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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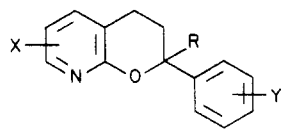
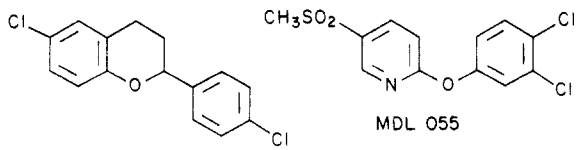
A general synthesis to the title compounds **1**, substituted in the 6-position and on the phenyl ring, is outlined. Eighteen analogues were compared with respect to in vitro activity against rhinovirus types 1A, 9, and 64. Compounds **1c** and **1h**, the 6-bromo- and 6-(methylsulfonyl)-3′,4′-dichlorophenyl 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



BW683C

MDL 055

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*]-

(1) Douglas, R. G., Jr. In *Antiviral Agents and Viral Diseases of Man*; Galasso, G. J., Merigan, T. C., Buchanan, R. A., Eds.; Raven: New York, 1979; pp 385–459.

(2) For recent work and leading references see (a) Diana, G. D. et al. *J. Med. Chem.* **1985**, *28*, 748. (b) Hideo et al. *Antimicrob. Agents Chemother.* **1982**, *22*, 611 and 617. (c) Selway, J. W. T. et al. *Nature (London)* **1981**, *292*, 369. (d) Wikel, J. H. et al. *J. Med. Chem.* **1980**, *23*, 368. (e) Galabov, A. S. *Arzneim. Forsch.* **1979**, *29*(II), 1863.

(3) Markley, L. D.; Tong, Y. C.; Dulworth, J. K.; Steward, D. L.; Goralski, C. T.; Johnston, H.; Wood, S. G.; Vinogradoff, A. P.; Bargar, T. M. *J. Med. Chem.* **1986**, *29*, 427. See also Markley, L. D.; Tong, Y. C.; Wood, S. G. U.S. Patent 4 371 537; *Chem. Abstr.* **1983**, *98*, 15211s.

(4) (a) Sliwa, H. *Bull. Soc. Chim. Fr.* **1970**, *631*. (b) Sliwa, H.; Delaunay, L. *J. Heterocyclic Chem.* **1979**, *16*, 939. (c) Moffett, R. B. *J. Org. Chem.* **1970**, *35*, 3596. (d) Bonnetaud, D.; Quequiner, G.; Pastour, P. *J. Heterocyclic Chem.* **1972**, *9*, 165. (e) Khalifa, M. A.; Elnagdi, M. H. *Indian J. Chem.* **1974**, *12*, 46.

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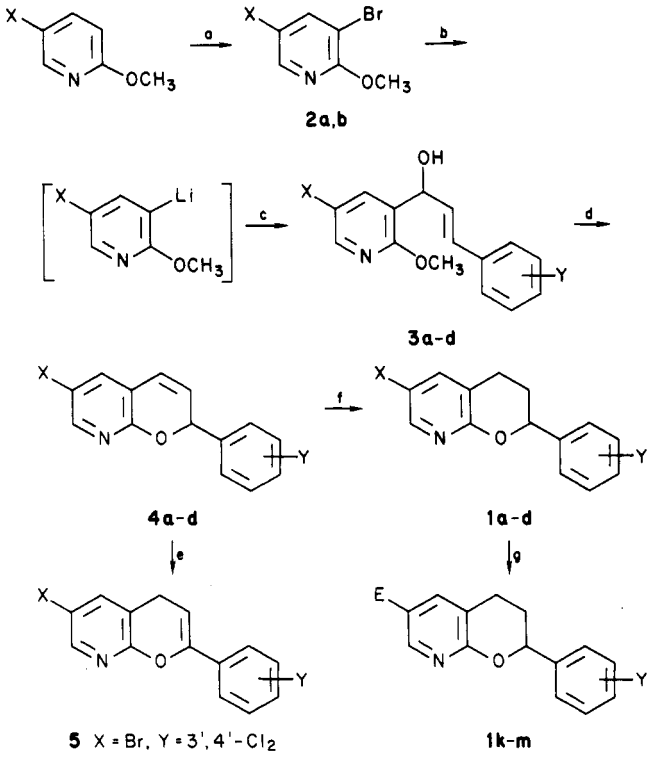
Table I. Antirhinovirus Activity of 2-Phenyl-2*H*-pyrano[2,3-*b*]pyridines

compd	X or E	Y	mp, °C	anal.[a]	ID_{50},[b] μM RV-1A	RV-9	RV-64	CGI,[c] μM
1a	Cl	4′-Cl	109–111	C, H, N	0.07	0.64	0.11	35
1b	Br	H	109–111	C, H, N	0.41	4.76	3.55	*d*
1c	Br	3′,4′-Cl_2	106–109	C, H, N	0.03	0.22	0.06	28
1d	Cl	3′,4′-Cl_2	106.5–107.5	C, H, N	0.06	0.29	0.03	16
1e	Br	4′-CH_3	126–127	C, H, N	0.07	0.39	0.23	*d*
1f	Br	4′-Cl	112.5–114	C, H, N	0.03	0.03	0.03	*d*
1g	CH_3SO_2	H	188–189	C, H, N	>17[e]	*d*	*d*	*d*
1h	CH_3SO_2	3′,4′-Cl_2	171.5–173	C, H, N	0.47	0.14	0.01	56
1i	CH_3SO	3′,4′-Cl_2	159–162	C, H, N	0.26	0.03	0.009	*d*
1j	CH_3SO_2	4′-Cl	187–189	C, H, N	1.42	1.42	0.25	*d*
1k	H	3′,4′-Cl_2	99–100	C, H, N	0.07	2.18	0.64	*d*
1l	*n*-C_4H_9S	3′,4′-Cl_2	59.5–61	C, H, N	2.83	6.30	1.39	*d*
1m	CH_3S	3′,4′-Cl_2	109–111	C, H, N	0.12	0.15	0.03	15
4a	Cl	4′-Cl	91.5–93	C, H, N	0.18	2.30	0.47	9.0
4b	Br	H	103.5–105	C, H, N	1.49	>3.47[e]	>3.47[e]	*d*
4c	Br	3′,4-Cl_2	100.5–101.5	C, H, N	0.53	0.11	0.06	14
5	Br	3′,4′-Cl_2	138–139.5	C, H, N	0.59	>14.0[e]	12.9	*d*
6	Cl	3′,4′-Cl_2	83–84	C, H	1.09	0.58	0.40	*d*
BW683C			96.5–97.5[f]		0.22	3.15	0.22	36

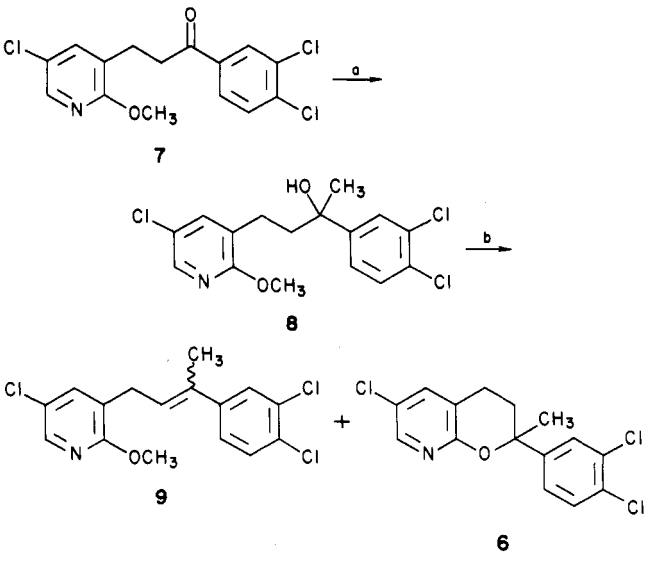
[a] Elemental analyses were within ±0.4% of the theoretical value. [b] ID_{50} denotes the concentration of test compound required to reduce virus-induced plaque formation in HeLa cell culture to 50% of control. [c] CGI (cell growth inhibition) denotes the lowest concentration at which effects on HeLa cell colony formation became apparent.[6] [d] Not tested. [e] The highest concentration tested failed to provide 50% protection. [f] Literature mp 101 °C.[2c]

Scheme I



Compound letter designations are as follows: (a) Br_2/HOAc; (b) *n*-BuLi/Et_2O, −70 °C; (c) substituted cinnamaldehyde; (d) 48% HBr/HOAc, 100 °C; (e) DBU/THF, 25 °C; (f) H_2, Raney Ni; (g) *t*-BuLi/Et_2O/$PhCH_3$, −100 °C, then E^+.

Scheme II



Compound letter designations are as follows: (a) CH_3MgCl/THF and (b) 48% HBr/HOAc, 100 °C.

pyridines **4** on brief treatment with 48% hydrobromic acid in hot acetic acid. Isomerization of the double bond of **4c** (X = Br, Y = 3′,4′-Cl_2) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded the corresponding 4*H*-pyrano[2,3-*b*]pyridine **5**. Catalytic reduction of the double bond of **4** was achieved by using hydrogen at 1 atm over Raney nickel. Bromo analogue **1c** (X = Br, Y = 3′,4′-Cl_2) underwent halogen–metal exchange on treatment with *tert*-butyllithium in ether/toluene at −100 °C, and the intermediate lithio derivative was trapped with a variety of electrophiles. Compound **6**, possessing an angular methyl group in the 2-position, was prepared as outlined in Scheme II. Ketone **7**[5] was allowed to react with methylmagnesium chloride, and the resulting tertiary alcohol **8** was subjected to the cyclization conditions of Scheme I to afford a mixture of olefin isomers **9** and pyranopyridine **6** in low overall yield. Synthesis of the complete series of 2-phenyl-2*H*-pyrano[2,3-*b*]pyridines and an alternative synthesis route are reported separately.[5]

Biology. Pyrano[2,3-*b*]pyridine derivatives were evaluated for antiviral activity in cell culture using a standard plaque reduction assay in which the concentration of compound required to reduce viral plaque formation in a cell monolayer by 50% (ID_{50}) compared to control was calculated.[6] In order to gauge a therapeutic ratio, several of the more active compounds were tested for their effect on the growth and morphology of HeLa cell colonies.[6]

(5) Bargar, T. M.; Wilson, T.; Daniel, J. K. *J. Heterocyclic Chem.* **1985**, *22*, 1583.
(6) Torney, H. L.; Dulworth, J. K.; Steward, D. L. *Antimicrob. Agents Chemother.* **1982**, *22*, 635.

These data are reported in Table I. Highly active compounds were tested against a collection of rhinovirus serotypes using a standard assay (CPE test) in which the approximate concentration of compound required to reduce the virus-induced cytopathic effect by 50% was determined (MIC_{50}).[6] Compounds selected on the basis of cell culture activity were given to mice via the oral route, and blood serum concentrations were determined by HPLC at several times after dosing.

Results and Discussion

The activity of the title compounds and some related derivatives in cell culture against rhinovirus types 1A, 9, and 64 is presented in Table I. Most of the analogues **1** were highly active. The unsaturated derivatives **4** also had activity, although somewhat less than **1**. Compare, for example, **4a** with **1a**. Interestingly, the double bond isomer **5** exhibited significantly reduced activity compared to **4c**, especially against RV-9 and RV-64, suggesting that a tetrahedral geometry at C-2 is preferred. Addition of a methyl group at C-2, as in compound **6**, however, resulted in greatly diminished activity compared with **1d**. Activity was dependent on the phenyl ring substituent. In the series of 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines substituted by bromine in the 6-position, the order of potency caused by phenyl ring substituent was 4′-Cl > 3′,4′-Cl_2 > 4′-CH_3 > H (comparing **1f**, **1c**, **1e**, and **1b**). When methylsulfonyl or chloro occupied the 6-position, the 3′,4′-Cl_2 substituent was preferred over the 4′-Cl. The 3′,4′-Cl_2 phenyl ring substituent was fixed, and the 6-substituent was allowed to vary. Chloro and bromo substituents were again favored. Activity against RV-9 and RV-64 was reduced when the 6-position was unsubstituted.

Importantly, sulfur substituents also exhibited potent activity as in the series of phenoxypyridines as represented by MDL 055.[3] The 6-substituted methylthio, methylsulfinyl, and methylsulfonyl analogues (**1m**, **1i**, **1h**) all were potent, suggesting that the activity may not depend on the electron-withdrawing character of the substituent. The more bulky and lipophilic butylthio group of **11** caused a significant loss of activity.

From this limited series of compounds we conclude that, for optimum activity, substituents on both the pyrano[2,3-*b*]pyridine and phenyl ring are required and the 2-position must have tetrahedral geometry. The favored substituents are halogen and $CH_3S(O)_n$ (n = 0, 1, 2) for the 6-position and chlorine for 3′- and 4′-positions.

The spectrum of activity of three of the more active analogues was assessed. Rhinoviruses were found to be the most sensitive. For example, **1c** and **1d** exhibited an MIC_{50} value of less than 0.5 μg/mL against 18 of 23 rhinovirus types.[7] Both compounds had a median MIC_{50} of 0.05 μg/mL. The sulfone **1h** was likewise active against 17 of 23 serotypes, having a median MIC_{50} of 0.13 μg/mL. When compared in a parallel experiment, 4′,6′-dichloroflavan (BW683C) was active at the 0.5 μg/mL level against 15 of 23 serotypes and had a median MIC_{50} of 0.25 μg/mL. The three pyranopyridines **1c**, **d**, and **1h** had little or no activity against several coxsackievirus types, polio type 2, and mengovirus. Echovirus serotypes exhibited variable sensitivity, with MIC_{50} values ranging from <0.06 μg/mL to 5.0 μg/mL.

There is no practical animal model for human rhinovirus infection; therefore, to assess the potential of the title compounds for in vivo activity, mice were administered orally with 200 mg/kg of a Methocel suspension of compounds **1c** or **1h** and, after the times indicated in Table II, were sacrificed and their sera were collected. The samples thus obtained were analyzed for parent compound by HPLC. The sulfone **1h** was found in higher concentration than the bromo analogue **1c**. Compound **1c** showed evidence of serum metabolites by comparison of HPLC traces of treated and untreated serum. No serum metabolites were observed for **1h**. Mouse sera from the treated groups were tested in the cytopathic effect assay against RV-2 and found to exhibit a level of activity consistent with the concentration of parent determined by HPLC. None of the compounds showed any signs of acute toxicity. Both compounds retained their activity in serum and reached concentrations well in excess of their plaque-reduction ID_{50} values against the three rhinoviruses of Table I. Thus, both have the potential to be orally effective drugs. Studies designed to better define the bioavailability of compounds **1c** and **1h** in several species are in progress as a part of the development of these compounds as clinical candidates.

Table II. Serum Concentrations (μM) by HPLC of Compounds **1c** and **1h** in Mice following an Oral Dose of 200 mg/kg

time, h, after dosing	compound	
	1c	**1h**
1	11.7	NT[a]
2	6.7	47.5
4	7.8	44.7
8	9.5	47.5
24	3.6	11.2

[a] Not tested.

Experimental Section

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR spectra were determined on a Perkin-Elmer Model R-32 Spectrometer (90 MHz) or on a Varian XL-300 instrument (300 MHz) and are reported in parts per million downfield from tetramethylsilane internal standard (δ). Mass spectra were obtained on a Finnegan 4000 spectrometer interfaced to an INCOS 2000 data system. Elemental analyses were performed by the Analytical Chemistry Department, Merrell Dow Research Institute, Cincinnati, OH. 4′,6-Dichloroflavan (BW683C) was prepared by the patented procedure.[8]

3-Bromo-5-chloro-2-methoxypyridine (2a). To a stirred suspension of 2.5 g (0.03 mol) of anhydrous NaOAc in 10 mL of HOAc was added 4.32 g (0.03 mol) of 5-chloro-2-methoxypyridine,[9] followed by a solution of 3.1 mL (0.06 mol) of Br_2 in 10 mL of HOAc. The mixture was warmed to 80 °C for 6 h, allowed to cool, and stirred at 23 °C for 64 h. The mixture was partitioned between ether and water, and the ether layer was washed with 1 N NaOH then with 5% $Na_2S_2O_3$, dried over K_2CO_3, and concentrated at reduced pressure to 5.5 g of brown solid. The residue was bulb-to-bulb distilled, and the material coming over at 140–150 °C at 20 torr was collected, affording 5.0 g (74%) of colorless solid: mp 46.5–47.5 °C; ^1H NMR ($CDCl_3$) δ 8.01 (d, 1 H, $J_{6,4}$ = 2 Hz, H-6), 7.77 (d, 1 H, $J_{4,6}$ = 2 Hz, H-4), 3.95 (s, 3 H, CH_3); mass spectrum (CI/CH_4), m/z 224 (100, M + 1), 222 (80, M + 1), 144 (25, M − Br + 1). Anal. ($C_6H_5BrClNO$) C, H, N; C: 32.39; found, 31.35.

3,5-Dibromo-2-methoxypyridine (2b). To a mechanically stirred solution of 111.35 g (1.0 mol) of 2-methoxypyridine in 500 mL of HOAc was added 164.1 g (2.0 mol) of anhydrous NaOAc in portions over about 5 min so as to avoid formation of lumps. Then 179.3 mL (3.5 mol) of Br_2 was added at a rate such that

(7) The rhinoviruses tested consisted of types 1A, 1B, 2, 4, 5, 8, 9, 10, 13, 14, 21, 29, 32, 33, 39, 44, 49, 55, 64, 68, 74, 89, and Hanks.

(8) Batchelor, J. F.; Bauer, J. D.; Hodson, H. F.; Talbot, J. W.; Selway, J. W. T.; Young, D. A. B. U.K. Patent Application GB 2 024 817 assigned to The Wellcome Foundation Ltd. See also *Drugs of the Future*; **1982**; Vol. VII, p 542.

(9) Spinner, E.; White, J. C. B. *J. Chem. Soc. B* **1966**, 991.

the temperature remained below 35 °C. The mixture was warmed to 80 °C for 6 h and then was stirred at 25 °C for 16 h. The mixture was poured into 2 L of water and extracted with two 500-mL portions of CCl_4. The organic phase was washed with 1 N NaOH and 1 N $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated in vacuo to a yellow liquid that solidified on cooling. The crude product was distilled through a short Vigreux column at 3 torr, and after a forerun consisting mainly of monobrominated product, the fraction boiling at 110–112 °C was collected, yielding 190.4 g (71%) of white solid: mp 49–51 °C; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1 H, $J_{6,4}$ = 2 Hz, H-6), 7.90 (d, 1 H, $J_{4,6}$ = 2 Hz, H-4), 3.99 (s, 3H, CH_3); mass spectrum (CI/CH_4), m/z 270 (50, M + 1), 268 (100, M + 1), 266 (50, M + 1), 190 (70, M – Br + 1), 188 (75, M – Br + 1). Anal. ($C_6H_5Br_2NO$) C, H, N.

(*E*)-5-Bromo-α-[2-(3,4-dichlorophenyl)ethenyl]-2-methoxy-3-pyridinemethanol (3c). A mechanically stirred solution of 60.55 g (0.227 mol) of 3,5-dibromo-2-methoxypyridine (**2b**) in 900 mL of anhydrous ether under N_2 was cooled to –70 °C to give a thick slurry. While the temperature was kept below –65 °C, 85.0 mL of 2.67 M *n*-BuLi/hexane (0.227 mol) was added dropwise. The reaction mixture became homogeneous upon completion of the addition. After 15 min at –70 °C a solution of 45.6 g (0.227 mol) of 3,4-dichlorocinnamaldehyde[10] in 200 mL of anhydrous THF was added dropwise, again keeping the temperature below –65 °C. The reaction mixture was quenched by addition of 100 mL of saturated $NaHCO_3$ solution, allowed to warm to –40 °C, then partitioned between ether and saturated $NaHCO_3$ solution. The aqueous layer was extracted with ether, and the combined ether layers were washed with saturated NaCl solution, dried over K_2CO_3, and concentrated to a pale yellow solid. Recrystallization from 2-propanol/ethyl acetate/hexane (1:3:5) gave 56.52 g of colorless crystals: mp 149–150 °C; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1 H, $J_{6,4}$ = 2 Hz, H-6 of pyridine ring), 7.77 (d, 1 H, $J_{4,6}$ = 2 Hz, H-4), 7.42 (d, 1 H, $J_{2',6'}$ = 2 Hz, H-2′ of benzene ring), 7.38 (d, 1 H, $J_{5',6'}$ = 10 Hz, H-5′), 7.15 (dd, 1 H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 10 Hz, H-6′), 6.62 (d, 1 H, J = 16 Hz, olefinic adjacent to benzene ring), 6.30 (dd, 1 H, J_1 = 5 Hz, J_2 = 16 Hz, olefinic), 5.47 (dd, 1 H, J_1 = 5 Hz, J_2 = 5 Hz, adjacent to OH), 3.96 (s, 3 H, CH_3), 2.64 (d, 1 H, J = 5 Hz, OH); mass spectrum (CI/CH_4), m/z 392 (20, M + 1), 390 (45, M + 1), 388 (30, M + 1), 370, 372, 374 (20, M + 1 – H_2O), 216, 218 (80, M – 3,4-dichlorostyrene). Anal. ($C_{15}H_{12}BrCl_2NO_2$) C, H, N.

(*E*)-5-Chloro-α-[2-(4-chlorophenyl)ethenyl]-2-methoxy-3-pyridinemethanol (3a). By use of the above procedure, reaction of **2a** (4.02 g, 18 mmol) with 4-chlorocinnamaldehyde[10] (3.0 g, 18 mmol) provided 3.5 g (73%) of title compound upon recrystallization from ethyl acetate/hexane: mp 135–139.5 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 1 H, $J_{6,4}$ = 2 Hz, H-6 of pyridine ring), 7.63 (d, 1 H, $J_{4,6}$ = 2 Hz, H-4), 7.27 (s, 4 H, benzene ring), 6.65 (d, 1 H, J = 15 Hz, olefinic adjacent to benzene ring), 6.28 (dd, 1 H, J_1 = 15 Hz, J_2 = 6 Hz, remaining olefinic), 5.47 (d, 1 H, J = 6 Hz, C*H*OH), 3.96 (s, 3 H, CH_3), 2.6 (br s, 1H, OH); mass spectrum (CI/CH_4), m/z 312 (50, M + 1), 310 (75, M + 1), 294 (70, M + 1 – H_2), 292 (100, M + 1 – H_2O), 172 (50, M – 4-chlorostyrene). Anal. ($C_{15}H_{13}Cl_2NO_2$) C, H, N.

(*E*)-5-Bromo-α-(2-phenylethenyl)-2-methoxy-3-pyridinemethanol (3b). By use of the above procedure, the reaction of **2b** (20.02 g, 75 mmol) with cinnamaldehyde (9.91 g, 75 mmol) provided the title compound (14.75 g, 61.5%) after recrystallization from hexane/2-propanol: mp 92–93 °C; ^{1}H NMR ($CDCl_3$) δ 8.01 (d, 1 H, $J_{6,4}$ = 3 Hz, H-6), 7.71 (d, 1 H, $J_{4,6}$ = 3 Hz, H-4), 7.25 (s, 5 H, phenyl), 6.65 (d, 1 H, J = 16 Hz, olefinic adjacent to Ph), 6.21 (dd, 1 H, J_1 = 7 Hz, J_2 = 16 Hz, remaining olefinic), 5.35 (t, 1 H, J = 7 Hz, C*H*OH), 3.92 (s, 3 H, CH_3), 2.72 (d, 1 H, J = 7 Hz, OH); mass spectrum (CI/CH_4), m/z 320, 322 (20, M + 1), 302, 304 (25, M – H_2O), 242 (50, M – Br), 224 (60, 242 – H_2O), 216 (45, M – CH=CHPh). Anal. ($C_{15}H_{14}BrNO_2$) C, H, N.

(*E*)-5-Chloro-α-[2-(3,4-dichlorophenyl)ethenyl]-2-methoxy-3-pyridinemethanol (3d). By the use of the above procedure, the reaction of **2a** (4.43 g, 19.9 mmol) and 3,4-dichlorocinnamaldehyde (4.00 g, 19.9 mmol) provided, after recrystallization from 2-propanol/ethyl acetate/hexane, 4.91 g (72%) of the title compound: mp 134.5–135.5 °C; ^{1}H NMR (d_6-Me_2SO) δ 7.95 (d, 1 H, $J_{6,4}$ = 2 Hz, H-6 of pyridine ring), 7.75 (d, 1 H, $J_{5,6}$ = 2 Hz, H-4), 7.35 (d, 1 H, $J_{2',6'}$ = 2 Hz, H-2′ of benzene ring), 7.30 (d, 1 H, $J_{5',6'}$ = 9 Hz, H-5′), 7.15 (dd, 1 H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 9 Hz, H-6′), 6.64 (d, 1 H, J = 16 Hz, olefinic adjacent to benzene ring), 6.22 (dd, 1 H, J_1 = 8 Hz, J_2 = 16 Hz, remaining olefinic), 5.39 (t, 1 H, J = 8 Hz, C*H*OH), 5.25 (d, 1 H, J = 8 Hz, OH), 3.95 (s, 3 H, CH_3); mass spectrum (CI/CH_4), m/z 344 (70, M + 1), 326 (60, M + 1 – H_2O), 172 (100, M – 3,4-dichlorostyrene). Anal. ($C_{15}H_9Cl_3NO_2$) C, H, N.

6-Bromo-2-(3,4-dichlorophenyl)-2*H*-pyrano[2,3-*b*]pyridine (4c). A mechanically stirred solution of 65.87 g (0.165 mol) of allylic alcohol, **3c**, in 600 mL of acetic acid was heated to 100 °C under N_2. Then 60 mL of 48% HBr was added all at once. After 15 min, the mixture was cooled rapidly to 20 °C in an ice-water bath and partitioned between 2 L of water and 1 L of ether. The ether layer was washed with three 1-L portions of water, then with saturated $NaHCO_3$ solution (carefully), then with saturated NaCl solution. After the solution was dried over $MgSO_4$, it was filtered and concentrated to approximately 60 g of dark yellow solid. The crude product was taken up in the minimum quantity of CH_2Cl_2 and passed through a short column of silica gel, eluting with CH_2Cl_2. Removal of solvent left 49.3 g of colorless product (83.5%). An analytical sample was obtained by recrystallization of a small portion from absolute ethanol: mp 100.5–101.5 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (d, 1 H, $J_{7,5}$ = 3 Hz, H-7), 7.3–7.7 (complex pattern, 4 H, H-5 and phenyl H), 6.54 (dd, 1 H, $J_{4,2}$ = 1 Hz, $J_{4,3}$ = 10 Hz, H-4), 6.15 (dd, 1 H, $J_{2,4}$ = 1 Hz, $J_{2,3}$ = 4 Hz, H-2), 5.90 (dd, 1 H, $J_{3,2}$ = 4 Hz, $J_{3,4}$ = 10 Hz, H-3); mass spectrum (CI/CH_4), m/z 356, 358, 360 (M + 1).

6-Chloro-2-(4-chlorophenyl)-2*H*-pyrano[2,3-*b*]pyridine (4a). By use of the procedure for preparation of **4c**, 6.18 g (20 mmol) of **3a** was cyclized with 9 mL of 48% HBr to provide, after recrystallization from hexane, 4.5 g (81%) of the title compound: mp 91.5–93 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1 H, $J_{7,5}$ = 3 Hz, H-7), 7.34 (s, 4 H, phenyl H), 7.30 (d, 1 H, $J_{5,7}$ = 3 Hz, H-5), 6.49 (dd, 1 H, $J_{4,2}$ = 1 Hz, $J_{4,3}$ = 10 Hz, H-4), 6.15 (dd, 1 H, $J_{2,4}$ = 1 Hz, $J_{2,3}$ = 4 Hz, H-2), 5.90 (dd, 1 H, $J_{3,2}$ = 4 Hz, $J_{3,4}$ = 10 Hz, H-3); mass spectrum (CI/CH_4), m/z 278 (100, M + 1), 166 (35, M – 4-chlorophenyl).

6-Bromo-2-phenyl-2*H*-pyrano[2,3-*b*]pyridine (4b). By use of the procedure for the preparation of **4c**, 14.40 g (45 mmol) of **3b** was cyclized using 10.8 mL of 48% HBr to provide, after recrystallization from hexane, 9.55 g (74%) of the title compound: mp 103.5–105 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (d, 1 H, $J_{7,5}$ = 3 Hz, H-7), 7.32 (s, 6 H, H-5 and phenyl H), 6.38 (dd, 1 H, $J_{4,2}$ = 1 Hz, $J_{4,3}$ = 10 Hz, H-4), 6.12 (dd, 1 H, $J_{2,4}$ = 1 Hz, $J_{2,3}$ = 4 Hz, H-2), 5.85 (dd, 1 H, $J_{3,2}$ = 4 Hz, $J_{3,4}$ = 10 Hz, H-3); mass spectrum (EI/70 eV), m/z 287, 289 (30, M^+), 286, 288 (35, M – H), 210, 212 (30, M – C_6H_5), 190 (25), 180 (60), 152 (100).

6-Bromo-2-(3,4-dichlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (1c). To a solution of 49.3 g (0.137 mole) of olefin, **4c**, in 220 mL of anhydrous THF was added 550 mL of absolute ethanol. The flask was flushed with N_2, and 60.4 g of an aqueous slurry of W-2 Raney nickel (Aldrich) was added. The atmosphere was replaced with H_2. After 6 h, the H_2 atmosphere was replaced with N_2, and the catalyst was filtered off through a pad of celite, washing with CH_2Cl_2 and taking case to keep the catalyst covered with solvent (fire hazard). The catalyst/celite mixture was moistened with water and transferred to a polyethylene bag for safe disposal. The filtrate was concentrated in vacuo to a small volume, and the resulting crystals were filtered off. The mother liquor was further concentrated and the residue flashed chromatographed (silica gel, CH_2Cl_2) to provide additional product. The combined yield was 29.4 g (59%). An analytical sample was obtained by recrystallization from ethanol: mp 106–109 °C; ^{1}H NMR ($CDCl_3$) δ 8.16 (d, 1 H, $J_{7,5}$ = 3 Hz, H-7), 7.55 (overlapping doublets, 2 H, H-5 and H-2′ of benzene ring), 7.35 (d, 1 H, $J_{5',6'}$ = 8 Hz, H-5′), 7.24 (dd, 1 H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 8 Hz, H-6′), 5.20 (dd, 1 H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 9 Hz, H-2), 2.7–3.1 (complex pattern, 2 H, H-4a,b), 1.7–2.3 (complex pattern, 2 H, H-3a,b); mass spectrum (EI/70 eV), m/z 357, 359, 361 (M^+), 322, 324, 326 (M – Cl), 198, 200 (100, M – $C_6H_3Cl_2CH_2$), 172, 174 (50, 3,4-$C_6H_3Cl_2$ – CH=CH_2^+).

6-Chloro-2-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (1a). By use of the procedure for the preparation of **1c**, 2.78 g (10 mmol) of **4a** was reduced over 3.0 g of Raney nickel

(10) Baker, R. R.; Doll, M. H. *J. Med. Chem.* **1971**, *14*, 793.

to provide, after recrystallization from ethyl acetate/hexane, 1.78 g (64%) of the title compound: mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 8.04 (d, 1 H, $J_{7,5}$ = 3 Hz, H-7), 7.35 (d, 1 H, $J_{5,7}$ = 3 Hz, H-5), 7.32 (s, 4 H, phenyl H), 5.21 (dd, 1 H, $J_{2,3a}$ = 4 Hz, $J_{2,3b}$ = 9 Hz, H-2), 2.7–3.0 (complex pattern, 2 H, H-4a,b), 1.8–2.4 (complex pattern, 2 H, H-3a,b); mass spectrum (CI/CH_4), m/z 280, 282 (M + 1), 244 (15, M – Cl), 168, 170 (50, M – C_6H_4Cl).

6-Bromo-3,4-dihydro-2-phenyl-2*H*-pyrano[2,3-*b*]pyridine (1b). By use of the procedure for the preparation of **1c**, 11.75 g (41 mmol) of **4b** was reduced over 14.4 g of Raney nickel to provide, after recrystallization from 2-propanol, 4.75 g (40%) of the title compound: mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1 H, $J_{7,5}$ = 2 Hz, H-7), 7.44 (d, 1 H, $J_{5,7}$ = 2 Hz, H-5), 7.31 (s, 5 H, phenyl H), 5.22 (dd, 1H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 9 Hz, H-2), 2.8–3.0 (complex pattern, 2 H, H-4a,b), 1.8–2.3 (complex pattern, 2 H, H-3a,b); mass spectrum (CI/CH_4), m/z 290, 292 (M + 1), 212, 214 (30, M – Ph), 186 (20, M – styrene), 117 (65, PhCH=CH_2 – CH_2^+).

6-Chloro-2-(3,4-dichlorophenyl)-3,4-dihydro-2*H*-pyrano-[2,3-*b*]pyridine (1d). By use of the procedure for the preparation of **1c**, 2.00 g (6.4 mmol) of **4d** was reduced over 3.0 g of Raney nickel to provide, after recrystallization from hexane/ethyl acetate, 1.10 g (56%) of the title compound: mp 106.5–107.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.90 (d, 1 H, $J_{7,5}$ = 3 Hz, H-7), 7.40 (overlapping doublets, 2 H, H-5 and H-2′ of benzene ring), 7.20 (d, 1 H, $J_{5',6'}$ = 8 Hz, H-5′), 7.05 (dd, 1 H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 8 Hz, H-6′), 5.05 (dd, 1 H, $J_{2,3a}$ = 4 Hz, $J_{2,3b}$ = 10 Hz, H-2), 2.6–3.1 (complex pattern, 2 H, H-4a,b), 1.5–2.4 (complex pattern, 2 H, H-3a,b); mass spectrum (EI/70 eV), m/z 313, 315 (M^+), 278 280 (M – Cl), 172, 174 (3,4-dichlorostyrene), 154, 156 (100, M – 3,4-dichlorostyrene).

6-Bromo-3,4-dihydro-2-(4-methylphenyl)-2*H*-pyrano[2,3-*b*]pyridine (1e). By the procedure used for the preparation of **1c**, 6-bromo-2-(4-methylphenyl)-2*H*-pyrano[2,3-*b*]pyridine[5] (1.25 g, 4.3 mmol) was reduced over 1.88 g of Raney nickel to provide, after recrystallization from 2-propanol/hexane, 0.47 g (37%) of the title compound: mp 126–127 °C; ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 1 H, $J_{7,5}$ = 2 Hz, H-7), 7.44 (d, 1 H, $J_{5,7}$ = 2 Hz, H-5), 7.20 (distorted dd, 4 H, phenyl H), 5.21 (dd, 1 H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 9 Hz, H-2), 2.7–3.0 (complex pattern, 2 H, H-4a,b), 2.35 (s, 3 H, CH_3), 1.9–2.3 (complex pattern, 2 H, H-3a,b); mass spectrum (CI/CH_4), m/z 304, 306 (100, M + 1), 226 (100, M – Br), 212, 214 (30, M – tolyl).

6-Bromo-2-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (1f). By the procedure used for the preparation of **1c**, 6-bromo-2-(4-chlorophenyl)-2*H*-pyrano[2,3-*b*]pyridine[5] (2.8 g, 10 mmol) was reduced over 3.5 g of Raney nickel to provide, after recrystallization from ethyl acetate/hexane, 0.90 g (32%) of the title compound: mp 112.5–114 °C; ^{1}H NMR 8.12 (d, 1 H, $J_{7,5}$ = 2 Hz, H-7), 7.49 (d, 1 H, $J_{5,7}$ = 2 Hz, H-5), 7.36 (s, 4 H, phenyl H), 5.18 (dd, 1 H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 10 Hz, H-2), 2.8–3.0 (complex pattern, 2 H, H-3a,b); mass spectrum (CI/CH_4), m/z 324, 326 (100, M + 1), 246 (55, M – Br), 212, 214 (M – 4-chlorophenyl).

2-(3,4-Dichlorophenyl)-3,4-dihydro-6-(methylthio)-2*H*-pyrano[2,3-*b*]pyridine (1m). A solution of 3.59 g (0.010 mol) of the bromo derivative, **1c**, in a mixture of 50 mL of toluene and 25 mL of anhydrous ether was cooled to –100 °C (liquid nitrogen/ether bath) under N_2, and 3.8 mL of 2.9 M *tert*-butyllithium/pentane (0.011 mol) was added dropwise over about 5 min, keeping the temperature below –100 °C. The mixture became deep blue-green. After 20 min, 1.8 mL (0.020 mol) of methyl disulfide was added. The mixture was allowed to warm to 0 °C, then was partitioned between ether and water. The ether layer was washed with saturated NaCl solution, dried over K_2CO_3, and concentrated to a yellow oil that solidified on cooling. Column chromatography on silica gel (20% ethyl acetate/hexane) provided 1.74 g of pure thioether (54%). An analytical sample was obtained on recrystallization from hexane/ethyl acetate as colorless needles: mp 109–111 °C; ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1 H, $J_{7,5}$ = 2 Hz, H-7), 7.53 (d, 1 H, $J_{5,7}$ = 2 Hz, H-5), 7.41 (d, 1 H, $J_{5',6'}$ = 8 Hz, H-5′), 7.40 (d, 1 H, $J_{2',6'}$ = 2 Hz, H-2′), 7.23 (dd, 1 H, $J_{6',5'}$ = 9 Hz, $J_{6',2'}$ = 2 Hz, H-6′), 5.20 (dd, 1 H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 9 Hz, H-2), 2.7–3.0 (complex pattern, 2 H, H-4a,b), 2.45 (s, 3 H, CH_3), 1.6–2.3 (complex pattern, 2 H, H-3a,b); mass spectrum (CI/CH_4), m/z 326, 329 (50, M + 1), 173, 175 (70, 3,4-dichlorobenzoyl), 154 (80, M – 3,4-dichlorostyrene).

2-(3,4-Dichlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]-pyridine (1k). The lithio intermediate, generated as above from the corresponding bromo compound (**1c**) (1.50 g, 4.3 mmol) was quenched with excess methanol at –85 °C. Chromatographic purification provided 0.71 g (59%) of cream-colored solid: mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (distorted dd, 1 H, H-7), 7.1–7.8 (complex pattern, 4 H, H-2′ + H-4′ + H-5 + H-6), 6.85 (dd, 1 H, $J_{6',2'}$ = 5 Hz, $J_{6',5'}$ = 8 Hz, H-6′), 5.16 (dd, 1 H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 9 Hz, H-2), 2.7–3.1 (complex pattern, 2 H, H-4a,b), 1.6–2.4 (complex pattern, 2 H, H-3a,b); mass spectrum (CI/CH_4), m/z 280, 282 (100, M + 1), 246 (40, M – Cl), 173 (20, 3,4-dichlorobenzoyl), 134, 136 (40), 108 (100, M – 3,4-dichlorostyrene).

6-(*n*-Butylthio)-2-(3,4-dichlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (1l). The lithio intermediate, generated as above from the corresponding bromo compound (**1c**) (0.85 g, 2.4 mmol), was quenched at –95 °C with excess *n*-butyl disulfide. Chromatographic purification provided 0.29 g of powdery white solid (33%). An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 59.5–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, 1 H, $J_{7,5}$ = 1.8 Hz, H-7), 7.57 (d, 1 H, $J_{5,7}$ = 1.8 Hz, H-5), 7.51 (d, 1 H, $J_{2',6'}$ = 1.5 Hz, H-2′), 7.46 (d, 1 H, $J_{5',6'}$ = 8.7 Hz, H-5′), 7.28 (dd, 1 H, $J_{6',2'}$ = 1.5 Hz, $J_{6',5'}$ = 8.7 Hz, H-6′), 5.22 (dd, 1 H, $J_{2,3a}$ = 1.8 Hz, $J_{2,3b}$ = 10.2 Hz, H-2), 2.90 (m, 1 H, H-4), 2.75–2.90 (complex pattern, 3 H, H-4 + CH_2S), 2.2–2.3 (complex pattern, 1 H, H-3), 1.9–2.1 (complex pattern, 1 H, H-3), 1.5–1.6 (m, 2 H, CH_2CH_3), 1.4–1.5 (m, 2 H, SCH_2CH_2), 0.91 (distorted t, 3 H, CH_3); mass spectrum (EI/70 eV), m/z 367 (15, M^+), 208 (100, M – 3,4-dichlorobenzyl).

2-(3,4-Dichlorophenyl)-3,4-dihydro-6-(methylsulfonyl)-2*H*-pyrano[2,3-*b*]pyridine (1h). Crude methylthio derivative, **1m** (prepared from 14.4 g (40 mmol) of **1c**, 10.8 mL of 2.33 M *t*-BuLi/pentane (46 mmol), and 10.8 mL (120 mmol) of methyl disulfide), was taken up in 80 mL of THF, diluted with 160 mL of CH_3OH, and cooled in an ice bath while a solution of 49.2 g (160 mmol) of 49.5% $KHSO_5$ (Oxone, Alfa) in 150 mL of water was added, keeping the temperature below 30 °C. A thick, white precipitate developed and efficient mechanical stirring was required. After 3 h the mixture was poured into 1 L of water and extracted with two portions of ethyl acetate. The combined organic phases were washed with saturated NaCl solution, dried over $MgSO_4$, and concentrated to a yellow solid, which was recrystallized from 2-propanol/ethyl acetate, providing 10.58 g (73% overall) of fine needles: mp 171.5–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, 1 H, $J_{7,5}$ = 2.4 Hz, H-7), 7.98 (d, 1 H, $J_{5,7}$ = 2.4 Hz, H-5), 7.56 (d, 1 H, $J_{2',6'}$ = 1.8 Hz, H-2′ of benzene ring), 7.49 (d, 1 H, $J_{5',6'}$ = 8.1 Hz, H-5′), 7.27 (dd, 1 H, $J_{6',2'}$ = 1.8 Hz, $J_{6',5'}$ = 8.1 Hz), 5.35 (dd, 1 H, $J_{2,3a}$ = 2.7 Hz, $J_{2,3b}$ = 10.2 Hz, H-2), 3.11 (s, 3 H, CH_3), 2.89–3.08 (complex pattern, 2 H, H-4a,b), 2.31 (complex pattern, 1 H, H-3), 2.05–2.11 (complex pattern, 1 H, H-3); mass spectrum (EI/70 eV), m/z 357, 359 (30, M^+), 322 (60, M – Cl), 198 (100, M – 3,4-dichlorobenzyl), 172 (40, 3,4-dichlorostyrene).

3,4-Dihydro-6-(methylsulfonyl)-2-phenyl-2*H*-pyrano[2,3-*b*]pyridine (1g). By use of the procedure for preparation of **1h**, 3,4-dihydro-6-(methylthio)-2-phenyl-2*H*-pyrano[2,3-*b*]pyridine[5] (1.00 g, 3.9 mmol) was oxidized with 4.78 g (7.8 mmol) of 49.5% $KHSO_5$ to provide, after recrystallization from 2-propanol/ethyl acetate, 0.90 g (80%) of the title compound: mp 188–189 °C; ^{1}H NMR ($CDCl_3$) δ 8.59 (d, 1 H, $J_{7,5}$ = 2 Hz, H-7), 7.84 (d, 1 H, $J_{5,7}$ = 2 Hz, H-5), 7.32 (s, 5 H, phenyl), 5.30 (dd, 1 H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 10 Hz, H-2), 3.05 (s, 3 H, CH_3), 2.7–3.1 (complex pattern, 2 H, H-4a,b), 1.8–2.3 (complex pattern, 2 H, H-3a,b); mass spectrum (EI/70 eV), m/z 289 (60, M^+), 274 (15, M – CH_3), 210 (25, M – SO_2CH_3), 209 (210 – H), 198 (100, M – benzyl).

2-(4-Chlorophenyl)-3,4-dihydro-6-(methylsulfonyl)-2*H*-pyrano[2,3-*b*]pyridine (1j). By use of the procedure for the preparation of **1h**, 2-(4-chlorophenyl)-3,4-dihydro-6-(methylthio)-2*H*-pyrano[2,3-*b*]pyridine[5] (0.26 g, 0.89 mmol) was oxidized with 0.83 g (2.7 mmol) of 49.5% $KHSO_5$ to provide, after recrystallization from 2-propanol/ethyl acetate, 0.24 g (73%) of the title compound: mp 187–189 °C; ^{1}H NMR ($CDCl_3$) δ 8.64 (d, 1 H, $J_{7,5}$ = 2 Hz, H-7), 7.92 (d, 1 H, $J_{5,7}$ = 2 Hz, H-5), 7.33 (s, 4 H, phenyl H), 5.35 (dd, 1 H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 10 Hz, H-2), 3.05 (s, 3 H, CH_3), 2.8–3.2 (complex pattern, 2 H, H-4a,b), 1.9–2.4 (complex pattern, 2 H, H-3a,b); mass spectrum (CI/CH_4), m/z 324 (100, M + 1), 212 (10, M – 4-chlorophenyl).

2-(3,4-Dichlorophenyl)-3,4-dihydro-6-(methylsulfinyl)-2*H*-pyrano[2,3-*b*]pyridine (1i). To a magnetically stirred so-

lution of 1.00 g (3 mmol) of thioether (**1m**) in 25 mL of dichloromethane at −25 °C was added dropwise a solution of 0.55 g (3.2 mmol) of 80–85% *m*-chloroperoxybenzoic acid (Aldrich) in 20 mL of dichloromethane over 5–10 min, keeping the temperature between −20 and −30 °C. A precipitate formed. The mixture was allowed to warm to −5 °C over 2 h; then it was extracted with saturated $NaHCO_3$ solution, then saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo to 1.01 g of pale yellow solid. Recrystallization from ethyl acetate/hexane provided 0.66 g (64%) of cream-colored sulfoxide: mp 159–162 °C; ^1H NMR ($CDCl_3$) δ 8.25 (d, 1 H, $J_{7,5}$ = 2 Hz, H-7), 7.82 (d, 1 H, $J_{5,7}$ = 2 Hz, H-5), 7.50 (d, 1H, $J_{2',6'}$ = 2 Hz, H-2′), 7.45 (d, 1 H, $J_{5',6'}$ = 8 Hz, H-5′), 7.21 (dd, 1 H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 8 Hz, H-6′), 5.21 (dd, 1 H, $J_{2,3a}$ = 3 Hz, $J_{2,3b}$ = 10 Hz, H-2), 2.6–3.1 (complex pattern, 2 H, H-4a,b), 2.75 (s, 3 H, CH_3), 1.8–2.5 (complex pattern, 2 H, H-3a,b); mass spectrum (EI/70 eV), *m/z* 341 (10, M^+), 326 (40, M − CH_3), 167 (100, 326 − 3,4-dichlorobenzyl); IR (KBr) 1045 cm^{-1} (S–O).

6-Bromo-2-(3,4-dichlorophenyl)-4*H*-pyrano[2,3-*b*]pyridine (5). To a solution of 2.88 g (8.0 mmol) of **1c** in 40 mL of THF was added 0.5 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After 1 h at 25 °C, the reaction mixture was partitioned between ethyl acetate and saturated NH_4Cl solution. The ethyl acetate layer was dried over $MgSO_4$ and concentrated to a solid residue. Recrystallization from ethanol provided 2.3 g (80%) of yellow crystals: mp 138–139.5 °C; ^1H NMR ($CDCl_3$) δ 8.12 (d, 1 H, $J_{7,5}$ = 2 Hz, H-7), 7.71 (d, 1 H, $J_{5,7}$ = 2 Hz, H-5), 7.2–7.6 (complex pattern, 3 H, phenyl protons), 5.46 (t, 1 H, $J_{3,4}$ = 4 Hz, H-3), 3.54 (d, 2 H, $J_{4,3}$ = 4 Hz, H-4); mass spectrum (EI/70 eV), *m/z* 355 (M^+), 320 (M − Cl), 210, (M − $C_6H_3Cl_2$).

6-Chloro-2-(3,4-dichlorophenyl)-3,4-dihydro-2-methyl-2*H*-pyrano[2,3-*b*]pyridine (6). To a magnetically stirred solution of 1.92 g (5.6 mmol) of 3-(5-chloro-2-methoxy-3-pyridinyl)-1-(3,4-dichlorophenyl)propan-1-one (**7**)[5] in 55 mL of anhydrous THF at 5 °C under N_2 was added via syringe 2.62 mL of 2.9 M (7.6 mmol) CH_3MgCl/THF over about 10 min. The yellow mixture was allowed to warm to 23 °C, and after 2 h was quenched by careful addition of 20 mL of 0.05 N HCl. The mixture was poured into water and extracted twice with ether. The combined extracts were washed with water, then saturated NaCl solution, then dried over Na_2SO_4. Removal of solvent under vacuum left 1.99 g of a yellow oil that exhibited IR and NMR spectra consistent with alcohol, **8**. A 1.15-g sample of crude **8** (3.2 mmol) was allowed to cyclize under the influence of 48% HBr in acetic acid according to the procedure described for preparation of **4c** to afford 0.67 g of a mixture of **6** and olefinic side products, **9**, which were separated by chromatography on silica gel. Olefin, **9** (0.11 g), was obtained as a colorless oil: NMR ($CDCl_3$) δ 7.90 (d, 1 H, $J_{6,4}$ = 2 Hz, H-6 of pyridine ring), 7.44 (d, 1 H, $J_{4,6}$ = 2 Hz, H-4), 7.1–7.4 (complex pattern, 3 H, phenyl protons), 5.85 (overlapping triplets, J = 10 Hz, olefinic), 3.95 (s, 3 H, OCH_3), 3.42 (d, 2 H, *J* = 10 Hz, CH_2), 2.05 (s, 3 H, CH_3); mass spectrum (EI/70 eV), *m/z* 341 (10, M^+), 326 (10, M − CH_3), 306 (20, M − Cl), 173 (85), 156 (95), 128 (100). Compound **6** (0.24 g) was further purified by preparative TLC (15% ethyl acetate/hexane) of a 0.1-g sample to provide 0.045 g of a white granular solid: mp 83–84 °C; NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 1 H, $J_{7,5}$ = 2.4 Hz, H-7), 7.47 (d, 1 H, $J_{5,7}$ = 2.4 Hz, H-5), 7.38 (d, 1 H, $J_{5',6'}$ = 8.1 Hz, H-5′), 7.32 (d, 1 H, $J_{2',6'}$ = 1.2 Hz, H-2′), 7.21 (dd, $J_{6',2'}$ = 1.2 Hz, $J_{6',5'}$ = 8.1 Hz, H-6′), 2.67–2.74 (complex pattern, 1 H, benzylic), 2.49–2.54 (complex pattern, 1 H, remaining benzylic), 2.33–2.44 (complex pattern, 2 H, CH_2), 1.69 (s, 3 H, CH_3); mass spectrum (EI/70 eV), *m/z* 327 (30, M^+) 312 (10, M − CH_3), 292 (100, M − Cl), 142 (100).

Biology. HeLa cells (GIBCO) were grown and maintained at 36 °C in Corning 75 cm^2 tissue culture flasks (Scientific Products) using Eagles minimum essential medium with Earles Salts (E-MEM, GIBCO) supplemented with a 1% antibiotic stock solution (PSN, GIBCO). Seven to ten percent heat-inactivated fetal calf serum (HIFCS, MA Bioproducts) was added to the medium for cell growth (growth medium), and the concentration was reduced to 1–2% for cell maintenance (maintenance medium). Cell stocks were maintained in liquid N_2.

Rhinovirus type 1A was obtained from B. D. Korant (Dupont) and was propagated in HeLa cells for preparation of stock virus. Rhinovirus type 9 was obtained from the American Type Culture Collection, Rockville, MD (VR489), and rhinovirus type 64 was obtained from J. Gwaltney (University of Virginia School of Medicine).

The CPE and plaque reduction assays were carried out by use of methods previously described.[6] The cell cultures were incubated for 48–72 h at 33 °C. Plaque counts as a percent of compound-free control plaques were plotted against the logarithm of the test compound concentration, and that concentration reducing the plaque count to 50% of control (ID_{50}) was determined by linear regression.

Determination of Compound in Mouse Serum. Test compounds were micronized and suspended in 0.5% hydroxypropyl methylcellulose (Methocel type Mc Premium, vis. 15 cps) by homogenization to a concentration sufficient to give 200 mg/kg of mouse weight in a dose of 0.2 mL. Control animals received compound-free 0.5% Methocel. Groups of 6–8 mice were used and compounds were administered by oral gavage. Test and control animals were exsanguinated by cardiac puncture or by decapitation and the resultant serum stored at −40 °C until assayed. Samples of 1 mL of serum were extracted with 5 mL of benzene and centrifuged. Aliquots (4 mL) of the extracts were evaporated to dryness under N_2. Residues were dissolved in 200 μL of CH_3CN, and aliquots (50 μL) were injected onto a Partisil 10 ODS column and eluted with the appropriate mixture of CH_3CN and water. A variable-wavelength detector was used at the respective λ_{max} of the compound. The chromatographic peak areas were compared to those of external calibration samples prepared in untreated mouse serum. An approximation of the serum concentration of biologically active species (parent plus metabolites, if any) was obtained by multiplying the highest serum dilution factor that inhibited viral cytopathic effect (CPE) by ≥50% by the lowest compound concentration, in the compound control cultures, which inhibited the viral CPE by ≥50%.

Registry No. **1a**, 102830-62-6; **1b**, 102830-63-7; **1c**, 102830-64-8; **1d**, 102830-65-9; **1e**, 102830-66-0; **1f**, 102830-67-1; **1g**, 102830-68-2; **1g** (sulfide) (X = CH_3S, Y = H), 102830-91-1; **1h**, 102830-69-3; **1i**, 102830-70-6; **1j**, 102830-71-7; **1j** (sulfide) (X = CH_3S, Y = 4-Cl), 102830-92-2; **1k**, 102830-72-8; **1l**, 102830-73-9; **1m**, 102830-74-0; **2a**, 102830-75-1; **2b**, 13472-60-1; **3a**, 102830-76-2; **3b**, 102830-77-3; **3c**, 102830-78-4; **3d**, 102830-79-5; **4a**, 102830-80-8; **4b**, 102830-81-9; **4b** (X = Br, Y = 4-CH_3), 102830-89-7; **4b** (X = Br, Y = 4-Cl), 102830-90-0; **4c**, 102830-82-0; **4d**, 102830-83-1; **5**, 102830-84-2; **6**, 102830-85-3; **7**, 102830-86-4; **8**, 102830-87-5; **9**, 102830-88-6; 5-chloro-2-methoxypyridine, 13473-01-3; 2-methoxypyridine, 1628-89-3; (*E*)-3,4-dichlorocinnamaldehyde, 62374-02-1; (*E*)-4-chlorocinnamaldehyde, 49678-02-6; (*E*)-cinnamaldehyde, 104-55-2.