3,4-Dihydro-2-phenyl-2*H*-pyrano[2,3-*b*]pyridines. Novel Aza Analogs of Flavans

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Complementary approaches to the synthesis of the title compounds **1** are described. Metallation of 3,5-dibromo-2-methoxypyridine (**5b**) by bromine/lithium exchange gave selectively the 3-lithio intermediate **6** which was trapped with substituted cinnamaldehydes **7**, providing allylic alcohols **8** in good yields. Methyl ether cleavage and concomitant cyclization occurred on exposure to concentrated hydrobromic acid in hot acetic acid. The resulting 2-phenyl-2*H*-pyrano[2,3-*b*]pyridines were hydrogenated over Raney nickel to the title compounds which had antiviral activity. Alternatively, **1** were synthesized by Heck reaction of appropriately substituted 3-halo-2-methoxypyridines (**5** or **24**) with vinyl carbinol **15** to furnish ketones **16** or **26** which, upon reduction of the carbonyl group, were cyclized directly to **1**.

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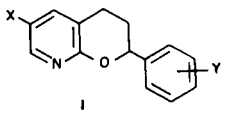
The parent 2*H*-pyrano[2,3-*b*]pyridine ring system as well as several examples of azaflavones and azacoumarins are known [1]. However, 2-phenyl-2*H*-pyrano[2,3-*b*]pyridines **1** appear to be the new to the literature. The antirhinovirus activity of flavan **2** and phenoxypyridine **3** has been noted [2]. We wish to describe several routes to the synthesis of **1**.



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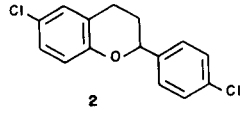

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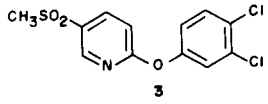

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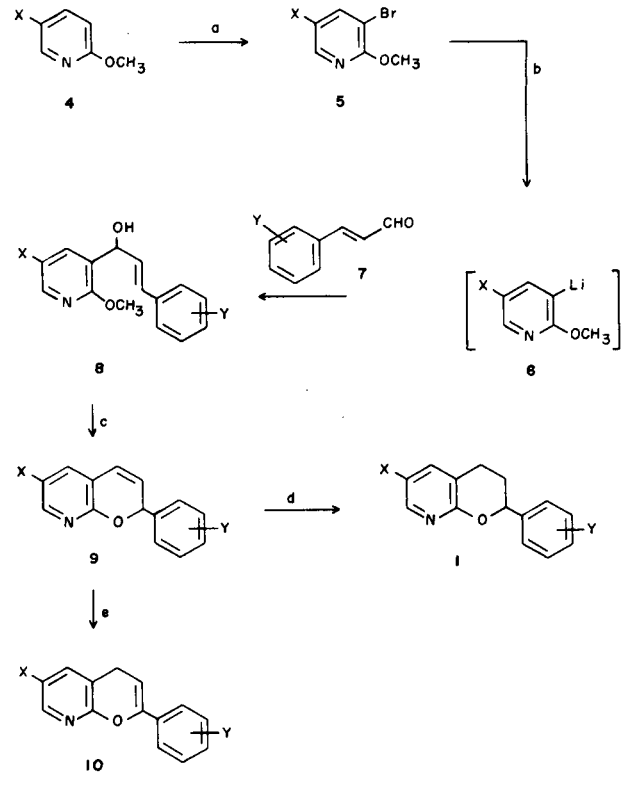
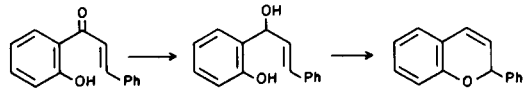
We developed two approaches to this ring system. The first, shown in Scheme I, depended on metallation of an appropriately substituted 3-bromo-2-methoxypyridine **5** to the corresponding 3-lithiopyridine **6**. Bromination of 5-chloro-2-methoxypyridine (**4a**) provided the 3-bromo derivative **5a** in 74% yield. Likewise, bromination of 2-methoxypyridine using an extra equivalent of bromine gave the dibromopyridine **5b** in 71% yield. Bromine-lithium exchange was effected with *n*-butyllithium in ether at −70° and the appropriate cinnamaldehyde **7** was added to afford allylic alcohols **8** in moderate to good yields [3]. In the case of dibromopyridine **5b**, metallation occurred preferentially at the desired 3-position, as demonstrated by water quench of the lithio intermediate and comparison of the product with an authentic sample of 5-bromo-2-methoxypyridine [4]. Allylic alcohols **8** underwent demethylation and cyclization in one pot to 2*H*-pyrano[2,3-*b*]pyridines **9** on brief treatment with 48% hydrobromic acid in hot acetic acid. This mode of cyclization finds analogy in the method used by Clark-Lewis and co-workers for the conversion of 2'-hydroxychalcones to flav-3-enes *via* the allylic alcohol generated by borohydride reduction of the chalcone (Eq. 1) [5]. Isomerization of the double bond of **9d** to give 4*H*-pyrano[2,3-*b*]pyridine **10** was accomplished

Scheme I

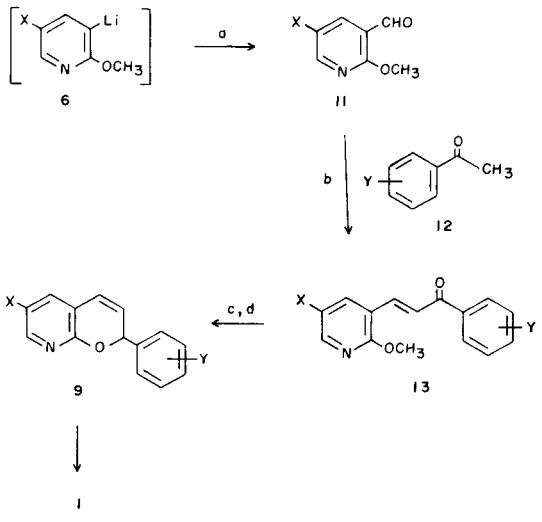


a) Br_2/HOAc/60-80°C. b) n-BuLi/ether/-70°C. c) HBr/HOAc/100°C
d) H_2/Raney Ni. e) DBU/THF/25°C

Eq (1)



Scheme II



a) DMF, then H_3O^+. b) KOH/EtOH. c) $NaBH_4$/THF/EtOH. d) HBr/HOAc/100°C.

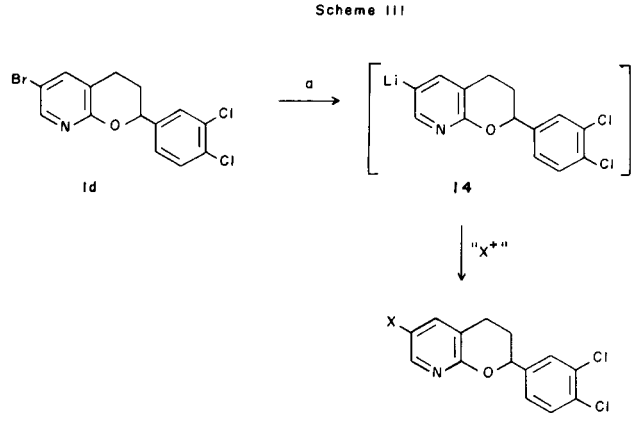
readily with DBU in THF. Catalytic reduction of olefins **9** was achieved with 1 atmosphere of hydrogen over Raney nickel. Other catalysts caused hydrogenolysis of the benzylic ether linkage as well as ring halogen at rates competitive with double bond reduction. Isomer **10** failed to undergo catalytic reduction of the double bond.

A modified approach is illustrated in Scheme II. The 3-lithio intermediate **6** was trapped with DMF and the resulting pyridine-3-carboxaldehyde **11** was allowed to condense with the appropriate acetophenone **12** to furnish enones **13**. Sodium borohydride effected 1,2-reduction of **13**. The resulting allylic alcohols, without purification, were allowed to cyclize under the influence of 48% hydrobromic acid in acetic acid as described above. This mode of cyclization also has precedent in the flavan series [6].

Bromo derivative **1d** proved to be a valuable intermediate (Scheme III). Treatment of **1d** as a dilute solution in toluene/ether at $-100°$ with one equivalent of *t*-butyllithium effected bromine-lithium exchange. The resulting lithio intermediate **14** was trapped with a variety of electrophiles to furnish a series of 6-substituted-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines.

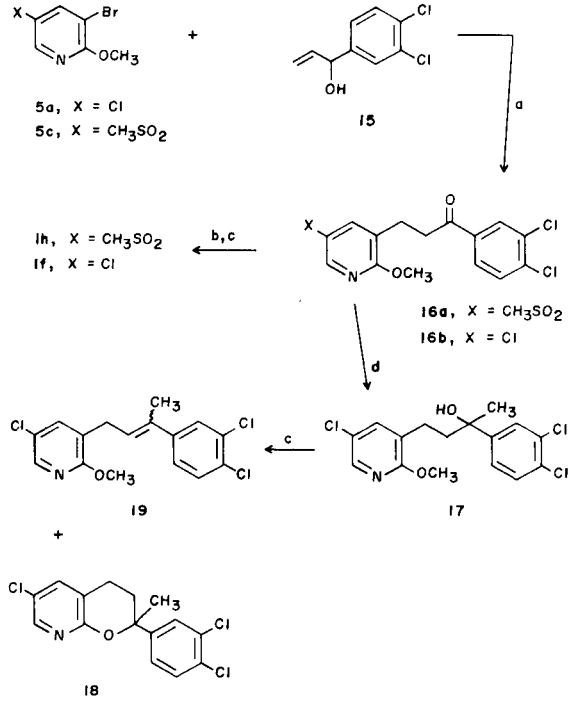
To avoid functional group compatibility problems inherent in organolithium chemistry, we explored a conceptually different route to the 2*H*-pyrano[2,3-*b*]pyridine ring system (Scheme IV). Bromopyridines **5a** and **5c** underwent the Heck reaction [7] with allylic alcohol **15** to furnish ketones **16a** and **16b** in moderate yields, by analogy with the reaction of Yoshida and co-workers [8]. Reduction with sodium borohydride, followed by demethylative cyclization of the corresponding alcohols with 48% hydrobromic acid in hot acetic acid produced the desired 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines directly, thereby avoiding the hydrogenation step of the method of Scheme I. Addition of ketone **16b** to methylmagnesium chloride gave the desired tertiary alcohol **17** which similarly cyclized to provide the angular methyl derivative **18**; however, elimination to olefin **19** also occurred.

Scheme III



a) t-BuLi/Et_2O/$PhCH_3$/−100°C

Scheme IV



a) $NaHCO_3$/$Pd(OAc)_2$(cat.)/DMF/120°C. b) $NaBH_4$/THF/EtOH.
c) 48% HBr/HOAc/100°C d) CH_3MgCl/THF

In an attempt to improve the efficiency of the palladium catalyzed coupling of pyridines with allylic alcohol **15**, we tested the reactivity of a 3-iodopyridine (Scheme V). 3-Iodo-5-nitro-2-pyridone (**20**) [9] gave an intractable mixture in the palladium catalyzed reaction with **15**. To improve solubility, **20** was *N*-methylated to provide **21**. When

Scheme V

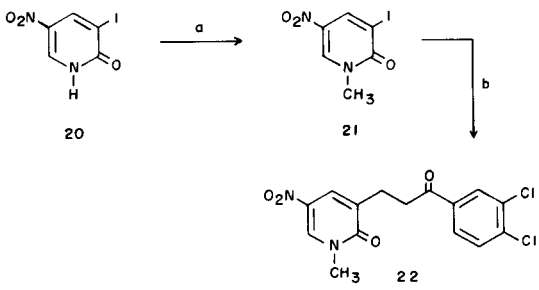


Table I

Physical Data for New Compounds

Compound	X	Y	Yield %	Mp (°C)	Analysis % Calcd./Found C	H	N
1a	Cl	4-Cl	64	109-111	60.02	3.96	5.00
					59.80	3.76	4.94
1b	Br	H	40	109-111	57.91	4.02	4.75
					57.95	4.17	4.83
1c	Br	4-CH_3	37	126-127	59.21	4.65	4.62
					58.88	4.75	4.96
1d	Br	3,4-Cl_2	65	106-109	46.83	2.81	3.90
					46.64	2.84	3.68
1e	Br	4-Cl	61	112.5-114	51.80	3.42	4.32
					51.91	3.21	4.18
1f	Cl	3,4-Cl_2	55	106.5-107.5	53.44	3.21	4.45
					53.29	3.31	4.49
1g	CH_3S	3,4-Cl_2	54	109-111	55.22	4.02	4.29
					55.06	3.99	4.19
1h	CH_3SO_2	3,4-Cl_2	73	171.5-173	50.29	3.66	3.91
					50.12	3.67	3.65
1i	CH_3SO	3,4-Cl_2	64	159-162	52.64	3.83	4.08
					52.85	3.91	4.14
1j	CH_3S	4-Cl	67	103-105	[a]		
1k	CH_3SO_2	4-Cl	73	187-189	55.64	4.36	4.33
					55.45	4.40	4.30
1l	H	3,4-Cl_2	59	99-100	60.02	3.96	5.00
					60.15	3.61	4.96
1m	n-C_4H_9S	3,4-Cl_2	33	59.5-61	58.69	5.20	3.80
					58.59	5.19	3.66
1n	PhCO	3,4-Cl_2	66	155-158	[b]		
1o	CH_3S	H	70	105-107	[b]		
1p	CH_3SO_2	H	80	188-189	61.88	5.42	4.74
					62.27	5.22	4.84
1q	OH	3,4-Cl_2	10	218-219	56.78	3.74	4.73
					56.51	3.97	4.42
4c	CH_3SO_2	—	72	85-86.5	44.91	4.85	7.48
					45.01	4.95	7.61
5a	Cl	—	74	46.5-47.5	32.39	2.27	6.30
					31.35	2.22	6.02
5b	Br	—	71	48-50.5	27.00	1.89	5.25
					27.28	1.87	5.13
5c	CH_3SO_2	—	34	148.5-150.5	31.59	3.03	5.26
					31.64	3.06	5.24
8a	Cl	4-Cl	73	139-139.5 dec	58.08	4.22	4.52
					57.86	4.14	4.25
8b	Cl	3,4-Cl_2	71	134.5-135.5	52.26	3.52	4.06
					51.95	3.49	3.60
8c	Br	3,4-Cl_2	66	149-150	46.31	3.11	3.60
					46.49	3.02	3.51

Table I (continued)

Physical Data for New Compounds

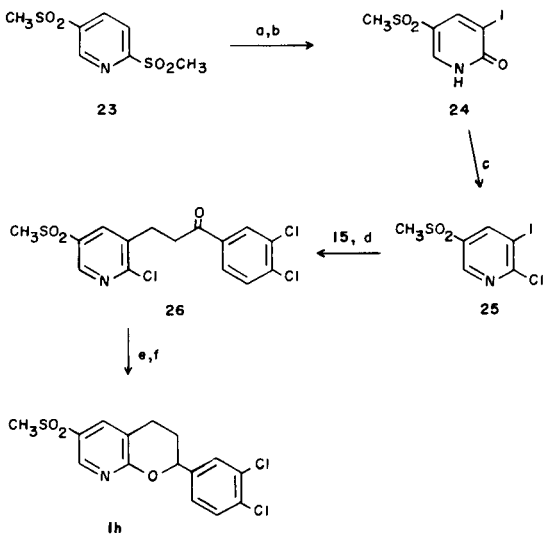
Compound	X	Y	Yield %	Mp (°C)	Analysis % Calcd./Found C	H	N
8d	Br	H	61	92-93	52.26	4.42	4.38
					56.18	4.47	4.21
9a	Cl	4-Cl	80	91.5-93	60.46	3.26	5.04
					60.47	3.08	4.83
9b	Br	H	47	103.5-105	58.36	3.50	4.86
					58.22	3.34	4.77
9c	Br	4-CH_3	27	87-90	59.61	4.01	4.63
					59.30	4.23	4.23
9d	Br	3,4-Cl_2	69	100.5-101.5	47.10	2.26	3.92
					47.19	2.00	3.77
9e	Cl	3,4-Cl_2	83	100-101	53.79	2.58	4.48
					53.59	2.54	4.88
10	Br	3,4-Cl_2	80	138-139.5	47.10	2.26	3.92
					46.82	2.35	4.06
11a	Cl	—	97	93-96	49.00	3.52	8.16
					48.85	3.63	8.06
11b	Br	—	61	92-95	38.92	2.80	6.48
					38.66	2.65	6.37
13a	Br	4-Cl	77	168.5-171.5	51.09	3.14	3.97
					50.89	3.21	3.89
13b	Br	3,4-Cl_2	76	202-203	46.54	2.60	3.62
					46.24	2.51	3.47
13c	Br	4-CH_3	72	143.5-144.5	57.84	4.26	4.22
					57.55	4.31	4.17
13d	Cl	4-Cl	92	163-165	58.46	3.60	4.55
					58.36	3.61	4.37
15	—	—	86	105-110/-0.7 [c]	53.23	3.97	—
					53.17	4.10	—
16a	CH_3SO_2	—	34	145-146	49.49	3.89	3.61
					49.61	3.98	3.65
16b	Cl	—	40	81-82.5	52.28	3.51	4.06
					52.29	3.51	3.84
18	—	—	5	83-84	54.82	3.68	4.26
					54.66	3.78	[d]
21	—	—	55	172-173.5	25.74	1.80	10.00
					25.80	1.87	10.05
22	—	—	78	148-151	50.73	3.41	7.89
					51.09	3.57	7.67
24	—	—	84	273-276 dec	24.10	2.02	4.68
					24.28	2.06	4.80
25	—	—	79	178.5-180.5	22.70	1.59	4.41
					22.66	1.64	4.48
26	—	—	53	128.5-130.5	45.88	3.08	3.57
					45.68	3.00	3.68

[a] Calcd.: C, 61.74; H, 4.84; N, 4.80. Found: C, 61.09; H, 4.67; N, 4.50. Obtained as an intermediate for the synthesis of **1k** and carried on without purification. [b] Not analyzed for C, H, N. [c] Bp/mm Hg. [d] Not determined.

21 was heated in DMF at 120° with alcohol **15**, excess sodium bicarbonate, and 2 mole percent of palladium acetate, the desired ketone **22** was isolated in 78% yield. Unfortunately, all attempts to remove the *N*-methyl group failed and this intermediate was not carried forward.

Encouraged by the use of the iodopyridine, we undertook synthesis of **1h**, cognate of antiviral phenoxypyridine **3**, as illustrated in Scheme VI. 2,5-Bis(methylsulfonyl)pyri-

Scheme VI



a) 20% H_2SO_4/100°C. b) KI/KIO_3/100°C c) $POCl_3$, reflux.
d) i-Pr_2NEt/$Pd(OAc)_2$ (cat.). e) i-Bu_2AlH/CH_2Cl_2/-70°C. f) NaH/DMSO/25°C.

dine (**23**) [10] was converted in 84% yield in one pot to 3-iodo-5-methylsulfonyl-2-pyridone (**24**). Subsequent treatment with phosphorus oxychloride furnished 2-chloro-3-iodo-5-(methylsulfonyl)pyridine (**25**) in 79% yield. The iodopyridine **25** underwent the Heck reaction with allylic alcohol **15** to provide ketone **26** in 53% yield. Ketone **26** was reduced cleanly to the corresponding secondary alcohol with diisobutylaluminium hydride and underwent cyclization, without prior purification, simply by exposure to sodium hydride in DMSO. The desired **1h** was obtained in 79% yield, based on ketone **26**.

Compounds **1a-q** were tested for antirhinovirus activity by the method of plaque reduction in standard cell culture assays. Several analogs were significatnly more potent than 4',6-dichloroflavan **2** and phenoxypyridine **3** when compared in simultaneous experiments. For example, the sulfone **1h** inhibited the virus induced cytopathic effect in HeLa cells by 50% at a median level of 0.06 μg/ml in a series of 17 rhinovirus types. A complete account of the antiviral activity of the 3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridines will be published [11].

In summary, we have described two complementary approaches to the 2-phenyl-2*H*-pyrano[2,3-*b*]pyridine ring system which are suitable for preparing derivatives with a wide variety of substituents. Notable features of the work include selective lithium halogen exchange on 3,5-dibromo-2-methoxypyridine (**5b**), demethylative cyclization of allylic alcohols **8** and extension of the palladium catalyzed coupling of bromopyridine with allylic alcohols, which were first reported by Yoshida and co-workers.

EXPERIMENTAL

The ^1H nmr spectra were obtained on a Perkin Elmer Model R-32 Spectrometer at 90 MHz or on a Varian EM-360 instrument at 60 MHz unless otherwise indicated, and are reported in ppm downfield from tetramethylsilane internal standard (δ). Mass spectra were obtained on a Finnigan 4000 spectrometer interfaced to an Incos 2000 data system. Infrared spectra were recorded on a Beckman Model 4020 instrument. Melting points were taken using a Thomas Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by the Analytical Chemistry Department, Merrell Dow Research Institute, Cincinnati, OH.

5-Chloro-2-methoxypyridine (**4a**) [4].

To a stirred suspension of 14.8 g (0.1 mole) of 2,5-dichloropyridine (Aldrich) in 50 ml of methanol was added 30 ml of a 25% solution of sodium methoxide in methanol and the mixture was heated to reflux under nitrogen. After 24 hours, another 30 ml of the sodium methoxide solution was added and reflux was continued for a total of 68 hours. The precipitated sodium chloride was removed by filtration and the filtrate was concentrated at 1 atmosphere to about ¼ volume and partitioned between ether and water. The aqueous layer was extracted with more ether, and the combined ether layers were washed with saturated sodium chloride solution, dried over potassium carbonate, and concentrated at 1 atmosphere to a pale brown oil. The residue was distilled to yield 10.7 g (75%) of colorless liquid, bp 82-84° at 20 torr; nmr (deuteriochloroform): δ 8.09 (d, 1H, $J_{6,4}$ = 2 Hz, H-6), 7.60 (dd, 1H, $J_{4,6}$ = 2 Hz, $J_{4,3}$ = 9 Hz, H-4), 6.66 (d, 1H, $J_{3,4}$ = 9 Hz, H-3), 3.91 (s, 3H, CH_3); ms (CI/methane): m/z 144 (100, M + 1).

The following was similarly prepared from 2,5-dibromopyridine:

5-Bromo-2-methoxypyridine (**4b**) [4].

This compound was obtained in 80% yield, bp 99-101°/28 torr; nmr (deuteriochloroform): δ 8.15 (d, 1H, $J_{6,4}$ = 3 Hz, H-6), 7.59 (dd, 1H, $J_{4,6}$ = 3 Hz, $J_{4,3}$ = 10 Hz, H-4), 6.62 (d, 1H, $J_{3,4}$ = 10 Hz, H-3), 3.86 (s, 3H, CH_3); ms (CI/methane): m/z 188, 190 (100, M + 1).

3-Bromo-5-chloro-2-methoxypyridine (**5a**).

To a stirred suspension of 2.5 g (0.03 mole) of anhydrous sodium acetate in 10 ml of acetic acid was added 4.32 g (0.03 mole) of 5-chloro-2-methoxypyridine (**4a**), followed by a solution of 3.1 ml (0.06 mole) of bromine in 10 ml of acetic acid. The mixture was warmed to 80° for 6 hours then allowed to cool and stirred at 23° for 64 hours. The mixture was partitioned between ether and water, and the ether layer was washed with 1 *N* sodium hydroxide then with 5% sodium thiosulfate solution, dried over potassium carbonate 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° at 20 torr was collected, affording 5.0 g (74%) of colorless solid, mp 45-47.5°; nmr (deuteriochloroform): δ 8.01 (d, 1H, $J_{6,4}$ = 2 Hz, H-6), 7.77 (d, 1H, $J_{4,6}$ = 2 Hz, H-4), 3.95 (s, 3H, CH_3); ms (CI/methane): m/z 224 (100, M + 1), 222 (80, M + 1), 144 (25, M-Br + 1).

3,5-Dibromo-2-methoxypyridine (**5b**).

To a mechanically stirred solution of 111.35 g (1.0 mole) of 2-methoxypyridine in 500 ml of acetic acid was added 164.1 g (2.0 moles) of anhydrous sodium acetate in portions over about 5 minutes so as to avoid formation of lumps. Then 179.3 ml (3.5 moles) of bromine was added at a rate sufficient to keep the temperature below 35°. Following completion of the bromine addition, the mixture was warmed to 80° for 6 hours, then was stirred at 25° for 16 hours. Some monobrominated product remained, but previous attempts to force the reaction to completion resulted in diminished yields. The mixture was poured into 2 ℓ of water and extracted with two 500 ml portions of carbon tetrachloride. The organic phase was washed with 1 *N* sodium hydroxide, 1 *N* sodium thiosulfate, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to a yellow liquid which solidified on cooling. The crude product was distilled through a short Vigreux column at 3 torr, and after a fore-run consisting

mainly of 5-bromo-2-methoxypyridine, the fraction boiling at 110-112° was collected, yielding 190.4 g (71%) of white solid, mp 49-51°; nmr (deuteriochloroform): δ 8.12 (d, 1H, J = 2 Hz, H-6), 7.90 (d, 1H, J = 2 Hz, H-4), 3.99 (s, 3H, CH_3); ms (CI/methane): m/z 270 (50, M+1), 268 (100, M+1), 266 (50, M+1), 190 (70, M-Br+1), 188 (75, M-Br+1).

(E)-5-Chloro-α-[2-(4-chlorophenyl)ethenyl]-2-methoxy-3-pyridinemethanol (**8a**).

A solution of 4.02 g (0.018 mole) of 3-bromo-5-chloromethoxypyridine in 50 ml of anhydrous ether was cooled to −70° under nitrogen. To the resulting rapidly stirred slurry was added 12.0 ml of 1.65 *M* *n*-butyllithium/hexane (0.0198 mole) dropwise over approximately 5 minutes keeping the temperature below −70°. The reaction became homogeneous. After 15 minutes, a solution of 3.0 g (0.018 mole) of *p*-chlorocinnamaldehyde [12] in 35 ml of ether was added dropwise, keeping the temperature below −60°. Without prior warming, the mixture was poured into saturated sodium bicarbonate solution and extracted with ether. The ether layer was washed with saturated sodium chloride solution, dried over potassium carbonate, and concentrated *in vacuo* to 4.86 g white solid. Recrystallization from ethyl acetate/hexane afforded 3.5 g of white needles, mp 135-139.5° dec. Concentration of the mother liquor provided an additional 0.57 g of product, total yield, 73%; nmr (deuteriochloroform): δ 8.01 (d, 1H, $J_{6,4}$ = 2 Hz, H-6 of pyridine ring), 7.63 (d, 1H, $J_{4,6}$ = 2 Hz, H-4), 7.27 (s, 4H, phenyl ring), 6.65 (d, 1H, J = 15 Hz, olefinic, adjacent to C_6H_4Cl), 6.28 (dd, 1H, J_1 = 15 Hz, J_2 = 6 Hz, olefinic), 5.47 (d, 1H, J = 6 Hz, adjacent to OH), 3.96 (s, 3H, CH_3), 2.6 (broad s, 1H, OH); ms (CI/methane): m/z 312 (50, M+1), 310 (75, M+1), 294 (70, M+1-H_2O), 292 (100, M+1-H_2O), 172 (50, M-*p*-chlorostyrene).

E-5-Chloro-α-[2-(3,4-dichlorophenyl)ethenyl]-2-methoxy-3-pyridinemethanol (**8b**).

This compound was prepared by the same method as that described above; nmr (hexadeuteriodimethylsulfoxide): δ 7.95 (d, 1H, $J_{6,4}$ = 2 Hz, H-6 of pyridine ring), 7.75 (d, 1H, $J_{5,6}$ = 2 Hz, H-4), 7.35 (d, 1H, $J_{2',6'}$ = 2 Hz, H-2′ of benzene ring), 7.30 (d, 1H, $J_{2',6'}$ = 9 Hz, H-5′), 7.15 (dd, 1H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 9 Hz, H-6′), 6.64 (d, 1H, J = 16 Hz, olefinic, adjacent to benzene ring), 6.22 (dd, 1H, J_1 = 8 Hz, J_2 = 16 Hz, remaining olefinic), 5.39 (t, 1H, J = 8 Hz, C*H*-OH), 5.25 (d, 1H, J = 8 Hz, OH), 3.95 (s, 3H, CH_3); ms (CI/methane): m/z 344 (70, M+1), 326 (60, M+1-H_2O), 172 (100, M-3,4-dichlorstyrene).

(E)-5-Bromo-α-[2-(3,4-dichlorophenyl)ethenyl]-2-methoxy-3-pyridinemethanol (**8c**).

A mechanically stirred solution of 60.55 g (0.227 mole) of 3,5-dibromo-2-methoxypyridine in 900 ml of anhydrous ether under nitrogen was cooled to −78° (dry-ice/acetone bath) to give a thick slurry. Efficient stirring was required to prevent the starting material from adhering in a layer to the wall of the reaction flask. While the temperature was kept below −65°, 85.0 ml of 2.67 *M* *n*-butyllithium/hexane (0.227 mole) was added dropwise. The reaction mixture was homogeneous upon completion of the addition. After 15 minutes at −78°, a solution of 45.6 g (0.227 mole) of 3,4-dichlorocinnamaldehyde [13] in 200 ml of anhydrous THF was added dropwise, keeping the temperature below −65°. When the addition was complete, 100 ml of saturated sodium bicarbonate solution was added to the cold reaction mixture. The mixture was allowed to warm to approximately −40°, then was partitioned between ether and saturated sodium bicarbonate solution. The aqueous layer was extracted with more ether and the combined ether layers were washed with saturated sodium chloride, dried over potassium carbonate, filtered, and concentrated to a pale yellow solid which was recrystallized from 2-propanol/ethyl acetate/hexane (1:3:5) to yield 51.34 g colorless crystals. A second crop weighed 5.18 g, total yield, 66%, mp 149-150°; nmr (deuteriochloroform): δ 8.12 (d, 1H, J = 2 Hz, H-6 of pyridine ring), 7.77 (d, 1H, J = 2 Hz, H-4), 7.42 (d, 1H, J = 2 Hz, H-2′ of phenyl ring), 7.38 (d, 1H, J = 10 Hz, H-5′) 7.15 (dd, 1H, J_1 = 2 Hz, J_2 = 10 Hz, H-6′), 6.62 (d, 1H, J = 16 Hz, olefinic adjacent to $C_6H_3Cl_2$), 6.30 (dd, 1H, J_1 = 5 Hz, J_2 = 16 Hz, olefinic), 5.47 (dd, 1H, J_1 = 5 Hz, J_2 = 5 Hz, adjacent to OH), 3.96 (s, 3H, CH_3), 2.64 (d, 1H, J = 5 Hz, OH); ms (CI/methane): m/z 392 (20, M+1), 390 (45, M+1), 388 (30, M+1), 370, 372, 374 (M+1-H_2O), 216, 218 (M-3,4-dichlorostyrene).

E-5-Bromo-α-(2-phenylethenyl)-2-methoxy-3-pyridinen ethanol (**8d**).

This compound was was similarly prepared; nmr (deuteriochloroform): δ 8.01 (d, 1H, $J_{6,4}$ = 3 Hz, H-6), 7.71 (d, 1H, $J_{4,6}$ = 3 Hz, H-4), 7.25 (s, 5H, phenyl), 6.65 (d, 1H, J = 16 Hz, olefinic adjacent to Ph), 6.21 (dd, 1H, J_1 = 7 Hz, J_2 = 16 Hz, remaining olefinic), 5.35 (t, 1H, J = 7 Hz, C*H*-OH), 3.92 (s, 3H, CH_3), 2.72 (d, 1H, J = 7 Hz, OH); ms (CI/methane): 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).

5-Bromo-2-methoxypyridine-3-carboxaldehyde (**11b**).

To a magnetically stirred suspension of 13.55 g (0.05 mole) of 3,5-dibromo-2-methoxypyridine in 200 ml of anhydrous ether at −70° under nitrogen was added dropwise 29.2 ml of 1.71 *M* (0.05 mole) *n*-butyllithium/hexane over about 20 minutes keeping the temperature below −70°. The mixture was stirred for 10 minutes, then a solution of 7.7 ml (0.1 mole) of DMF in 10 ml of ether was added. The temperature rose to −55°, and was allowed to cool again to −70°, then after 15 minutes the mixture was poured into excess 1 *M* hydrochloric acid without prior warming. The mixture was shaken until it came to room temperature, the layers were separated, and the aqueous layer was extracted with more ether. The combined ether layers were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to a pale yellow solid. Recrystallization from hexane afforded 6.6 g (61%) of pale yellow crystals, mp 92-95°. The nmr spectrum showed the presence of the other possible aldehyde isomer (3-bromo-2-methoxy-5-pyridinecarboxaldehyde). By integration of the aldehyde proton signals, the ratio of **11b** to undesired isomer was 12:1; nmr (deuteriochloroform): δ 10.25 (s, 1H, CHO), 8.41 (d, 1H, $J_{6,4}$ = 2 Hz, H-6), 8.16 (dd, 1H, $J_{4,6}$ = 2 Hz, H-4), 4.06 (s, 3H, CH_3); ir (potassium bromide): 1705, 1685 cm^{-1} (aromatic CHO); ms (CI/methane): m/z 217, 215 (M+1).

5-Chloro-2-methoxypyridine-3-carboxaldehyde (**11a**).

This compound was similarly prepared in 97% yield, mp 93-96°; nmr (deuteriochloroform): δ 10.40 (s, 1H, CHO), 8.30 (d, 1H, $J_{6,4}$ = 2 Hz, H-6), 8.00 (d, 1H, $J_{4,6}$ = 2 Hz, H-4), 4.09 (s, 3H, CH_3); ir (potassium bromide): 1715, 1675 cm^{-1} (aromatic CHO); ms (CI/methane): m/z 171 (80, M^+), 142 (100, M-CHO), 114 (50, M-CH_3OCN), 113 (70), 78 (70).

6-Bromo-2-(3,4-dichlorophenyl)-2*H*-pyrano[2,3-*b*]pyridine (**9b**). According to Scheme I.

A mechanically stirred solution of 65.87 g (0.165 mole) of allylic alcohol **8c** in 600 ml of acetic acid was heated to 100° under nitrogen to afford (by tlc, 20% ethyl acetate/hexane) a mixture of allylic acetates and starting material. Then 60 ml of 48% aqueous hydrobromic acid was added all at once and progress of the reaction was monitored by tlc. The temperature was maintained at 95-100°. After no more than 15 minutes, the mixture was cooled rapidly to 20° in an ice-water bath and poured into 2 liters of water. Ether (1 liter) was used to extract the product. The ether layer was washed with three 1000-ml portions of water, then with saturated sodium bicarbonate solution (carefully), then with saturated sodium chloride solution. After drying over magnesium sulfate, the solution was filtered and concentrated *in vacuo* to approximately 60 g of dark yellow solid. The major low r_f impurity was removed by a chromatographic filtration (silica gel) of a dichloromethane solution of the crude product to afford 49.3 g of colorless solid (84%). An analytical sample was obtained by recrystallization from absolute ethanol, mp 100.5-101°; nmr (deuteriochloroform): δ 8.10 (d, 1H, $J_{7,5}$ = 3 Hz, H-7), 7.3-7.7 (complex pattern, 4H, H-5 and phenyl protons), 6.54 (dd, 1H, $J_{4,2}$ = 1 Hz, $J_{4,3}$ = 10 Hz, H-4), 6.15 (dd, 1H, $J_{2,4}$ = 1 Hz, $J_{2,3}$ = 4 Hz, H-2), 5.90 (dd, 1H, $J_{3,2}$ = 4 Hz, $J_{3,4}$ = 10 Hz, H-3); ms (CI/methane): m/z 356, 358, 360 (M+1).

Similarly prepared were the following:

6-Chloro-2-(4-chlorophenyl)-2*H*-pyrano[2,3-*b*]pyridine (**9a**).

This compound had nmr (deuteriochloroform): δ 7.95 (d, 1H, $J_{7,5}$ = 3 Hz, H-7), 7.34 (s, 4H, phenyl protons), 7.30 (d, 1H, $J_{5,7}$ = 3 Hz, H-5), 6.49 (dd, 1H, $J_{4,2}$ = 1 Hz, $J_{4,3}$ = 10 Hz, H-4), 6.15 (dd, 1H, $J_{2,4}$ = 1 Hz, $J_{2,3}$ = 4 Hz, H-2), 5.90 (dd, 1H, $J_{3,2}$ = 4 Hz, $J_{3,4}$ = 10 Hz, H-3); ms (CI/methane): m/z 278 (100, M + 1), 166 (35, M-4-chlorophenyl).

6-Bromo-2-phenyl-2*H*-pyrano[2,3-*b*]pyridine (**9b**).

This compound had nmr (deuteriochloroform): δ 7.95 (d, 1H, $J_{7,5}$ = 3 Hz, H-7), 7.32 (s, 6H, H-5 and phenyl protons), 6.38 (dd, 1H, $J_{4,2}$ = 1 Hz, $J_{4,3}$ = 10 Hz, H-4), 6.12 (dd, 1H, $J_{2,4}$ = 1 Hz, $J_{2,3}$ = 4 Hz, H-2), 5.85 (dd 1H, $J_{3,2}$ = 4 Hz, $J_{3,4}$ = 10 Hz, H-3); ms (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-Chloro-2-(3,4-dichlorophenyl)-2*H*-pyrano[2,3-*b*]pyridine (**9e**).

This compound had nmr (deuteriochloroform): δ 7.95 (d, 1H, $J_{7,5}$ = 3 Hz, H-7), 7.45 (d, 1H, $J_{5,7}$ = 3 Hz, H-5), 7.1-7.4 (complex pattern, 3H, phenyl ring), 6.45 (dd, 1H, $J_{4,2}$ = 1 Hz, $J_{4,3}$ = 10 Hz, H-4), 6.15 (dd, 1H, $J_{2,4}$ = 1 Hz, $J_{2,3}$ = 4 Hz, H-2), 5.90 (dd, 1H, $J_{3,4}$ = 4 Hz, $J_{3,4}$ = 10 Hz, H-3); ms (EI/70 eV): m/z 311 (40, M^+), 279 (50, M-Cl), 166 (100, M-3,4-dichlorophenyl).

(E)-3-(5-Bromo-2-methoxy-3-pyridinyl)-1-(4-chlorophenyl)-2-propen-1-one (**13a**).

To a solution under nitrogen of 6.5 g (0.03 mole) of 5-bromo-2-methoxypyridine-3-carboxaldehyde in 30 ml of THF was added 100 ml of methanol, followed by 4.64 g (0.03 mole) of 4-chloroacetophenone. Then a solution of 6.6 g of 85% potassium hydroxide (0.1 mole) in 15 ml of water was added. The mixture warmed, became yellow, and deposited a thick precipitate. The mixture was stirred mechanically until it returned to 25° (about 1.5 hours), then was cooled in an ice bath and neutralized by addition of 20 ml of 5*N* hydrochloric acid in small portions. The pasty reaction mixture was poured into 400 ml of water, acidified to *p*H 1 with 1 *N* hydrochloric acid, and filtered. The damp product was boiled with 2-propanol/ethyl acetate (3:1), cooled, and filtered. The filter cake was dried *in vacuo* to afford 8.14 g (77%) of pale yellow solid, mp 168.5-171.5°; nmr (trifluoroacetic acid): δ 8.78 (d, 1H, $J_{6,4}$ = 2 Hz, H-6 of pyridine ring), 8.40 (d, 1H, $J_{4,6}$ = 2 Hz, H-4), 8.05 (d, 2H, J = 9 Hz, H-2′ of phenyl ring), 7.93 (s, 2H, olefinic), 7.60 (d, 2H, J = 9 Hz, H-3′), 4.55 (s, 3H, CH_3); ms (CI/methane): m/z 352, 354, 356 (M + 1); ir (potassium bromide): 1670 (C=O), 1615 (C=C) cm^{-1}.

Similarly prepared were the following:

(E)-3-(5-Bromo-2-methoxy-3-pyridinyl)-1-(3,4-dichlorophenyl)-2-propen-1-one (**13b**).

This compound had nmr (hexadeuteriodimethylsulfoxide): δ 8.62 (d, 1H, $J_{6,4}$ = 3 Hz, H-6 of pyridine ring), 8.31 (d, 1H, $J_{4,6}$ = 3 Hz, H-4), 8.28 (d, 1H, $J_{2',6'}$ = 2 Hz, H-2′ of benzene ring), 8.09 (dd, 1H, $J_{6',5'}$ = 9 Hz, H-6′), 7.91 (d, 2H, J = 9 Hz, olefinic), 7.75 (d, 1H, $J_{5',6'}$ = 9 Hz, H-5′), 3.93 (s, 3H, CH_3); ms (CI/methane): m/z 386, 388 (100, M + 1).

(E)-3-(5-Bromo-2-methoxy-3-pyridinyl)-1-(4-methylphenyl)-2-propen-1-one (**13c**).

This compound had nmr (trifluoroacetic acid): δ 8.13 (d, 1H, $J_{6,4}$ = 3 Hz, H-6 of pyridine ring), 7.87 (d, 2H, J = 10 Hz, H-2′ and H-6′ of benzene ring), 7.84 (d, 1H, $J_{4,6}$ = 3 Hz, H-4), 7.65 (d, J = 2 Hz, 2H, olefinic), 7.20 (d, 2H, J = 10 Hz, H-3′ and H-5′), 3.99 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3); ms (CI/methane): m/z 332, 334 (100, M + 1); ir (potassium bromide): 1660 (C=O), 1615 (C=C) cm^{-1}.

(E)-3-(5-Chloro-2-methoxy-3-pyridinyl)-1-(4-chlorophenyl)-2-propen-1-one (**13d**).

This compound had nmr (trifluoroacetic acid): δ 8.69 (d, 1H, $J_{6,4}$ = 2 Hz, H-6 of pyridine ring), 8.33 (d, 1H, $J_{4,6}$ = 2 Hz, H-4), 8.05 (d, 2H, J = 9 Hz, H-2′ of benzene ring), 7.95 (s, 2H, olefinic), 7.60 (d, 2H, J = 9 Hz, H-3′) 4.57 (s, 3H, CH_3); ms (CI/methane): m/z 308 (100, M + 1), 196 (50, M-4-chlorophenyl), 139 (50, 4-chlorobenzoyl); ir (potassium bromide): 1670 (C=O), 1615 (C=C) cm^{-1}.

6-Bromo-2-(3,4-dichlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (**1d**).

To a solution of 49.3 g of **9d** in 220 ml of anhydrous THF was added 550 ml of absolute ethanol. The flask was flushed with nitrogen, and 60.4 g of an aqueous slurry of W-2 Raney Nickel (Aldrich) was added. The rapidly stirred mixture was placed under a hydrogen atmosphere for a total of 6 hours. Progress of the reaction was monitored by color spot test because the starting material and product fail to separate by tlc. Aliquots periodically withdrawn by syringe were spotted on a tlc plate and developed in 15% ethyl acetate/hexane. The plate was dipped into a 1% solution of *p*-toluenesulfonic acid in ethanol, wiped dry, and heated on a hot plate for a few minutes. The olefinic starting material produced a dark yellow-brown spot. When the color spot test gave only a faint yellow discoloration, the reaction was judged complete. The hydrogen atmosphere was replaced by nitrogen and the catalyst was filtered off through a pad of celite, washing thoroughly with dichloromethane taking care to keep the nickel 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 (21.3 g). The mother liquor was concentrated and flash chromatographed (silica gel, dichloromethane) to afford an additional 8.10 g of product. Combined yield: 29.4 g (59%). An analytical sample was obtained by recrystallization from ethanol, mp 106-109°; nmr (deuteriochloroform): δ 8.16 (d, 1H, $J_{7,5}$ = 3 Hz, H-7), 7.55 (overlapping doublets, 2H, H-5 and H-2 of benzene ring), 7.35 (d, 1H, $J_{5',6'}$ = 8 Hz, H-5′), 7.24 (dd, 1H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 8 Hz, H-6′), 5.20 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 9 Hz, H-2), 2.7-3.1 (complex pattern, 2H, H-4), 1.7-2.3 (complex pattern, 2H, H-3); ms (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^+).

Similarly prepared were the following compounds:

6-Chloro-2-(4-chlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (**1a**).

This compound had nmr (deuteriochloroform): δ 8.04 (d, 1H, $J_{7,5}$ = 3 Hz, H-7), 7.35 (d, 1H, $J_{5,7}$ = 3 Hz, H-5), 7.32 (s, 4H, phenyl protons), 5.21 (dd, 1H, $J_{2,3}$ = 4 Hz, $J_{2,3}$ = 9 Hz, H-2), 2.7-3.0 (complex pattern, 2H, H-4), 1.8-2.4 (complex pattern, 2H, H-3); ms (CI/methane): 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**).

This compound had nmr (deuteriochloroform): δ 8.08 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.44 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.31 (s, 5H, phenyl), 5.22 (dd, 1H, $J_{2,3}$ = 9 Hz, $J_{2,3}$ = 3 Hz, H-2), 2.8-3.0 (complex pattern, 2H, H-4), 1.8-2.3 (complex pattern, 2H, H-3); ms (CI/methane): m/z 290, 292 (100, M + 1), 212, 214 (30, M-Ph), 186 (20, M-styrene), 117 (65, PhCH=CH-CH_2^+).

6-Bromo-3,4-dihydro-2-(4-methylphenyl)-2*H*-pyrano[2,3-*b*]pyridine (**1c**).

This compound had nmr (deuteriochloroform): δ 8.12 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.44 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.20 (distorted dd, 4H, phenyl protons), 5.21 ((dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 9 Hz, H-2), 2.7-3.0 (complex pattern, 2H, H-4), 2.35 (s, 3H, CH_3), 1.9-2.3 (complex pattern, 2H, H-3); ms (CI/methane): 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 (**1e**).

This compound had nmr (deuteriochloroform): δ 8.12 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.49 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.36 (s, 4H, phenyl protons), 5.18 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 10 Hz, H-2), 2.8-3.0 (complex pattern, 2H, H-4), 1.7-2.2 (complex pattern, 2H, H-3); ms (CI/methane): m/z 324, 326 (100, M + 1), 246 (55, M-Br), 212, 214 (M-*p*-chlorophenyl).

6-Chloro-2-(3,4-dichlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (**1f**).

This compound had nmr (deuteriochloroform): δ 7.90 (d, 1H, $J_{7,5}$ = 3 Hz, H-7), 7.40 (overlapping doublets, 2H, H-5 and H-2′ of benzene ring),

7.20 (d, 1H, $J_{5',6'}$ = 8 Hz, H-5'), 7.05 (dd, 1H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 8 Hz, H-6'), 5.05 (dd, 1H, $J_{2,3}$ = 4 Hz, $J_{2,3}$ = 10 Hz, H-2), 2.6-3.1 (complex pattern, 2H, H-4), 1.5-2.4 (complex pattern, 2H, H-3); ms (EI/70 eV): m/z 313, 315 (M^+), 278, 280 (M-Cl), 172, 174 (3,4-dichlorostyrene), 154, 156 (100, M-3,4-dichlorostyrene).

Preparation of 6-Bromo-2-(3,4-dichlorophenyl)-2*H*-pyrano[2,3-*b*]pyridine (**9d**) According to Scheme II.

To a stirred suspension of 30.0 g (0.077 mole) of chalcone **13b** in 275 ml of THF and 260 ml of absolute ethanol was added 6.0 g (0.155 mole) of sodium borohydride. After 1 hour under nitrogen, the reaction mixture was partitioned between 1 *N* sodium hydroxide and ether. The ether layer was washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated *in vacuo* to 29.8 g of pale yellow oil. To a stirred solution of 25.9 g (0.665 mole) of the crude alcohol in 400 ml of acetic acid under nitrogen was added 25 ml of 48% aqueous hydrobromic acid. The mixture was heated to 85° for about 30 minutes, then was cooled rapidly to 23° in an ice-bath, and partitioned between water and ether. The ether layer was washed several times with water, then successively with saturated sodium bicarbonate and sodium chloride solutions. After drying over sodium sulfate evaporation *in vacuo* afforded 21.9 g of a pale yellow oil. Chromatographic filtration through a layer of silica gel using chloroform as eluent provided 15.6 g (66%) of a pale yellow solid, exhibiting the same characteristics as material prepared *via* Scheme I.

Similarly prepared was the following compound:

6-Bromo-2-(4-methylphenyl)-2*H*-pyrano[2,3-*b*]pyridine (**9c**).

This compound had nmr (300 MHz, deuteriochloroform): δ 8.04 (d, 1H, $J_{7,5}$ = 2.4 Hz, H-7), 7.40 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 7.30 (d, 2H, J = 7.8 Hz, H-2' and H-6'), 7.17 (d, 2H, J = 7.8 Hz, H-3' and H-5'), 6.46 (dd, 1H, $J_{4,2}$ = 1.8 Hz, $J_{4,3}$ = 9.9 Hz, H-4), 6.16 (dd, 1H, $J_{2,4}$ = 1.8 Hz, $J_{2,3}$ = 3.6 Hz, H-2), 5.93 (dd, 1H, $J_{3,2}$ = 3.6 Hz, $J_{3,4}$ = 9.9 Hz), 2.34 (s, 3H, CH_3); ms (EI/70 eV): m/z 301 (100, M^+), 286, 288 (70, M-CH_3).

6-Bromo-2-(3,4-dichlorophenyl)-4*H*-pyrano[2,3-*b*]pyridine (**10**).

To a solution of 2.88 g (0.008 mole) of 6-bromo-2-(3,4-dichlorophenyl)-2*H*-pyrano[2,3-*b*]pyridine (**9d**) in 40 ml of THF was added 0.5 ml of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). After 1 hour at 25°, the reaction mixture was partitioned between ethyl acetate and saturated ammonium chloride solution. The ethyl acetate layer was dried over magnesium sulfate and concentrated to a solid residue. Recrystallization from ethanol provided 2.3 g (80%) of yellow crystals, mp 138-139.5°; nmr (deuteriochloroform): δ 8.12 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.71 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.2-7.6 (complex pattern, 3H, phenyl protons), 5.46 (t, 1H, $J_{3,4}$ = 4 Hz, H-3), 3.54 (d, 2H, $J_{4,3}$ = 4 Hz, H-4); ms (EI/70 eV): m/z 355 (M^+), 320 (M-Cl), 210 (M-$C_6H_3Cl_2$).

3-Bromo-2-methoxy-5-(methylsulfonyl)pyridine (**5c**).

To a rapidly stirred suspension of 23.5 g (0.1 mole) of 2,5-bis(methylsulfonyl)pyridine [10] in 200 ml of methanol under nitrogen was added 24 ml of 25% sodium methoxide in methanol (Aldrich). The mixture was warmed to 50° for 20 minutes to give a homogeneous black solution. The solvent was removed by rotary evaporation and the resulting slurry was partitioned between ethyl acetate and water. The ethyl acetate layer was washed with saturated sodium chloride solution and dried over magnesium sulfate. Carbon was added, the mixture was swirled for a few minutes, then filtered through celite to give a pale yellow filtrate. Concentration *in vacuo* provided a pale yellow oil which solidified on cooling. Recrystallization from 2-propanol yielded 13.4 g of colorless crystals (72%), mp 85-86.5°; nmr (deuteriochloroform): δ 8.65 (d, 1H, $J_{6,4}$ = 3 Hz, H-6), 7.99 (dd, 1H, $J_{4,6}$ = 3 Hz, H-4), 6.85 (d, 1H, $J_{3,4}$ = 9 Hz, H-3), 4.00 (s, 3H, OCH_3), 3.08 (s, 3H, SO_2CH_3); ms (EI/70 eV): m/z 187 (100, M^+), 172 (10, M-CH_3), 157 (30, M-CH_2O), 124 (M-$SOCH_3$), 188 (50, M-SO_2CH_3).

The resulting 2-methoxy-5-(methylsulfonyl)pyridine (**4c**) was brominated by the same procedure used for preparation of 3-bromo-5-chloro-2-methoxypyridine (**4a**); nmr (deuteriochloroform): δ 8.65 (d, 1H, $J_{6,4}$ = 3 Hz, H-6), 8.30 (d, 1H, $J_{4,6}$ = 3 Hz, H-4), 4.12 (s, 3H, OCH_3), 3.10 (s, 3H, SO_2CH_3); ms (EI/70 eV): m/z 265, 267 (100, M^+), 264 (75, M-H), 236, 238 (55, M-CHO), 235 (25, M-CH_2O), 186 (45, M-SO_2CH_3).

3,4-Dichloro-α-ethenylbenzenemethanol (**15**).

This compound was prepared using the general method of Kuivila and coworkers [14], bp 105-110° (0.7 torr); nmr (deuteriochloroform): δ 7.47 (d, 1H, $J_{2,6}$ = 1 Hz, H-2 of benzene ring), 7.41 (d, 1H, $J_{5,6}$ = 8 Hz, H-5), 7.20 (dd, 1H, $J_{6,5}$ = 8 Hz, $J_{6,2}$ = 1 Hz, H-6), 5.96 (complex pattern, 1H, olefinic proton), 5.1-5.4 (complex pattern, 3H, ArCH and terminal olefinic protons), 2.16 (s, 1H, OH); ir (sodium chloride plates, neat): 3450 cm^{-1} (OH); ms (CI/methane): m/z 185 (100, M + 1).

3-[2-Methoxy-5-(methylsulfonyl)-3-pyridinyl]-1-(3,4-dichlorophenyl)-propan-1-one (**16a**).

A mixture consisting of 2.67 g (0.010 mole) of 3-bromo-2-methoxy-5-(methylsulfonyl)pyridine, 3.05 g of α-ethenyl-3,4-dichlorobenzenemethanol (**15**) (0.015 mole), 1.26 g (0.015 mole) of sodium bicarbonate, 10 ml of DMF, and 0.112 g (0.0005 mole) of palladium acetate was placed under nitrogen and heated to 120° with magnetic stirring. After 6 hours, tlc (2:1 hexane/ethyl acetate) showed no remaining bromopyridine. The mixture was cooled, diluted with ethyl acetate, and filtered through celite. The ethyl acetate solution was washed with water, then twice with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to a black oil. The excess alcohol was removed by Kugelrohr distillation (120°, 0.05 torr). The glassy pot residue was taken up in dichloromethane and chromatographed on silica gel (25% ethyl acetate/hexane) to yield 1.5 g of pale yellow solid as the major fraction. Recrystallization from ethanol/ethyl acetate provided an analytical sample, 1.32 g (34%) mp 145-146°; nmr (300 MHz, deuteriochloroform): δ 8.61 (d, 1H, $J_{6,4}$ = 2.4 Hz, H-6 of pyridine ring), 8.04 (d, 1H, $J_{2',6'}$ = 1.8 Hz, H-2' of benzene ring), 7.96 (d, 1H, $J_{4,6}$ = 2.4 Hz, H-4), 7.78 (dd, 1H, $J_{6',2'}$ = 1.8 Hz, $J_{6',5'}$ = 8.1 Hz, H-6'), 7.56 (d, 1H, $J_{5',6'}$ = 8.1 Hz, H-5'), 4.07 (s, 3H, OCH_3), 3.27 (t, 2H, J = 7.5 Hz, -CH_2CO-), 3.08 (s, 3H, CH_3SO_2-), 3.06 (t, 2H, J = 7.5 Hz, remaining CH_2); ms (CI/methane): m/z 388, 390 (100, M + 1), 354 (10, M-Cl); ir (potassium bromide): 1693 cm^{-1} (C=O).

3-(5-Chloro-2-methoxy-3-pyridinyl)-1-(3,4-dichlorophenyl)propan-1-one (**16b**).

This compound was prepared similarly, 40% yield, mp 81-82.5°; nmr (300 MHz, deuteriochloroform): δ 8.04 (d, 1H, $J_{6,4}$ = 2.1 Hz, H-6 of pyridine ring), 7.98 (d, 1H, $J_{2',6'}$ = 1.8 Hz, H-2' of benzene ring), 7.77 (dd, 1H, $J_{6',2'}$ = 1.8 Hz, $J_{6',5'}$ = 5.7 Hz, H-6'), 7.55 (d, 1H, $J_{5',6'}$ = 5.7 Hz, H-5'), 7.47 (d, 1H, $J_{4,6}$ = 2.1 Hz, H-4 of pyridine ring), 3.95 (s, 3H, OCH_3), 3.23 (t, 2H, J = 7.2 Hz, -CH_2CO-), 2.96 (t, 2H, J = 7.2 Hz, remaining CH_2); ms (EI/70 eV): m/z 343, 345 (10, M^+), 175 (60), 173 (100), 170 (70), 156 (30), 145 (40); ir (potassium bromide): 1680 cm^{-1} (C=O).

Preparation of 6-Chloro-2-(3,4-dichlorophenyl)-3,4-dihydro-2*H*-pyrano-[2,3-*b*]pyridine (**1f**) According to Scheme IV.

A solution of 0.35 (0.001 mole) of the ketone 3-(5-chloro-2-methoxy-3-pyridinyl)-1-(3,4-dichlorophenyl)propan-1-one in 4 ml of THF was added to a rapidly stirred suspension of 0.05 g (0.0013 mole) of sodium borohydride in 4 ml of absolute ethanol After 5 minutes tlc (2:1 hexane/ethyl acetate) showed complete conversion to a lower r_f material. The reaction mixture was partitioned between ether and water and the ether was washed with saturated sodium chloride, dried over potassium carbonate, and concentrated to 0.39 g of colorless oil which later solidified; ir (potassium bromide): 3390 cm^{-1} (broad band, -OH); ms (CI/methane): m/z 346, 348 (60, M + 1), 328, 330 (20, M-H_2O), 156 (100, 3,4-dichlorobenzyl).

A solution of the resulting crude alcohol (0.32 g, 0.0009 mole) in 4 ml of acetic acid was heated at 100° (oil bath) under nitrogen. The tlc (2:1 hexane/ethyl acetate) showed no change. Then 0.5 ml of 48% aqueous hydrobromic acid (0.003 mole) was added and heating was continued for 3 hours. The cooled reaction mixture was partitioned between ether and water, and the ether layer was twice extracted wtih saturated sodium bicarbonate solution, then dried over magnesium sulfate and concentrated to 0.21 g of colorless oil which later solidified. Preparative tlc (25% ethyl acetate/hexane) gave a major high r_f band which provided 0.17 g (60% yield overall) of colorless solid, identical in all respects with compound prepared according to Scheme I.

2-(3,4-Dichlorophenyl)-3,4-dihydro-6-(methylsulfonyl)-2*H*-pyrano[2,3-*b*]-pyridine (**1h**).

This compound was similarly prepared according to Scheme IV; nmr (300 MHz, deuteriochloroform): δ 8.70 (d, 1H, $J_{7,5}$ = 2.4 Hz, H-7), 7.98 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 7.56 (d, 1H, $J_{2',6'}$ = 1.8 Hz, H-2' of benzene ring), 7.49 (d, 1H, $J_{5',6'}$ = 8.1 Hz, H-5'), 7.27 (d, 1H, $J_{6',2'}$ = 1.8 Hz, $J_{6',5'}$ = 8.1 Hz), 5.35 (dd, 1H, $J_{2,3}$ = 2.7 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 3.11 (s, 3H, CH_3), 2.89-3.08 (complex pattern, 2H, H-4), 2.31 (complex pattern, 1H, H-3), 2.05-2.11 (complex pattern, 1H, H-3); ms (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-Iodo-1-methyl-5-nitro-2(1*H*)-pyridinone (**21**).

To a magnetically stirred suspension of 1.68 g (35 mmoles) of a 50% oil dispersion of sodium hydride (previously freed of oil by washing with hexane) in 100 ml of DMF under nitrogen was added 7.98 g (30 mmoles) of 3-iodo-5-nitro-2(1*H*)-pyridinone (**20**) [9] in portions. When the effervescence subsided, 2.2 ml (35 mmoles) of iodomethane was added. The mixture warmed slightly. After 20 minutes the mixture was quenched by careful addition of water, then was partitioned between ethyl acetate and water. The ethyl acetate layer was washed twice with water, then twice with saturated sodium chloride solution, then was dried over magnesium sulfate, filtered, and concentrated to 6.3 g of a pale yellow solid. Recrystallization from ethanol/ethyl acetate provided 4.6 g of pale yellow crystals, mp 172-173.5°; nmr (300 MHz, hexadeuteriodimethylsulfoxide): δ 9.26 (d, 1H, $J_{6,4}$ = 1 Hz, H-6), 8.70 (d, 1H, $J_{4,6}$ = 1 Hz, H-4), 3.61 (s, 3H, CH_3); ir (potassium bromide): 1665 cm^{-1} (C=O); ms (EI/70 eV): m/z 280 (100, M⁺).

3-[3-(3,4-Dichlorophenyl)-3-oxopropyl-1-methyl-5-nitro]-2(1*H*)-pyridinone (**22**).

A mixture of 2.24 g (8 mmoles) of pyridinone **21**, 2.44 g (12 mmoles) of allylic alcohol **15**, 1.34 g (16 mmoles) of sodium bicarbonate, 0.04 g (about 2 mole percent) of palladium acetate, and 11 ml of DMF was placed under nitrogen and warmed to 110° for 5.5 hours. The cooled reaction mixture was diluted with ethyl acetate, filtered through celite and extracted twice with water and twice with saturated sodium chloride solution, then was dried over magnesium sulfate, filtered, and concentrated to a black oil which solidified on cooling. Flash chromatography (silica gel, 1:1 ethyl acetate/hexane) gave 2.22 g of pure product (78%). An analytical sample was prepared by recrystallization from ethanol/ethyl acetate, mp 148-151°; nmr (300 MHz, deuteriochloroform): δ 8.55 (d, 1H, $J_{6,4}$ = 1 Hz, H-6 of pyridine ring), 8.12 (d, 1H, $J_{2',6'}$ = 1 Hz, H-2' of benzene ring), 8.04 (d, 1H, $J_{4,6}$ = 1 Hz, H-4), 7.79 (dd, 1H, $J_{6',5'}$ = 6 Hz, $J_{6',2'}$ = 1 Hz, H-6'), 7.54 (d, 1H, $J_{5',6'}$ = 6 Hz, H-5'), 3.67 (s, 3H, CH_3), 3.32 (t, 2H, J = 7 Hz, CH_2CO), 3.01 (t, 2H, J = 7 Hz, remaining CH_2); ir (potassium bromide): 1685 cm^{-1} (C=O); ms (CI/methane): m/z 355 (100, M + 1).

3-Iodo-5-(methylsulfonyl)-2(1*H*)-pyridinone (**24**).

A suspension of 11.75 g (0.05 mole) of 2,5-bis(methylsulfonyl)pyridine [10] in 100 ml of 20% sulfuric acid was refluxed for 2.5 hours. Tlc (10% methanol/dichloromethane) showed complete conversion to the corresponding 2-pyridinone. Then 14.9 g (0.07 mole) of potassium iodate was added carefully to the rapidly stirred reaction mixture, maintaining the temperature at 90-100°. Iodine was liberated in an exothermic reaction. After 0.5 hour, 8.0 g (0.05 mole) of potassium iodide in 20 ml of water was added dropwise over 1.5 hours. A thick precipitate developed during the potassium iodide addition. The mixture was allowed to cool to 25°, then was diluted to 200 ml with water and filtered. The collected precipitate was washed sequentially with water, then with 5% sodium bisulfite solution, more water, and twice with anhydrous ethanol. Drying *in vacuo* left 12.57 g (84% yield) of pale brown crystals, mp 273-276° dec; nmr (300 MHz, deuteriochloroform + trifluoroacetic acid): δ 8.57 (d, 1H, $J_{6,4}$ = 2.4 Hz, H-6), 8.31 (d, 1H, $J_{4,6}$ = 2.4 Hz, H-4), 3.23 (s, 3H, CH_3); ms (EI/70 eV): m/z 299 (25, M⁺), 284 (10, M-CH_3), 236 (10, M-$SOCH_3$), 220 (20, M-SO_2CH_3), 208 (10, 236-CO), 192 (45, 220-CO), 165 (40, 192-HCN), 127 (15, I⁺), 93 (80, 220-I), 65 (100, 93-CO); ir (potassium bromide): 1640 cm^{-1} (N-C=O).

2-Chloro-3-iodo-5-(methylsulfonyl)pyridine (**25**).

A suspension of 8.97 g (0.030 mole) of 3-iodo-5-(methylsulfonyl)-2(1*H*)-pyridinone (**24**) in 30 ml of phosphorus oxychloride was refluxed under nitrogen for 4 hours. The mixture became homogeneous. The reaction mixture solidified on cooling. Unreacted phosphorus oxychloride was removed on rotary evaporation and the white solid residue was taken up in dichloromethane and extracted with water (carefully), then twice with 1*N* sodium hydroxide. The mixture was shaken until the aqueous phase remained basic. The dichloromethane solution was dried over magnesium sulfate and concentrated to a white solid residue. Recrystallization from ethyl acetate/hexane provided 5.28 g of colorless needles, mp 178.5-180.5°. The mother liquor was concentrated to dryness *in vacuo* and the residue was recrystallized from ethanol/ethyl acetate to provide another 2.20 g of product, total yield, 7.48 g (79%); nmr (300 MHz, deuteriochloroform): δ 8.88 (d, 1H, $J_{6,4}$ = 2.4 Hz, H-6), 8.63 (d, 1H, $J_{4,6}$ = 2.4 Hz, H-4), 3.14 (s, 3H, CH_3); ms (EI/70 eV): m/z 317 (50, M⁺), 302 (15, M-CH_3), 225 (10, M-CH_2SO), 238 (50, M-SO_2CH_3), 226 (35, 255-CHO), 127 (20, I⁺), 111 (100, 238-I).

3-[2-Chloro-5-(methylsulfonyl)-3-pyridinyl]-1-(3,4-dichlorophenyl)propan-1-one (**26**).

A mixture consisting of 0.95 g (0.003 mole) of 2-chloro-3-iodo-5-(methylsulfonyl)pyridine (**25**), 0.91 g (0.0045 mole) of α-ethenyl-3,4-dichlorobenzenemethanol (**15**), 0.77 g (0.006 mole) of *N,N*-diisopropylethylamine, 0.04 g (0.00012 mole) of tri-*o*-tolylphosphine, 0.02 g (0.00006 mole) of palladium acetate and 3 ml of DMF was placed under nitrogen and heated to 100° (oil bath). After 20 minutes, tlc (1:1 ethyl acetate/hexane) showed about half of the iodopyridine remained, and side products of lower r_f forming. The mixture was warmed to 116° for 20 minutes more. Tlc showed no iodopyridine. The cooled reaction mixture was partitioned between 1*N* hydrochloric acid and ethyl acetate. The ethyl acetate layer was twice washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and concentrated to a black solid residue.

Column chromatography (silica gel, 1:1 ethyl acetate/hexane) afforded 0.62 g (53%) of pale yellow solid. An analytical sample was obtained by recrystallization from ethanol/ethyl acetate; mp 128.5-130.5°; nmr (300 MHz, deuteriochloroform): δ 8.81 (d, 1H, $J_{6,4}$ = 2.4 Hz, H-6), 8.25 (d, 1H, $J_{4,6}$ = 2.4 Hz, H-4), 8.04 (d, 1H, $J_{2',6'}$ = 2.1 Hz, H-2' of benzene ring), 7.79 (dd, 1H, $J_{6',2'}$ = 2.4 Hz, $J_{6',5'}$ = 8.4 Hz, H-6'), 7.58 (d, 1H, $J_{5',6'}$ = 8.4 Hz, H-5'), 3.40 (t, 2H, J = 4.8 Hz, CH_2CO), 3.30 (t, 2H, J = 4.8 Hz, benzylic CH_2), 3.14 (s, 3H, CH_3); ms (EI/70 eV): m/z 391 (2, M⁺), 356, 358 (40, M-Cl), 218 (10, M-3,4-dichlorobenzoyl), 173, 175 (100, 3,4-dichlorobenzoyl); ir (potassium bromide): 1687 cm^{-1} (C=O).

Preparation of 2-(3,4-Dichlorophenyl)-3,4-dihydro-6-(methylsulfonyl)-2*H*-pyrano[2,3-*b*]pyridine (**1h**) According to Scheme VI.

A solution of the ketone **26** (0.39 g, 0.001 mole) in 15 ml of dichloromethane was cooled under nitrogen to −70°, then a solution of 1.0 ml of 1.5 *M* diisobutylaluminum hydride/toluene (0.0015 mole) was added dropwise over 3 minutes, keeping the temperature below −65°. After 5 minutes, the mixture was quenched by careful addition of 1.5 ml of a mixture of 10% water, 40% acetic acid, and 50% ether. The reaction mixture was allowed to warm to 0°, then was partitioned between water and dichloromethane. The dichloromethane layer was washed with saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered, and concentrated to 0.36 g colorless solid; ms (CI/methane): m/z 394 (20, M + 1), 376 (80, M + 1-H_2O), 358 (M + 1-HCl); ir (potassium bromide): 3415 cm^{-1} (OH). Without purification, the alcohol product (0.36 g) in 2 ml of anhydrous DMSO was added to a magnetically stirred suspension of 0.07 g (0.0015 mole) of 50% sodium hydride (previously freed of oil by washing with hexane) in 10 ml of DMSO under nitrogen. Gas was evolved, and the mixture became lavender, then cherry red. After 15 minutes, the mixture was partitioned between ethyl acetate and 1 *N* hydrochloric acid. The yellow ethyl acetate layer was washed with water, then twice with saturated sodium chloride solution, dried over magnesium sulfate, filtered, and con-

centrated to 0.35 g of pale yellow solid. Recrystallization from 2-propanol/ethyl acetate provided 0.22 g colorless fluffy solid, mp 171.5-172.5°. Preparative tlc of the mother liquor (1:1 ethyl acetate/chloroform) yielded an additional 0.04 g of product. Total yield: 0.26 g (72% overall). This product exhibited the same spectral characteristics as the material produced according to Scheme III.

2-(3,4-Dichlorophenyl)-3,4-dihydro-6-(methylthio)-2*H*-pyrano[2,3-*b*]pyridine (**1g**).

A solution of 3.59 g (0.010 mole) of the bromo derivative **1d** in a mixtue of 50 ml of toluene and 25 ml of anhydrous ether was cooled to −100° (liquid nitrogen/ether bath) under nitrogen and 3.8 ml of 2.9 *M* *t*-butyllithium/pentane (0.011 mole) was added dropwise over about 5 minutes, keeping the temperature below −100°. The mixture became deep blue-green. After 20 minutes, 1.8 ml (0.020 mole) of methyl disulfide was added. The mixture was allowed to warm to 0°, then was partitioned between ether and water. The ether layer was washed with saturated sodium chloride solution, dried over potassium carbonate, and concentrated to a yellow oil which 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°; nmr (deuteriochloroform): δ 8.08 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.53 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.41 (d, 1H, $J_{5',6'}$ = 8 Hz, H-5'), 7.40 (d, 1H, $J_{2',6'}$ = 2 Hz, H-2'), 7.23 (dd, 1H, $J_{6',5'}$ = 8 Hz, $J_{6',2'}$ = 2 Hz, H-6), 5.20 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 9 Hz, H-2), 2.7-3.0 (complex pattern, 2H, H-4), 2.45 (s, 3H, CH_3), 1.6-2.3 (complex pattern, 2H, H-3); ms (CI/methane): m/z 326, 329 (50, M + 1), 173, 175 (70, 3,4-dichlorobenzoyl), 154 (80, M-3,4-dichlorostyrene).

Similarly prepared were:

2-(4-Chlorophenyl)-3,4-dihydro-6-(methylthio)-2*H*-pyrano[2,3-*b*]pyridine (**1j**).

This compound had nmr (deuteriochloroform): δ 8.16 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.40 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.31 (s, 4H, phenyl protons), 5.22 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 9 Hz, H-2), 2.75-3.00 (complex pattern, 2H, H-4), 2.45 (s, 3H, CH_3), 1.8-2.3 (complex pattern, 2H, H-3); ms (EI/70 eV): m/z 291 (15, M⁺), 166 (100, M-*p*-chlorobenzyl).

3,4-Dihydro-6-(methylthio)-2-phenyl-2*H*-pyrano[2,3-*b*]pyridine (**1o**).

This compound had nmr (deuteriochloroform): δ 8.05 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.30 (broad s, 6H, H-5 + phenyl), 5.15 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 9 Hz, H-2), 2.6-2.9 (complex pattern, 2H, H-4), 2.38 (s, 3H, CH_3), 1.7-2.2 (complex pattern, 2H, H-3); ms (EI/70 eV): m/z 257 (60, M⁺), 166 (100, M-benzyl).

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 (**1d**) (1.50 g, 0.0043 mole) was quenched with excess methanol at −85°. Chromatographic purification provided 0.71 g (59%) of cream colored solid, mp 99-100°; nmr (deuteriochloroform): δ 8.10 (distorted dd, 1H, H-7), 7.1-7.8 (complex pattern, 4H, H-2' + H-4' + H-5 + H-6), 6.85 (dd, 1H, $J_{6',2'}$ = 5 Hz, $J_{6',5'}$ = 8 Hz, H-6'), 5.16 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 9 Hz, H-2), 2.7-3.1 (complex pattern, 2H, H-4), 1.6-2.4 (complex pattern, 2H, H-3); ms (CI/methane): 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 (**1m**).

The lithio intermediate, generated as above from the corresponding bromo compound (**1d**) (0.85 g, 0.0024 mole) was quenched at −95° with excess *n*-butyl disulfide. Chromatographic purification provided 0.29 g of powdery white solid (33%), mp 59.5-61°; nmr (300 MHz, deuteriochloroform): δ 8.16 (d, 1H, $J_{7,5}$ = 1.8 Hz, H-7), 7.57 (d, 1H, $J_{5,7}$ = 1.8 Hz, H-5), 7.51 (d, 1H, $J_{2',6'}$ = 1.5 Hz, H-2'), 7.46 (d, 1H, $J_{5',6'}$ = 8.7 Hz, H-5'), 7.28 (dd, 1H, $J_{6',2'}$ = 1.5 Hz, $J_{6',5'}$ = 8.7 Hz, H-6'), 5.22 (dd, 1H, $J_{2,3}$ = 1.8 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 2.90 (m, 1H, H-4), 2.75-2.90 (complex pattern, 3H, H-4 + -CH_2S-), 2.2-2.3 (complex pattern, 1H, H-3), 1.9-2.1 (complex pattern, 1H, H-3), 1.5-1.6 (m, 2H, -CH_2CH_3), 1.4-1.5 (m, 2H, -SCH_2CH_2-), 0.91 (distorted t, 3H, CH_3); ms (EI/70 eV): m/z 367 (15, M⁺), 208 (100, M-3,4-dichlorobenzyl).

6-Benzoyl-2-(3,4-dichlorophenyl)-3,4-dihydro-2*H*-pyrano[2,3-*b*]pyridine (**1n**).

The lithio intermediate, generated as above from the corresponding bromo compound (1.30 g, 0.0037 mole) was quenched at −100° with a solution of 0.80 g (0.0077 mole) of benzonitrile in 4 ml of toluene. Chromatographic purification (silica gel, 2:1 hexane/ethyl acetate) provided 0.30 g (21%) of light yellow solid, mp 155-158°; nmr (deuteriochloroform): δ 8.52 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.95 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.1-7.9 (complex pattern, 8H, remaining aromatic), 5.28 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 10 Hz, H-2), 2.8-3.2 (complex pattern, 2H, H-4), 1.7-2.5 (complex pattern, 2H, H-3); ms (EI/70 eV): m/z 383 (15, M⁺), 348 (15, M-Cl), 224 (85, M-3,4-dichlorobenzyl), 105 (100, benzoyl), 77 (90, phenyl); ir (nujol mull): 1620 cm^{-1} (aromatic C=O).

2-(3,4-Dichlorophenyl)-3,4-dihydro-6-hydroxy-2*H*-pyrano[2,3-*b*]pyridine (**1g**).

The lithio intermediate, generated as above from the corresponding bromo compound (1.50 g, 0.0043 mole) was quenched at −90° with 1.32 ml (0.0049 mole) of tri-*n*-butyl borate. The resulting dark solution was stirred at −75° for 2 hours, then was allowed to warm to 0°. The reaction mixture was acidified with 3 *N* hydrochloric acid, the organic phase was separated, and the aqueous layer was extracted with ether. The combined ether layers were concentrated to 0.37 g of light brown, tacky solid. To this material was added 25 ml of 30% hydrogen peroxide and the resulting mixture was warmed to 60° for 30 minutes. The cooled mixture was diluted with 75 ml of water and extracted with dichloromethane (2 × 50 ml). The extracts were washed with saturated sodium chloride solution, dried over sodium sulfate, and concentrated to 0.26 g of a yellow solid. Column chromatography (silica gel, 3% ethyl acetate/hexane) afforded a pure fraction (0.045 g), mp 218-219°. A less pure fraction (0.085 g) was recrystallized from ethyl acetate to provide an additional 0.025 g of desired product; total yield, 10%; nmr (hexadeuteriodimethylsulfoxide): δ 9.3 (broad s, 1H, -OH), 7.65 (d, 1H, $J_{5',6'}$ = 8 Hz, H-5'), 7.63 (d, 1H, $J_{2',6'}$ = 2 Hz, H-2'), 7.55 (d, 1H, $J_{7,5}$ = 3 Hz, H-7), 7.38 (dd, 1H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 8 Hz, H-6'), 6.95 (d, 1H, $J_{5,7}$ = 3 Hz, H-5), 5.16 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 9 Hz, H-2), 2.4-2.7 (complex pattern, 2H, H-4), 1.5-2.2 (complex pattern, 2H, H-3); ms (CI/methane): m/z 296 (100, M + 1), 262 (20, M-Cl), 150 (30, M-3,4-dichlorophenyl), 124 (95, M-3,4-dichlorostyrene).

2-(3,4-Dichlorophenyl)-3,4-dihydro-6-(methylsulfonyl)-2*H*-pyrano[2,3-*b*]pyridine (**1h**).

The lithio intermediate, generated as above from the corresponding bromo compound (14.4 g, 0.040 mole) in a mixture of 400 ml of toluene and 200 ml of ether at −100° was quenched by addition of 10.8 ml (0.120 mole) of methyl disulfide. The mixture was allowed to warm to −50°, then was partitioned between water and ether. The aqueous layer was extracted with ether and the combined ether layers were washed with saturated sodium chloride solution, dried over potassium carbonate, filtered, and concentrated *in vacuo* to a dark yellow oil which later solidified. The crude thioether was taken up in 80 ml of THF, diluted with 160 ml of methanol, and cooled in an ice-water bath while a solution of 49.2 g (0.16 mole) of 49.5% potassium persulfate (oxone® , Alfa) in 150 ml of water was added at a rate to keep the temperature below 30°. A thick white precipitate developed and efficient mechanical stirring was required. After 3 hours, the mixture was poured into 1 liter of water and extracted with ethyl acetate. The aqueous layer was extracted with more ethyl acetate, and the combined organic phases were washed with saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to a yellow solid. Recrystallization from 2-propanol/ethyl acetate provided 9.0 g of white solid. A second crop was obtained by concentrating the mother liquor (1.58 g). Combined yield: 10.5 g (73% overall), mp 172-173.5°. This product was identical in all respects with material pre-

pared according to Schemes IV and VI.

Similarly prepared were:

2-(4-Chlorophehyl)-3,4-dihydro-6-(methylsulfonyl)-2*H*-pyrano[2,3-*b*]pyridine (**1k**).

This compound had nmr (deuteriochloroform): δ 8.64 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.92 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.33 (s, 4H, phenyl protons), 5.35 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 10 Hz, H-2), 3.05 (s, 3H, CH_3), 2.8-3.2 (complex pattern, 2H, H-4), 1.9-2.4 (complex pattern, 2H, H-3); ms (CI/methane): m/z 324 (100, M + 1), 212 (10, M-*p*-chlorophenyl).

3,4-Dihydro-6-(methylsulfonyl)-2-phenyl-2*H*-pyrano[2,3-*b*]pyridine (**1p**).

This compound had nmr (deuteriochloroform): δ 8.59 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.84 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.32 (s, 5H, phenyl), 5.30 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 10 Hz, H-2), 3.05 (s, 3H, CH_3), 2.7-3.1 (complex pattern, 2H, H-4), 1.8-2.3 (complex pattern, 2H, H-3); ms (EI/70 eV): m/z 289 (60, M⁺), 274 (15, M-CH_3), 210 (25, M-SO_2CH_3), 209 (25, 210-H), 198 (100, M-benzyl).

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

To a magnetically stirred solution of 1.00 g (0.003 mole) of thioether **1g** in 25 ml of dichloromethane at −25° was added dropwise a solution of 0.55 g (0.0032 mole) of 80-85% *m*-chloroperoxybenzoic acid (Aldrich) in 20 ml of dichloromethane over 5-10 minutes keeping the temperature between −20° and −30°. A precipitate formed. The mixture was allowed to warm to −5° over 2 hours, then was extracted wtih saturated sodium bicarbonate solution, then saturated sodium chloride solution, dried over sodium sulfate, 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°; nmr (deuteriochloroform): δ 8.25 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.82 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.50 (d, 1H, $J_{2',6'}$ = 2 Hz, H-2'), 7.45 (d, 1H, $J_{5',6'}$ = 8 Hz, H-5'), 7.21 (dd, 1H, $J_{6',2'}$ = 2 Hz, $J_{6',5'}$ = 8 Hz, H-6'), 5.21 (dd, 1H, $J_{2,3}$ = 3 Hz, $J_{2,3}$ = 10 Hz, H-2), 2.6-3.1 (complex pattern, 2H, H-4), 2.75 (s, 3H, CH_3), 1.8-2.5 (complex pattern, 2H, H-3); ms (EI/70 eV): m/z 341 (10, M⁺), 326 (40, M-CH_3), 167 (100, 326-3,4-dichlorobenzyl); ir (potassium bromide): 1045 cm^{-1} (S-O).

6-Chloro-2-(3,4-dichlorophenyl)-3,4-dihydro-2-methyl-2*H*-pyrano[2,3-*b*]pyridine (**18**).

To a magnetically stirred solution of 1.92 g (0.0056 mole) of ketone **16** in 55 ml of anhydrous THF at 5° under nitrogen was added *via* syringe 2.62 ml (0.0076 mole) of 2.9 *M* methylmagnesium chloride/THF (Alfa) over about 10 minutes. The yellow mixture was allowed to warm to 23°, and after 2 hours was quenched by careful addition of 20 ml of 0.05 *N* hydrochloric acid. The mixture was poured into 50 ml of water and extracted with ether (2 × 50 ml). The combined extracts were washed wth water, then saturated sodium chloride solution, then dried over sodium sulfate. Removal of solvent under vacuum left 1.99 g of yellow oil, consistent with alcohol **17**; nmr (deuteriochloroform): δ 7.90 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.55 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.2-7.4 (complex pattern, 3H, phenyl protons), 3.90 (s, 3H, OCH_3), 2.3-2.8 (complex pattern, 2H, benzylic CH_2), 2.20 (broad s, 1H, OH), 1.7-2.2 (complex pattern, 2H, remaining CH_2), 1.60 (s, 3H, CH_3); ir (neat): 3400 cm^{-1} (broad band, OH). To a solution of 1.15 g (0.0032 mole) of alcohol **17** in 25 ml of acetic acid under nitrogen was added 1.2 ml of 48% hydrobromic acid. The magnetically stirred solution was warmed to 100° (oil bath). After 10 minutes, the mixture was cooled to 25° and partitioned between ether and water. The ether layer was washed with saturated sodium bicarbonate solution (2 × 75 ml), then saturated sodium chloride solution, dried over sodium sulfate, and concentrated to 0.67 g of viscous orange oil. A 0.60-g sample was subjected to column chromatography (silica gel, 5% ethyl acetate/hexane initially, then 7% ethyl acetate/hexane, and finally with 1:1 ethyl acetate/hexane). The major, high r_f fraction (0.11 g), colorless oil, exhibited spectral characteristics of olefins **10**; nmr (deuteriochloroform): δ 7.90 (d, 1H, $J_{7,5}$ = 2 Hz, H-7), 7.44 (d, 1H, $J_{5,7}$ = 2 Hz, H-5), 7.1-7.4 (complex pattern, 3H, phenyl protons), 5.85 (overlapping triplets, J = 10 Hz, 1H, olefinic), 3.95 (s, 3H, OCH_3), 3.42 (d, 2H, J = 10 Hz, CH_2), 2.05 (s, 3H, CH_3); ms (EI/70 eV): m/z 341 (10, M⁺), 326 (10, M-CH_3), 306 (20, M-Cl), 173 (85), 156 (95), 128 (100). The lower r_f fraction (0.24 g) was a mixture of at least five side products. Preparative tlc (15% ethyl acetate/hexane) of a 0.1 g sample afforded 0.06 g of colorless oil. On trituration with hexane and removal of supernatant, 0.045 g of white granular solid was obtained, mp 83-84°, consistent with desired product; nmr (300 MHz, deuteriochloroform): δ 8.10 (d, 1H, $J_{7,5}$ = 2.4 Hz, H-7), 7.47 (d, 1H, $J_{5,7}$ = 2.4 Hz, H-5), 7.38 (d, 1H, $J_{5',6'}$ = 8.1 Hz, H-5'), 7.32 (d, 1H, $J_{2',6'}$ = 1.2 Hz, H-2'), 7.21 (d, 1H, $J_{6',2'}$ = 1.2 Hz, $J_{6',5'}$ = 8.1 Hz, H-6'), 2.67-2.74 (complex pattern, 1H, benzylic), 2.49-2.54 (complex pattern, 1H, remaining benzylic), 2.33-2.44 (complex pattern, 1H, remaining CH_2 proton), 1.69 (s, 3H, CH_3); ms (EI/70 eV): m/z 327 (30, M⁺), 312 (10, M-CH_3), 292 (100, M-Cl), 142 (100).

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