluorodopamine (**2a**) has been prepared[5-7] and its effects on dopamine receptors studied in detail.[8] In contrast to 2-fluoronorepinephrine, which more closely resembled isoproterenol in its biological effects, **2a** was indistinguishable from dopamine. In light of these results, it was surprising to find no mention of 2-chlorodopamine (**2b**) in the literature.




**1a**: X = Cl
**b**: X = F
**c**: X = H




**2a**: X = F, R = H
**b**: X = Cl, R = H
**c**: X = Cl, R = $CH_3$
**d**: X = Cl, R = $CH_2CH_3$
**e**: X = Cl, R = $CH_2CH_2CH_3$

Our interest in dopamine receptor activation[9,10] has prompted us to report the synthesis and renal effects of

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(2) For recent discussions on dopamine receptors, see: (a) Goldberg, L. I.; Kohli, J. D. *Trends Pharmacol. Sci.* **1983**, *4*, 64. (b) Cannon, J. G. *Annu. Rev. Pharmacol. Toxicol.* **1983**, *23*, 103. (c) *Dopamine Receptor Agonists*; Poste, G., Crooks, S. T., Eds.; Plenum: New York, 1984.
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**Table I.** Effects of **2b–e** and Dopamine on Renal Blood Flow (RBF)

| | | RBF: Δ, mL/min | | | | |
|---|---|---|---|---|---|---|
| compd | dose,[a] nmol | control 1 | after SCH 23390 | control 2 | after propranolol | after SCH 23390 + propranolol |
| **2b** | 100 | 46 ± 8[b] | 4 ± 2**[d] | 44 ± 9 | 43 ± 10 | |
| | 300 | 60 ± 12 | 8 ± 1** | 55 ± 12 | 58 ± 11 | |
| **2c** | 100 | 50 ± 4 | 8 ± 3** | 33 ± 3 | 34 ± 7 | |
| | 300 | 63 ± 8 | 15 ± 3** | 48 ± 3 | 49 ± 5 | |
| **2d** | 300 | 53 ± 16 | 22 ± 5* | 36 ± 8 | 25 ± 8* | −2 ± 2** |
| | 1000 | 71 ± 16 | 32 ± 6** | 52 ± 10 | 40 ± 10 | 2 ± 5** |
| **2e** | 3000 | 20 ± 2 | 11 ± 1* | 20 ± 4 | 11 ± 2** | −2 ± 2** |
| | 10000 | 27 ± 3 | 17 ± 2* | 25 ± 4 | 17 ± 1* | −5 ± 4** |
| dopamine | 30 | 60 ± 5 | 11 ± 1** | 50 ± 4 | 54 ± 5 | 9 ± 2[c]** |
| | 100 | 74 ± 6 | 15 ± 2** | 68 ± 5 | 69 ± 6 | 14 ± 2[c]** |

[a] Doses administered into the left renal artery of anesthetized dogs ($N$ = 4–5/group, except dopamine where $N$ = 18) (see experimental section). Alpha receptor blockade was established with phenoxybenzamine in all experiments. Dose–response curves were established for each compound (control 1), then repeated after SCH 23390. At least 1.5 h after the infusion of SCH 23390 was terminated, control responses were repeated (control 2), and the effects of propranolol on increases in renal blood flow were determined. For **2d** and **2e**, SCH 23390 infusion was then repeated with propranolol. [b] Mean ± SEM. [c] $N$ = 10. [d] (*) $p < 0.05$, (**) $p < 0.01$ vs. control.

**2b** and several of its $N$-alkyl derivatives (**2c–e**). $N$-Alkyl analogues of dopamine were reported to increase renal blood flow by stimulating β-adrenergic rather than dopaminergic receptors.[11] Thus, the preparation of **2c–e** was important for determining the significance of the $o$-chloro group for DA receptor activation by dopamine derivatives.

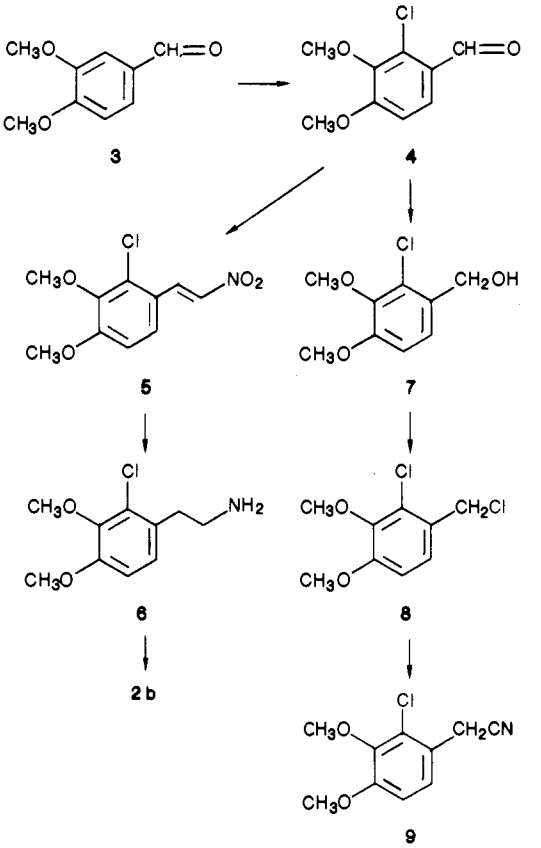
**Chemistry.** 2-Chlorodopamine (**2b**) was prepared in four steps from 3,4-dimethoxybenzaldehyde (**3**) (Scheme I). Lithiation of **3** by the procedure of Comins[12] and quenching the resulting dianion with hexachloroethane gave 2-chloro-3,4-dimethoxybenzaldehyde (**4**) in 62% yield. Previously, **4** was prepared from veratrole via a multistep procedure containing a chloromethylation step.[13] Condensation of **4** with nitromethane yielded the nitrostyrene **5** in 95% yield. Nitrostyrene **5** was reduced to 2-chlorohomoveratrylamine (**6**) with lithium aluminum hydride and aluminum chloride in THF, in 80% yield.

2-Chlorodopamine was isolated as the crystalline hydrochloride salt (**2b**) by the removal of the methoxy groups on **6** with trimethylsilyl iodide ($Me_3SiI$). We found $Me_3SiI$ to be a convenient reagent for deblocking veratroleethylamines, since the progress of the reactions was readily monitored by $^1H$ NMR and the catecholamines were isolated directly from the reaction mixture. In our hands, the use of 48% HBr proved very efficient for the conversion of 3,4-dimethoxyphenethylamine to dopamine hydrobromide[14] but led to dark reaction mixtures and noncrystalline products for the 2-chlorohomoveratrylamines **6** and **11c–e**.

Title compound **2b** was initially prepared from the known compound 2-(2-chloro-3,4-dimethoxyphenyl)-acetonitrile (**9**)[15] by reduction to **6** with lithium aluminum hydride followed by deprotection with MeSiI. However, the literature preparation of **9** is long and cumbersome. It should be noted that a much-improved synthesis of **9** is now available via intermediate **4** (see Scheme I) and that the improved synthesis shortens the route to fenoldopam (**1a**).[4a] Even with the improved synthesis of **9**, the preparation of **2b** via **4**, **5**, and **6** is still the preferred route.

$N$-Methyl-, ethyl-, and $n$-propyl-2-chlorodopamine (**2c–e**, respectively) were prepared from the pivotal intermediate **6** (Scheme II). Compound **6** was treated with either formic acetic anhydride, acetic anhydride, or propionic anhydride to provide the desired amide (**10c–e**). Reduction with borane–methyl sulfide[16] and deblocking of the resulting amines (**11c–e**) with $Me_3SiI$ provided **2c–e** as crystalline hydrochloride salts.

**Scheme I**




## Results and Discussion

The effects of compounds **2b–e** and dopamine on renal blood flow were obtained in α-blocked anesthetized dogs. Four ascending doses of each test agent were administered into the renal artery, and maximal increases in renal blood flow were measured. Changes in renal flow were normalized by defining the response produced by the highest

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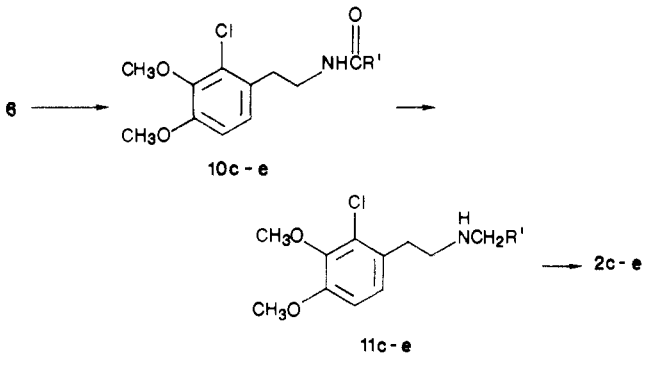
**Scheme II**




c, R'=H; d, R'=CH3; e, R'=CH2CH3

**Table II.** $ED_{30}$ Values for Producing Renal Vasodilation in the Anesthetized Dog

| compound | $ED_{30}$,[a] nmol | N |
|---|---|---|
| **2b** | 13.5 ± 1.7[b] | 4 |
| **2c** | 11.5 ± 2.4 | 4 |
| **2d** | 67.4 ± 22.2*[c] | 5 |
| **2e** | 2166 ± 294* | 5 |
| dopamine | 5.5 ± 0.3 | 18 |

[a] $ED_{30}$ values were obtained by normalizing data. The increase in renal blood flow observed after 100 nm of dopamine was defined as the maximal response (100%) for each dog. Responses to test compounds were calculated as a percentage of the maximum dopamine response. See experimental section for details. [b] Mean ± SEM. [c] (*) $p < 0.05$ vs. dopamine (Kruskal-Wallis nonparametric procedure with Turkey pairwise comparison).

dose of dopamine (100 nmol) as maximal (100%). Responses to test compounds were then calculated as a percentage of the response to dopamine, and $ED_{30}$ values were established as the dose of compound required to increase renal blood flow by 30%.

Renal blood flow responses to the two highest doses of each compound are presented in Table I, and $ED_{30}$ values for renal vasodilation are contained in Table II. All compounds increased renal blood flow in a dose-dependent manner; the order of potency was dopamine = **2b** = **2c** > **2d** ≫ **2e** (Table II). Treatment with (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine (SCH 23390),[17] a $DA_1$ receptor antagonist, attenuated the responses produced by all test agents (Table I), although much greater inhibition was observed for dopamine and compounds **2b** and **2c**. β-Adrenergic receptor blockade with propranolol also attenuated the vasodilatory effects of compounds **2d** and **2e** but had no effect on responses produced by the other test agents. Combined $DA_1$ and β-receptor blockade completely eliminated the changes in renal blood flow caused by **2d** and **2e** (Table I), suggesting that these agents produce renal vasodilation through a mixed action on vascular dopaminergic and β-adrenergic receptors.

It is noteworthy that the addition of a chlorine substituent to the 2-position of either dopamine or *N*-methyldopamine had no statistically significant effect on the potency of these compounds (Table II). In addition, the effects of dopamine, as well as **2b** and **2c**, on renal blood flow were blocked by (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine but were not inhibited by propranolol. These results indicate that 2-chloro substitution does not affect the selectivity of dopamine for renal vascular catecholaminergic receptors and that addition of an *N*-methyl group does not significantly reduce the potency of 2-chlorodopamine as a renal vasodilator.

The potencies of the *N*-ethyl (**2d**) and *N*-*n*-propyl (**2e**) analogues were, however, substantially reduced with respect to the parent compound (Table II). These findings are consistent with the results of Kohli et al.[11] in which *N*-alkyldopamine derivatives produced similarly diminished effects on renal blood flow. These investigators attributed the increases in renal blood flow produced by *N*-*n*-propyldopamine to activation of β-adrenergic receptors. It is of interest, therefore, that the vasodilatory effects of **2d** and **2e** were attenuated by both (*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine and propranolol but were completely inhibited by a combination of both receptor blockers. Thus, our results suggest that an *o*-chlorine substitution enhances the activity of these N-alkylated derivatives at vascular $DA_1$ receptors.

## Experimental Section

**2-Chloro-3,4-dimethoxybenzaldehyde (4).** To a dry three-neck 1-L flask equipped with a nitrogen inlet valve, thermometer, and septum was added dry THF (200 mL) and *N,N,N'*-trimethylethylenediamine (21.5 g, 0.21 mol, dried over 4A molecular sieves). The reaction was cooled to −45 °C, and 1.6 M *n*-butyllithium (132 mL, 0.21 mol) was added rapidly. After being stirred for 30 min with the temperatures between −30 and −45 °C, the reaction mixture was cooled to −70 °C and a solution of 3,4-dimethoxybenzaldehyde (**3**, 34.8 g, 0.21 mol) in dry THF (100 mL) was added rapidly to the reaction mixture via syringe. The reaction mixture was again stirred for 30 min at −30 to −45 °C and recooled to −70 °C. An additional 132 mL of 1.6 M *n*-butyllithium (0.21 mol) was added, and the solution was allowed to warm to −30 °C and was maintained at this temperature for 8 h. Inverse addition of the cold anion to a solution of hexachloroethane (149 g, 0.63 mol) in dry THF (250 mL) at 25 °C, followed by stirring of the solution at room temperature for 3 h, provided essentially pure product as indicated by TLC. The solution was poured into 5 N HCl (200 mL) with stirring. The aqueous layer was extracted with ether (200 mL), and the combined organic layers were washed with 1 N NaOH, 1 N HCl, and brine and dried ($MgSO_4$). The resulting product (31 g), obtained after evaporation of the solution, was purified by flash chromatography (1 L Merck silica gel) with ethyl acetate–hexane (25:75), providing 26 g (62%) of **4**. Recrystallization of a small sample from hexane provided an analytical sample: mp 69–70 °C (lit.[13] mp 70.5–72 °C); $^1H$ NMR ($CDCl_3$) δ 3.9 (s, 3 H), 4.0 (s, 3 H), 6.9 (d, 1 H), 7.7 (d, 1 H), 10.3 (s, 1 H); MS (CI/$CH_4$), *m/z* 201 ($MH^+$).

**2-Chloro-3,4-dimethoxy-β-nitrostyrene (5).** A mixture of **4** (1.5 g, 7.5 mmol), dry nitromethane (2 mL), and ammonium acetate (0.58 g, 7.5 mmol) was refluxed in glacial acetic acid (6 mL) for 3 h, diluted with brine (100 mL), and extracted with ethyl acetate (2 × 50 mL). The combined extracts were washed with water (3 × 100 mL), dried ($MgSO_4$), and evaporated to a crystalline solid (1.73 g, 95%): mp 88–91 °C (EtOH); $^1H$ NMR ($CDCl_3$) δ 3.9 (s, 3 H), 3.95 (s, 3 H), 6.9 (d, 1 H, *J* = 1.75 Hz), 7.35 (d, 1 H, *J* = 1.75 Hz), 7.6 (d, 1 H, *J* = 2.45 Hz), 8.35 (d, 1 H, *J* = 2.45 Hz). Anal. ($C_{10}H_{10}NO_4Cl$) C, H, N.

**2-Chlorohomoveratrylamine (6).**[4a] **Method A.** To a dry three-neck 100-mL flask equipped with a magnetic stirring bar, dry addition funnel with septum, nitrogen inlet valve, and septum was added dry THF (15 mL) and lithium aluminum hydride (0.47 g, 12.4 mmol). The mixture was cooled in an ice bath, and a solution of dry $AlCl_3$ (1.65 g, 12.4 mmol) in dry THF (20 mL) (prepared at −20 °C) was added via a syringe. A solution of **5** (1.5 g, 6.2 mmol) in THF (25 mL) was added dropwise over 20 min. The reaction mixture was stirred at room temperature for 16 h; water (2 mL) was added dropwise followed by 5 N HCl (15 mL). The mixture was washed with ether (2 × 50 mL); the aqueous phase was made basic with 5 N NaOH and extracted with ether (3 × 50 mL). The extracts were dried ($MgSO_4$) and concentrated to an oil that crystallized on standing (1.1 g, 80%): $^1H$ NMR ($CDCl_3$) δ 1.8 (s, 2 H), 2.9 (t, 4 H), 3.8 (s, 6 H), 6.7 (d, 1

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H), 6.95 (d, 1 H); MS (CI/$CH_4$), $m/z$ 216 ($MH^+$).

**Method B.** The nitrile **9** (5 g, 23.6 mmol) was dissolved in dry THF (30 mL) and added dropwise to a mixture of $LiAlH_4$ (3 g, 79 mmol) in THF (40 mL). This was stirred overnight at ambient temperature and quenched with $H_2O$ (3 mL, in 30 mL of THF) followed by 15% NaOH (5 mL). The mixture was filtered and the filtrate was dried ($MgSO_4$) and concentrated to an oil (2.6 g, 51%) that had identical spectroscopic properties with that of **6** prepared by method A.

**2-Chloro-3,4-dimethoxybenzyl Alcohol (7).** Aldehyde **4** (18 g, 90 mmol) was dissolved in dry THF (100 mL) and added dropwise to a mixture of $LiAlH_4$ (4.5 g, 118 mmol) in dry THF (100 mL). The reaction mixture was stirred at ambient temperature for 1 h and quenched by the consecutive dropwise addition of 5 mL of $H_2O$ in 20 mL of THF and 10 mL of 15% NaOH. The solid was filtered and rinsed with THF. The filtrate was dried over $MgSO_4$ and concentrated to an oil (16.4 g, 90%), which crystallized on standing. Recrystallization from hexane provided analytically pure **7**: mp 68–70 °C; $^1H$ NMR ($CDCl_3$) $\delta$ 3.3 (s, 1 H), 3.8 (s, 6 H), 4.55 (br s, 2 H), 7.0 (d, 1 H), 7.2 (d, 1 H); MS (CI/$CH_3$), $m/z$ 203 ($MH^+$), 185 (M – OH), 173 ($MH^+$ – O=$CH_2$), 151 (185 – Cl + H). Anal. ($C_9H_{11}ClO_3$) C, H, N.

**2-Chloro-3,4-dimethoxybenzyl Chloride (8).** The alcohol **7** (24 g, 118 mmol) was mixed with an excess of $SOCl_2$ (30 mL), refluxed for 24 h, and concentrated in vacuo to an oil. Purification by bulb-to-bulb distillation at 175 °C (0.5 mm) provided 22 g (84%) of **8**: $^1H$ NMR ($CDCl_3$) $\delta$ 3.8 (s, 6 H), 4.6 (s, 2 H), 6.7 (d, 1 H), 7.1 (d, 1 H); MS (EI/70 eV), $m/z$ 220 ($M^+$). Anal. ($C_9H_{10}ClO_2$) C, H.

**2-(2-Chloro-3,4-dimethoxyphenyl)acetonitrile (9).** The benzyl chloride **8** (12 g, 54 mmol) was heated at reflux for 7 days with 7.1 g (108 mmol) of dry KCN in dry $CH_3CN$ (25 mL) and a catalytic amount of 18-crown-6. The reaction mixture was filtered and the filtrate concentrated to an oil. Purification by flash chromatography ($CHCl_3$–hexane) (80:20) provided **9** (7.7 g, 67%) as a crystalline solid (from hexane cooled in a dry ice–acetone bath). An analytical sample was obtained by dissolving 1 g in 10 mL of $CS_2$ and slowly concentrating in vacuo without heat until crystals formed: mp 56–57 °C (lit.[15] mp 65–65.5 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 3.7 (s, 2 H), 3.8 (s, 6 H), 6.75 (d, 1 H), 7.7 (d, 1 H); MS (CI/$CH_4$), $m/z$ 212 ($MH^+$). Anal. ($C_{10}H_{10}ClNO_2$) C, H, N.

**(2-Chlorohomoveratryl)formamide (10c).** The product was obtained from **6** and formic acetic anhydride as in the preparation of **10d**. Purification by flash chromatography ($CHCl_3$–MeOH) (95:5) provided **10c** as a low-melting crystalline solid in 75% yield: $^1H$ NMR ($CDCl_3$) $\delta$ 2.7–3.0 (m, 2 H), 3.3–3.65 (m, 2 H), 3.8 (s, 6 H), 6.7–7.1 (m, 3 H), 8.2 (s, 1 H); MS (CI/$CH_4$), $m/z$ 244 ($MH^+$). Anal. ($C_{11}H_{14}ClNO_2$) C, H, N.

**2-Chlorohomoveratrylacetamide (10d).** A solution of **6** (2.4 g, 11 mmol) in $CH_2Cl_2$ (25 mL) was added to a mixture of acetic anhydride (1.19 g, 11.7 mmol) and 4-(dimethylamino)pyridine (1.42 g, 11.7 mmol) in $CH_2Cl_2$ (10 mL) cooled to 0 °C. The reaction mixture was stirred overnight at room temperature and refluxed 3 hrs. The resulting solution was concentrated to an oil and purified by flash chromatography using $CHCl_3$–MeOH (95:5), providing 2.69 g (93%) of **10d** as a colorless oil. Bulb-to-bulb distillation at 1 mm Hg and 220 °C provided the analytical sample: $^1H$ NMR ($CDCl_3$) $\delta$ 1.9 (s, 3 H), 2.8 (m, 2 H), 3.3 (m, 2 H), 3.75 (s, 6 H), 6.3 (s, 1 H), 7.65 (d, 1 H), 7.85 (d, 1 H); MS (EI/70 eV), $m/z$ 257. Anal. ($C_{12}H_{16}NO_3Cl$) C, H, N.

***N*-(2-Chlorohomoveratryl)propanamide (10e).** The product was prepared in a similar manner to that for **10d**, providing **10e** in 95% yield after flash chromatography ($CHCl_3$–$CH_3OH$) (99:1). Bulb-to-bulb distillation at 1 mm Hg and 240 °C gave a clear colorless oil, which crystallized on standing: mp 60–62 °C; IR (KBr) 1650 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.1 (m, 3 H), 2.2 (m, 2 H), 2.9 (m, 2 H), 3.45 (m, 2 H), 4.8 (s, 6 H), 6.0 (br s, 1 H), 7.0 (d, 1 H), 7.9 (d, 1 H); MS (CI/$CH_4$), $m/z$ 272 ($MH^+$). Anal. ($C_{13}H_{18}NO_3Cl$) C, H, N.

***N*-Methyl-2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (11c).** Formamide **10c** (3.4 g, 13.9 mmol) was dissolved in dry THF (10 mL) and 2 M $BH_3{\cdot}S(CH_3)_2$ (35 mL, 70 mmol) was added via syringe. The reaction mixture was refluxed for 8 h, quenched with MeOH (10 mL), and saturated with HCl gas. The solution was refluxed for 1 h and concentrated in vacuo. The resulting oil was partitioned between 1 N NaOH and ethyl acetate. The organic layer was evaporated and purified by flash chromatography ($CHCl_3$–MeOH–$NH_4OH$) (89:10:1) and gave **11c** (2.5 g, 78%) as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.6 (br s, 1 H), 2.4 (s, 3 H), 2.8 (m, 4 H), 3.8 (s, 6 H), 6.7 (d, 1 H), 6.9 (d, 1 H); MS (CI/$CH_4$), $m/z$ 230 ($MH^+$).

***N*-Ethyl-2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (11d).** Acetamide **10d** (2.3 g, 9 mmol) was treated as in the preparation of **11c**. Purification of the oil obtained from the reaction by flash chromatography with $CHCl_3$–MeOH–$NH_4OH$ (94:5:1) provided **11d** (1.5 g, 69%) as a colorless oil: $^1H$ NMR ($CDCl_3$) $\delta$ 6.95 (d, 1 H), 6.7 (d, 1 H), 3.9 (s, 6 H), 2.9 (m, 6 H), 1.7 (s, 1 H), 1.1 (t, 3 H); MS (CI/$CH_4$), $m/z$ 244 ($MH^+$).

***N*-(*n*-Propyl)-2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (11e).** The amide **10e** (2.8 g, 10.3 mmol) was treated with 2 M $BH_3{\cdot}S(CH_3)_2$ (15 mL, 30 mmol) as in the preparation of **11c**. Flash chromatography with $CHCl_3$–MeOH–$NH_4OH$ (94:5:1) followed by bulb-to-bulb distillation at 210 °C (1 mm) provided 2.1 g (79%) of analytically pure **11e** as an oil: $^1H$ NMR ($CDCl_3$) $\delta$ 6.9 (d, 1 H), 6.75 (d, 1 H), 3.8 (s, 6 H), 2.85 (s, 4 H), 2.6 (m, 2 H), 1.45 (m, 3 H), 0.9 (m, 3 H); MS (EI/70 eV), $m/z$ 258 ($MH^+$). Anal. ($C_{13}H_{20}NClO_2$) C, H, N.

**2-Chlorodopamine Hydrochloride (2b).** The phenethylamine **6** (1.5 g, 7 mmol) was dissolved in $CHCl_3$ (20 mL) in a four-neck 250-mL flask equipped with a magnetic stirring bar, reflux condenser with a Firestone valve, and rubber septum. Trimethylsilyl iodide ($Me_3SiI$) (8.8 g, 44 mmol) was added followed by sulfolane (8 mL) (to dissolve the resulting precipitate). The solution was heated at 50 °C, and the progress of the reaction was monitored by $^1H$ NMR, which showed the disappearance of the methoxy peaks at $\delta$ 3.85. After 3 days, the reaction was quenched with saturated methanolic HCl (5 mL) and the reflux condenser was removed. The solution was concentrated with a warm water bath in vacuo and diluted with ether (40 mL), $CHCl_3$ (40 mL), and EtOH (4 mL). The resulting pasty precipitated was stirred overnight, and the crystals that formed were collected by filtration and washed with $CHCl_3$–EtOH (85:15). Recrystallization from MeOH–$CH_3CN$ (dissolved in MeOH and $CH_3CN$ added while cooling) provided analytically pure **2b**, (600 mg, 39%): mp 191–193 °C dec; $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 2.83 (br s, 4 H), 6.55 (d, 1 H), 6.65 (d, 1 H), 8.00 (br s, 3 H), 9.10 (s, 1 H), 9.7 (s, 1 H). Anal. ($C_8H_{10}NCl{\cdot}2HCl$) C, H, N.

***N*-Methyl-2-chlorodopamine Hydrochloride (2c).** The product was prepared by the same method as **2b** in 48% yield: mp 174–176 °C ($CH_3OH$–$CH_3CN$); $^1H$ NMR ($Me_2SO$-$d_6$, 300 MHz) $\delta$ 2.6 (s, 3 H), 2.9 (m, 4 H), 6.6 (d, 1 H), 6.7 (d, 1 H), 8.9 (br s, 2 H), 9.1 (s, 1 H), 9.7 (s, 1 H); MS (CI/$CH_4$), $m/z$ 202 ($MH^+$). Anal. ($C_9H_{12}ClNO_2{\cdot}HCl$) C, H, N.

***N*-Ethyl-2-chlorodopamine Hydrochloride (2d).** The product was prepared by a similar method to that for **2b** in 37% yield: mp 150–153 °C ($CH_3OH$–$CH_3CN$); $^1H$ NMR ($Me_SO$-$d_6$, 300 MHz) $\delta$ 1.0, (m, 3 H), 2.6 (m, 6 H), 6.4 (d, 1 H), 6.9 (d, 1 H), 8.4 (b, s, 2 H), 8.9 (s, 1 H), 9.4 (s, 1 H); MS (CI/$CH_4$), $m/z$ 216 ($MH^+$). Anal. ($C_{10}H_{14}NClO_2{\cdot}HCl$) C, H, N.

***N*-Propyl-2-chlorodopamine Hydrochloride (2e).** The product was prepared from **11e** by a similar method to that for **2b** in 20% yield: mp 173–175 °C ($CH_3CN$); $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 0.9 (t, 3 H, 1.6 (m, 2 H), 2.5 (m, 2 H), 2.9 (br s, 4 H), br s, 2 H), 6.15 (d, 1 H), 6.25 (d, 1 H), 8.5 (br s, 1 H), 9.75 (br s, 1 H); MS (CI/$CH_4$), $m/z$ 230 ($MH^+$). Anal. ($C_{11}H_{16}NClO_2{\cdot}HCl$) C, H, N.

**Pharmacology.** Mongrel dogs of either sex ($N$ = 18; BarWan Farms, Inc., Crocker, MO) weighing 16–22 kg were anesthetized with sodium pentobarbital (30 mg/kg iv); supplemental anesthetic was administered as needed. After endotracheal intubation, the dogs were placed on a Harvard apparatus respirator and ventilated with room air at a rate of 15 breaths/min and a volume of 15–20 mL/kg body weight. Catheters were placed in femoral artery and vein for measurement of arterial blood pressure (Model P23ID Statham Pressure Transducer) and heart rate (Gould biotachometer) and for infusion of isotonic saline, respectively. An incision was made in the left flank, and the left kidney was exposed via a retroperitoneal approach. A precalibrated noncannulating electromagnetic flow probe (Carolina Medical Electronics) was positioned around the left renal artery for continuous measurement of renal blood flow. A nonoccluding needle-tip catheter was inserted into the renal artery distal to the flow probe, and a

continuous infusion of isotonic saline (0.8 mL/min) was initiated. All drugs were injected directly into the renal artery (ia) through a side port. α-Adrenergic receptor blockade was established using phenoxybenzamine, 5 mg/kg ia, infused at 1.1 mL/min for 30 minutes. Blockade was verified by examination of the effects of norepinephrine (0.3 and 1.0 μg ia) on renal blood flow before and after the phenoxybenzamine treatment. Isotonic saline was infused iv (10 mL/min) during the phenoxybenzamine infusion in order to maintain arterial blood pressure; subsequently, the infusion was reduced to 1 mL/min for the remainder of the experiment.

Dopamine (3–100 nmol) was administered as a bolus injection ia, and maximal increases in renal blood flow were recorded. Doses of test compounds (3–10 000 nmol ia; one test compound per dog) were then given, and changes in renal blood flow were measured. All doses were administered in 0.2-mL volumes of isotonic saline. In a manner similar to that reported by Kohli et al.,[11] the response to 100 nmol of dopamine was defined as maximal (100%) for each dog. Responses to subsequent test doses were calculated as a percentage of the maximal response to dopamine and were used for comparison between compounds based on $ED_{30}$ values. $ED_{30}$ was defined as the dose of test compound required to increase renal blood flow by 30%. After initial responses were established, SCH 23390 was infused at 0.5 μg $kg^{-1}$ $min^{-1}$ iv. Five minutes after the onset of the infusion, the doses of dopamine and test compounds were repeated. The infusion was then stopped and the animals were allowed to recover for at least 1.5 h. The dopamine and test compounds were repeated ia to verify that $DA_1$ receptor blockade had dissipated. Propranolol was then infused at 0.5 mg/kg ia over a 15-min period (0.764 mL/min) to establish β-receptor blockade; this was verified by examination of the vasodilatory effects of isoproterenol (0.1 and 0.3 μg ia) before and after propranolol. Dopamine and test compounds were again administered, and when responses were attenuated by propranolol (compounds **2d** and **2e**), the SCH 23390 infusion was repeated. Test compounds were readministered, and changes in renal blood flow were examined during combined dopamine and β-receptor blockade.

**Registry No.** **2b**, 88408-41-7; **2b** (base), 102851-70-7; **2c**, 102851-67-2; **2c** (base), 102851-71-8; **2d**, 102851-68-3; **2d** (base), 102851-72-9; **2e**, 102851-69-4; **2e** (base), 102851-73-0; **3**, 120-14-9; **4**, 5417-17-4; **5**, 41122-35-4; **6**, 67287-36-9; **7**, 93983-13-2; **8**, 93983-14-3; **9**, 7537-07-7; **10c**, 102851-63-8; **10d**, 102851-64-9; **10e**, 99318-58-8; **11c**, 102851-65-0; **11d**, 102851-66-1; **11e**, 99318-59-9; nitromethane, 75-52-5.

# 3,4-Dihydro-2-phenyl-2*H*-pyrano[2,3-*b*]pyridines with Potent Antirhinovirus Activity

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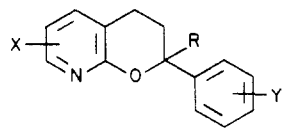
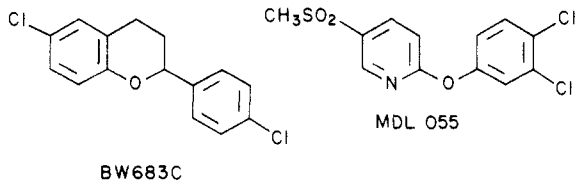
A general synthesis to the title compounds **1**, substituted in the 6-position and on the phenyl ring, is outlined. Eighteen analogues were compared with respect to in vitro activity against rhinovirus types 1A, 9, and 64. Compounds **1c** and **1h**, the 6-bromo- and 6-(methylsulfonyl)-3′,4′-dichlorophenyl analogues, afforded median $MIC_{50}$ values against 23 rhinovirus serotypes of 0.05 and 0.13 μg/mL, respectively. Mice dosed orally with 200 mg/kg of **1c** or **1h** exhibited serum levels well in excess of each compound's $MIC_{50}$, indicating that some analogues have the potential to be orally effective drugs.

Rhinoviruses have been shown to be an important causative agent for the common cold.[1] The widespread nature of this affliction, the economic consequences, and the well-known impracticality of vaccine development have justified the search for chemotherapeutic agents.[2]

We describe preliminary studies on the antiviral activity of title compounds **1** and their potential utility as chemotherapeutic agents. Antirhinovirus activity has been observed in compounds of related structure such as the series of flavans exemplified by the 4′,6′-dichloro derivative BW683C and the phenoxypyridines exemplified by MDL 055.[2c,3] The parent 2*H*-pyrano[2,3-*b*]pyridine ring system as well as several aza analogues of related flavones and coumarins have been described;[4] however, 3,4-dihydro-2-phenyl-2*H*-pyrano[2,3-*b*]pyridines **1** appear to be new.




**1**, R = H
**6**, R = $CH_3$




**Chemistry.** The general synthesis route for the title compounds is outlined in Scheme I. Bromination of 5-chloro-2-methoxypyridine produced the 3-bromo derivative **2a**. Similarly, bromination of 2-methoxypyridine with an extra equivalent of bromine gave the dibromopyridine **2b**. Bromine–lithium exchange was effected with *n*-butyllithium in ether at −70 °C, and the intermediate lithiopyridines were trapped with the appropriate cinnamaldehyde, affording allylic alcohols **3**. In the case of dibromopyridine **2b** lithiation occurred preferentially at the desired 3-position. Allylic alcohols **3** underwent concomitant demethylation and cyclization to 2*H*-pyrano[2,3-*b*]-

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