Synthesis of 2,3-Dihydro[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones and 1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ones

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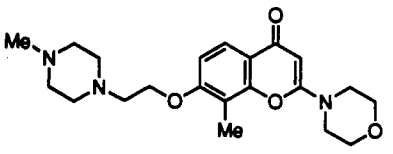
As part of an effort to prepare antiplatelet compounds related to 2-aminochromone **1** with improved pharmaceutical properties,[1-3] we required an efficient synthesis of the tricyclic derivatives **2** and **3**. Although catalytic



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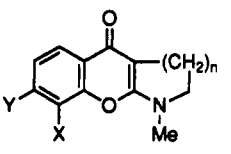
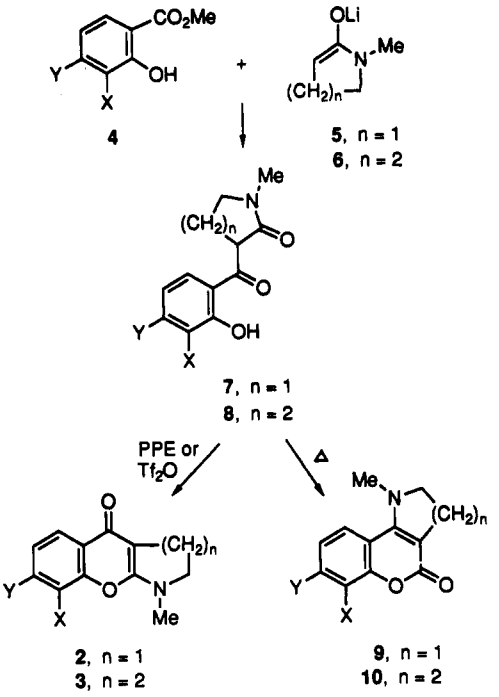


2, n = 1
3, n = 2

hydrogenation of 5*H*-[1]benzoprano[2,3-*b*]pyridin-5-ones was an established route to the 1,2,3,4-tetrahydro-5*H*-[1]-benzopyrano[2,3-*b*]pyridin-5-one skeleton,[4] we were interested in a method with sufficient flexibility to provide both the 6,6,6 and 6,6,5 ring systems. Eiden has described the preparation of lactams **7a** and **8a** and the subsequent thermolysis of **7a** to afford the cyclic aminocoumarin derivative **9a**.[5] Although considered as a potential product from this reaction, the corresponding cyclic aminochromone **2a** was not observed.[5] We have recently developed a new synthesis of 2-aminochromones from the cyclodehydration of a series of related salicylacetamides with triflic anhydride[6] (Tf_2O) or polyphosphoric ester[7] (PPE).[8] In this paper we report the successful application of this methodology to the preparation of 2,3-dihydro[1]benzopyrano-[2,3-*b*]pyrrol-4(1*H*)-ones **2** and 1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ones **3** via the cyclodehydration of lactams **7** and **8**, respectively.

Lactams **7** and **8** were synthesized from a series of methyl salicylates **4** by a modification of the procedure of Eiden utilizing the corresponding lithium enolates of *N*-methyl-2-pyrrolidinone (**5**) and *N*-methyl-2-piperidone (**6**), respectively (Scheme I).[5] Yields for the preparation of **8** ranged from 56 to 87% whereas those for **7** were lower (30–70%) due to the formation of a carbinol byproduct resulting from the addition of a second equivalent of **5** to the ketone of **7**. Attempts to suppress the generation of this carbinol by inverse addition of the enolate or use of lower temperatures met with only moderate success.

Scheme I



4 **5**, n = 1 **6**, n = 2 **7**, n = 1 **8**, n = 2 **2**, n = 1 **3**, n = 2 **9**, n = 1 **10**, n = 2

Confirmation of the cyclization mode recorded by Eiden was obtained via the formation of aminocoumarin **9a** in 87% yield upon heating of **7a** at 205–215 °C for 2.5 h.[5] However, in contrast to this earilier report, we were *successful* in promoting the thermolysis of the corresponding piperidinone **8a** (215 °C, 4 h) to provide a 95% recovery of an 8:1 mixture of **10a** and the cyclic aminochromone **3a**. Similar results were obtained with the corresponding 4-hydroxy-3-methyl derivatives **7b** and **8b**. Thermolysis of each substrate (250 °C, 1 h) was followed by acetylation of the crude reaction mixture to provide exclusively the aminocoumarin **9h** (X = Me, Y = OAc, from **7b**) and ca. a 2:1 mixture of **10h** and **3h** (X = Me, Y = OAc, from **8b**).

In contrast, the alternate mode of cyclization, providing almost exclusively the cyclic aminochromones **2** and **3**, was observed when lactams **7** and **8**, respectively, were subjected to dehydration conditions. As was found for our synthesis of 2-aminochromones, both PPE and Tf_2O were useful for this transformation (50–88% yields, Tables I and II). Although these reagents proved to be equally effective for the converison of **8** to **3**, somewhat better yields of the cyclic aminochromones **2** were realized through the use of Tf_2O (PPE, 43%, vs. Tf_2O, 78%, for **2a**).[8] As testimony to the selectivity of this process, the corresponding cyclic aminocoumarin was seen as a side product in only one example (**8a** → **3a**). The unambiguous structural assignments of the coumarin and chromone cyclization products were provided by comparison of the 2D long-range heteronuclear correlation (COLOC) NMR spectrum of (**9h** and **10h**, X = Me, Y = OAc) and (**2h** and

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(3) Morris, J.; Wishka, D. G.; Fang, Y. *J. Org. Chem.* **1992**, *57*, 6502.

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(6) (a) Hendrickson, J. B.; Bair, K. W.; Keehn, P. M. *Tetrahedron Lett.* **1976**, 603. (b) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1987**, 4137. (c) Hendrickson, J. B.; Hussoin, M. S. *J. Org. Chem.* **1989**, 1144. (d) Gramstad, T.; Husebye, S.; Sæbö *Acta Chem. Scand. B* **1985**, *39*, 505. (e) Baldwin, J. E.; O'Neil, I. A. *Synlett* **1990**, 603.

(7) (a) Kanaoka, Y.; Kuga, T.; Tanizawa, K. *Chem. Pharm. Bull. Jpn.* **1970**, *18*, 397. (b) Kanoaka, Y.; Machida, M.; Yonemitsu, O.; Ban, Y. *Chem. Pharm. Bull. Jpn.* **1965**, *13*, 1065.

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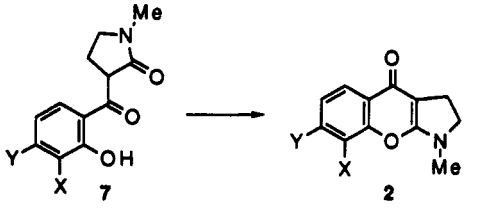
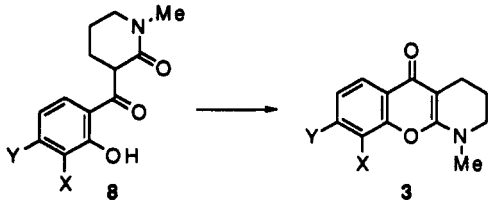
Table I. Synthesis of 2,3-Dihydro[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-ones



entry	X	Y	% yield (PPE)	% yield (Tf_2O)
a	H	H	43	78
b	Me	OH	50	
c	H	OMe		87
d	H	Cl		88
e	H	NHAc	50	
f	OMe	H		80
g	OH	H		61

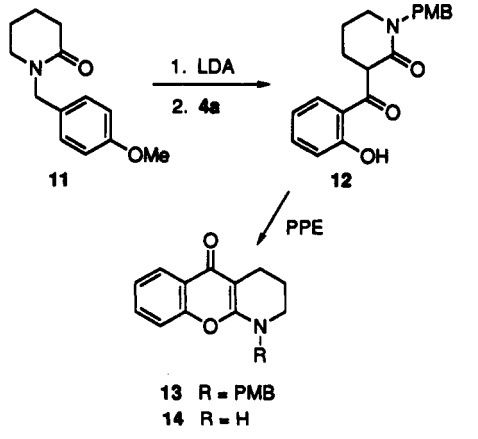
Table II. Synthesis of 1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ones



entry	X	Y	% yield (PPE)	% yield (Tf_2O)
a	H	H	64[a]	66
b	Me	OH	58	
c	H	OMe		87
d	H	Cl		75
e	H	NHAc	64	
f	OMe	H		56
g	OH	H		51

[a] An 8.5% yield of **10a** was also isolated from this reaction.

Scheme II

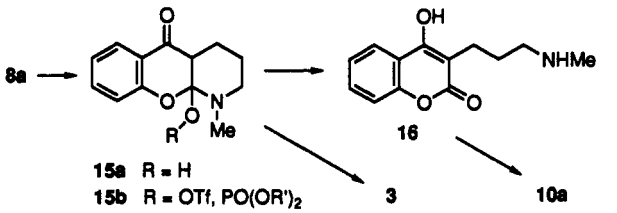


3h, X = Me, Y = OAc),[9] respectively. The chromones were readily distinguished from the coumarins on the basis of a three bond ($^3J_{C-H}$) coupling detected between the C-4 carbonyl and the C-5 proton in **2h** and between the C-5 carbonyl and the C-6 proton in **3h**.

This methodology was expanded to the synthesis of 1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ones with substituents other than methyl on the vinylogous amide nitrogen (Scheme II). The strategy called for protection of the 2-piperidone nitrogen with the acid labile

(9) Compounds **2h** and **3h** were prepared via the acetylation of **2b** and **3b**, respectively (see experimental procedures in supplementary material).

Scheme III



4-methoxybenzyl (PMB) group. The lithium enolate of **11**[10] was condensed with methyl salicylate (**4a**) to afford β-ketoamide **12** in 69% yield. Cyclodehydration of **12** with PPE gave **13** (54%) which upon treatment with trifluoroacetic acid/H_2SO_4 (1:1) afforded an 88% yield of the tricyclic aminochromone **14**.

Attempted hydrolysis of aminochromone **3a** with 5% HCl/CH_3CN (rt, 24 h) left it unchanged in contrast to its acyclic 2-amino-3-methyl counterpart which was readily converted to the corresponding 4-hydroxy-3-methylcoumarin under similar conditions.[3] In addition, the failure of **3a** to react under thermal conditions (215 °C, 4 h) disqualifies it as a potential intermediate during the conversion of **8a** to **10a**. The dichotamous modes of cyclization observed under thermal and dehydration conditions can be rationalized as follows (Scheme III). During thermolysis, the phenolic proton acts as an internal acid catalyst to provide the tetrahedral intermediate **15a** which favors elimination of the amine and cyclization at the C-4 position of the corresponding hydroxycoumarin derivative **16**.[11] Under dehydration conditions, the related tetrahedral intermediate **15b** possesses a phosphate or triflate leaving group favoring direct elimination to give the tricyclic 2-aminochromone.

In summary, we have developed an efficient method for the synthesis of the 5- and 6-membered cyclic aminochromone derivatives **2** and **3** in two steps starting from salicylic esters. The key cyclodehydration step providing the chromone product contrasts with a related thermal cyclization to the corresponding aminocoumarin.

Experimental Section

IR spectra were taken as a Nujol mull. UV spectra were obtained in EtOH. ^1H and ^{13}C NMR spectra were obtained in $CDCl_3$ (unless otherwise indicated) at 300 MHz. Melting points are uncorrected. Thin layer chromatography was performed on Merck precoated glass TLC plates with silica gel 60-F254 and stained with a solution of 75 g of ammonium molybdate, 2.5 g of cerric sulfate, and 500 mL of 10% H_2SO_4 (v/v). Column (flash) chromatography was performed with Merck silica gel 60 (230–400 mesh).

3-(2-Hydroxybenzoyl)-1-methyl-2-pyrrolidinone (7a). A solution of 1-methyl-2-pyrrolidinone (12.7 mL, 132 mmol) in 100 mL of dry THF under N_2 at −20 °C was treated slowly dropwise with a solution of LDA (66 mL, 132 mmol, 2 M in heptane/THF/ethylbenzene). The mixture was stirred for 30 min at −20 °C, treated slowly dropwise with methyl salicylate (5.2 mL, 40 mmol, internal temperature <−10 °C), and stirred overnight as the cooling bath expired. The mixture was cooled to 0 °C, was quenched with 25 mL of H_2O, and the pH was adjusted to 6.8 with 10% HCl. The aqueous layer was washed with 2 × 50 mL of CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The oil was chromatographed over 200 g of silica gel (3% MeOH/CH_2Cl_2 to provide 5.6 g (63%) of **7a** (after filtration through a silica gel plug, EtOAc) along with 2.56 g (20%) of the bis addition product. **7a**: ^1H NMR δ 2.28

(10) *N*-(4-Methoxybenzyl)-δ-valerolactam (**11**) was prepared in 94% yield from the reaction of 2-piperidone with 4-methoxybenzyl chloride (NaH, reflux, THF, 23 h).

(11) Tabakovic, K.; Tabakovic, I; Ajdini, N.; Leci, O. *Synthesis* **1987**, 308.

(m, 2), 2.62 (m, 2), 2.91 (s, 3), 3.40 (m, 2), 3.49 (m, 2), 4.49 (dd, J = 5, 9 Hz, 1), 6.96 (m, 2), 7.50 (m, 1), 8.00 (m, 1), 12.05 (bs, 1); ^{13}C NMR δ 18.0, 21.9, 48.1, 50.0, 118.2, 119.2, 119.3, 132.1, 136.9, 162.9, 169.7, 201.8; IR 1692, 1635, 1488, 1447, 1273 cm^{-1}. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.42; H, 6.13; N, 6.28. Bis adduct: mp 160–162 °C; ^{1}H NMR δ 1.91–3.36 (m, 4), 2.75 (s, 3), 2.85 (s, 3), 2.80-3.34 (m, 4), 3.70 (m, 1), 4.05 (m, 1), 6.72–6.92 (m, 3), 7.10 (m, 1); IR 1692, 1662, 1458, 1295, cm^{-1}. Anal. Calcd for $C_{17}H_{22}N_2O_4$ (0.86% H_2O found): C, 63.58, H, 7.00, N, 8.72. Found: C, 63.30, H, 6.98, N, 8.72.

3-(2,4-Dihydroxy-3-methylbenzoyl)-1-methyl-2-pyrrolidinone (7b) was prepared according to the procedure for **7a** except that the reaction was warmed at reflux overnight: yield 2.1 g (30%); mp 236–237.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.87 (s, 3), 2.05–2.29 (m, 2), 2.65 (s, 3), 3.27 (m, 2), 4.48 (m, 1), 6.38 (m, 1), 7.67 (m, 1), 12.82 (s, 1); ^{13}C NMR (DMSO-d_6) δ 7.8, 22.2, 29.7, 47.4, 48.9, 107.6, 110.3, 112.4, 131.7, 163.1, 163.3, 170.2, 201.6; IR 1680, 1619, 1459, 1244 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.58; H, 6.02; N, 5.69.

3-(2-Hydroxybenzoyl)-1-methyl-2-piperidone (8a). A solution of 1-methyl-2-piperidone (9.4 mL, 82.5 mmol) in 50 mL of dry THF under N_2 at 0 °C was treated with a solution of LDA (41.3 mL, 82.5 mmol) and stirred for 30 min. The mixture was treated at 0 °C with methyl salicylate (3.24 mL, 25 mmol) and was stirred for 1 h at rt. Workup as for **7a** followed by chromatography over 150 g of silica gel (2.5% MeOH/CH_2Cl_2) afforded 5.06 g (87%) of **8a**: mp 190–192 °C (lit.[5] mp 198 °C); ^{1}H NMR δ 1.78–1.91 (m, 1), 2.00–2.37 (m, 3), 3.03 (s, 3), 3.27–3.49 (m, 2), 4.46 (m, 1), 6.85–6.99 (m, 2), 7.48 (m, 1), 7.78 (m, 1), 12.15 (bs, 1); ^{13}C NMR δ 21.4, 25.8, 49.6, 49.7, 118.6, 119.1, 131.0, 136.7, 163.0, 166.4, 211.6; IR 1630, 1447, 1207 cm^{-1}. Anal. Calcd for $C_{13}H_{15}NO_3$ (0.89% H_2O found): C, 66.32; H, 6.52; N, 5.95. Found: C, 66.08; H, 6.68; N, 6.15.

3-(2,4-Dihydroxy-3-methylbenzoyl)-1-methyl-2-piperidone (8b) was prepared according to the procedure of **8a** except that purification was by crystallization from Et_2O/EtOAc: yield 6.04 g (80%); mp 208–210 °C; ^{1}H NMR (DMSO-d_6) δ 1.75 (m, 4), 1.89 (s, 3), 2.75 (s, 3), 3.24 (m, 2), 4.39 (m, 1), 6.40 (m, 1), 7.62 (m, 1), 10.59 (s, 1), 12.90 (s, 1); ^{13}C NMR (DMSO-d_6) δ 7.6, 20.7, 26.1, 34.3, 48.5, 49.2, 107.4, 110.4, 112.0 130.8, 163.0, 163.1, 166.3, 203.7; IR 1619, 1498, 1455, 1236 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.61; H, 6.52; N, 5.33.

2,3-Dihydro-1-methyl[1]benzopyrano[4,3-*b*]pyrrol-4(1*H*)-one (9a). **7a** (440 mg, 2.0 mmol) was heated at 205–215 °C for 2.5 h under N_2. The mixture was chromatographed over 20 g of silica gel (3% MeOH/CH_2Cl_2) to afford 350 mg (87%) of **9a**; mp 163 °C (lit.[5] mp 168 °C); ^{1}H NMR δ 2.95 (t, J = 9.8 Hz, 2), 3.37 (s, 3), 3.77 (t, J = 9.8 Hz, 2), 7.20 (m, 1), 7.32 (m, 1), 7.49 (m, 1), 7.89 (m, 1); ^{13}C NMR δ 24.5, 37.3, 57.0, 98.8, 113.3, 118.1, 123.1, 123.1, 131.4, 155.4, 157.6, 160.4; UV 251, 300, 310, 340, 347, 365 nm; IR 1682, 1541 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.68; H, 5.60; N, 6.98.

1-Methyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-one (10a). **8a** (466 mg, 2.0 mmol) was heated at 215 °C for 4 h under N_2. ^{1}H NMR of the crude reaction showed an 8:1 mixture of **10a**/**3a**. The material was chromatographed over 25 g of silica gel (3% MeOH/CH_2Cl_2) to afford 146 mg (34%) of **10a**: mp 95–96.5 °C (EtOAc); ^{1}H NMR δ 1.91 (m, 2), 2.60 (t, J = 6.4 Hz, 2), 3.18 (s, 3), 3.24 (t, J = 5.5 Hz, 2), 7.24 (m, 1), 7.29 (m, 1), 7.43 (m, 1), 7.69 (m, 1); ^{13}C NMR δ 19.0, 22.3, 43.4, 51.8, 104.4, 116.6, 117.5, 122.8, 124.9, 130.2, 153.0, 154.5, 162.5; UV 251, 297, 310, 327 nm; IR 1675, 1598 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.61; H, 6.20; N, 6.54.

7-(Acetyloxy)-2,3-dihydro-1,6-dimethyl[1]benzopyrano-[4,3-*b*]pyrrol-4(1*H*)-one (9h). **7b** (235 mg, 0.94 mmol) was heated at 240 °C for 40 min under vacuum. The residue (190 mg) was suspended in 6 mL of CH_2Cl_2 and treated with Et_3N (395 μL, 2.83 mmol) and acetyl chloride (200 μL, 2.83 mmol). The reaction was heated at reflux for 2 h, diluted with CH_2Cl_2, and washed with 10 mL of saturated $NaHCO_3$. The aqueous layer was extracted with 10 mL of CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The material was chromatographed over 15 g of silica gel (3% MeOH/CH_2Cl_2) to afford 90 mg (33%) of **9h**: mp 176–178 °C (EtOAc); ^{1}H NMR δ 2.28 (s, 3), 2.37 (s, 3), 2.95 (t, J = 9.7 Hz, 2), 3.33 (s, 3), 3.78 (t, J = 9.7 Hz, 2), 6.93 (m, 1), 7.75 (m, 1); ^{13}C NMR δ 9.8, 20.8, 24.4, 37.3, 57.1, 98.2, 111.1, 117.1, 120.2, 120.9, 151.2, 154.7, 157.7, 160.3, 168.8; IR 1763, 1692, 1199 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_4$ (0.5% H_2O found): C, 65.59; H, 5.56; N, 5.10. Found: C, 65.25; H, 5.45; N, 4.89.

8-(Acetyloxy)-1,7-dimethyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[4,3-*b*]pyridin-5-one (10h) was prepared according to the procedure for **9h**. Yield of **10h**, 89 mg (33%); **3h**, 52 mg (19%). **10h**: mp 149–150 °C (EtOAc); ^{1}H NMR δ 1.88 (m, 2), 2.29 (s, 3), 2.40 (s, 3), 2.59 (t, J = 6 Hz, 2), 3.14 (s, 3), 3.22 (t, J = 5.4 Hz, 2), 6.93 (m, 1), 7.53 (m, 1); ^{13}C NMR δ 9.4, 18.9, 20.8, 22.2, 43.5, 51.8, 104.0, 114.4, 116.7, 119.4, 122.6, 150.2, 152.1, 154.7, 162.4, 168.9, 172.5; IR 1758, 1685, 1605 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.90; H, 5.80; N, 4.85.

2,3-Dihydro-1-methyl[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (2a). Method A. A solution of **7a** (1.7 g, 7.75 mmol) in 24 mL of PPE/$CHCl_3$ (124 g/250 mL) under N_2 was heated to reflux for 3.5 h. The volatiles were removed *in vacuo*, and the residue was added to 125 mL of 2 N NaOH at 0 °C. The mixture was extracted with 4 × 50 mL of CH_2Cl_2, and the organics were dried over $MgSO_4$ and concentrated *in vacuo*. The solid was chromatographed over 50 g of silica gel (3% MeOH/CH_2Cl_2) to afford 664 mg (43%) of **2a**. Method B. A solution of **7a** (1.85 g, 8.4 mmol) in 20 mL of CH_2Cl_2 under N_2 was treated with Tf_2O (3.1 mL, 18.6 mmol) (CAUTION: exotherm) and stirred for 23 h at rt. The mixture was concentrated *in vacuo* and diluted with 20 mL of MeOH and stirred for 1.5 h at rt. The volatiles were removed, and the solid was partitioned between 1 × 15 mL of 1 N KOH and 3 × 25 mL of CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* to provide 1.32 g (78%) of **2a**: mp 167–168 °C; ^{1}H NMR (DMSO-d_6) δ 2.72 (t, J = 8.5 Hz, 2), 3.13 (s, 3), 3.49 (t, J = 8.5 Hz, 2), 7.32 (m, 1), 7.37 (m, 1), 7.49 (m, 1), 7.88 (m, 1); ^{13}C NMR (DMSO-d_6) δ 22.1, 31.4, 50.2, 94.5, 116.8, 124.4, 124.6, 125.1, 131.1, 153.3, 165.4, 169.1; UV 257, 281, 292, 323 nm; IR 1641, 1615 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.82; H, 5.57; N, 7.09.

2,3-Dihydro-1,8-dimethyl-7-hydroxy[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (2b). A solution of **7b** (1.7 g, 6.82 mmol) in 24 mL of PPE/$CHCl_3$ (124 g/250 mL) under N_2 was heated to reflux for 5 h. The volatiles were removed *in vacuo*, and the residue was added to 60 mL of 2 N NaOH at 0 °C. The mixture was treated with 10% HCl (to pH 7), and the precipitate was collected, washed with H_2O and Et_2O, and dried. The solid was recrystallized from MeOH/CH_2Cl_2 to give 789 mg (50%) of **2b**: mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 2.27 (s, 3), 2.83 (t, J = 9 Hz, 2), 3.02 (s, 3), 3.62 (t, J = 9 Hz, 2), 6.90 (m, 1), 7.68 (m, 1); IR 1628, 1589. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.45; H, 5.77; N, 6.03.

2,3-Dihydro-7-methoxy-1-methyl[1]benzopyrano[2,3-*b*]-pyrrol-4(1*H*)-one (2c) was prepared according to the procedures for **2a**: yield (method A) 812 mg (44%), (method B) 1.61 g (87%); mp 204.5–206.5 °C (EtOAc); ^{1}H NMR (MeOH-d_4) δ 2.82 (t, J = 9 Hz, 2), 2.92 (s, 3), 3.58 (t, J = 9 Hz, 2), 3.78 (s, 3), 6.86 (m, 2), 7.83 (m, 1); ^{13}C NMR (MeOH-d_4) δ 22.7, 31.5, 51.7, 56.4, 96.1, 101.8, 114.0, 117.9, 126.6, 156.3, 163.9, 168.0, 172.1; UV 252, 282, 290, 324 nm; IR 1612, 1554 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.39; H, 5.63; N, 6.06.

7-Chloro-2,3-dihydro-1-methyl[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (2d) was prepared according to the procedure for **2a**: yield (method B) 1.64 g (88%); mp 173–174 °C (EtOAc); ^{1}H NMR δ 3.02 (s, 3), 3.04 (t, J = 9 Hz, 2), 3.64 (t, J = 9 Hz, 2), 7.30 (m, 2), 8.11 (m, 1); ^{13}C NMR δ 22.3, 31.7, 51.0, 95.7, 116.6, 123.1, 125.6, 126.6, 136.4, 153.6, 165.7, 169.7; UV 253, 259, 284, 295, 331 nm; IR 1632, 1599 cm^{-1}. Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 60.92; H, 4.30; N, 5.86.

***N*-(2,3-Dihydro-1-methyl-4(1*H*)-oxo[1]benzopyrano[2,3-*b*]-pyrrol-7-yl)acetamide (2e)** was prepared according to the procedure for **2a**: yield (method A) 930 mg (50%); mp >300 °C (MeOH/CH_2Cl_2/EtOAc (1:2:3)); ^{1}H NMR (MeOH-d_4) δ 2.07 (s, 3), 2.86 (t, J = 9 Hz, 2), 2.94 (s, 3), 3.60 (t, J = 9 Hz, 2), 7.22 (m, 2), 7.81 (m, 1), 7.89 (m, 1); UV 264, 284, 297, 333 nm; IR 1699, 1621 cm^{-1}; HRMS calcd for $C_{14}H_{14}N_2O_3$ 258.1004, found 258.1006.

2,3-Dihydro-8-methoxy-1-methyl[1]benzopyrano[2,3-*b*]-pyrrol-4(1*H*)-one (2f) was prepared according to the procedure for **2a**: yield (method B) 1.76 g (80%); mp 180–181 °C (EtOAc); ^{1}H NMR δ 3.03 (s, 3), 3.01 (t, J = 9 Hz, 2), 3.64 (t, J = 9 Hz, 2),

3.94 (s, 3), 7.05 (m, 1), 7.25 (m, 1), 7.72 (m, 1); ^{13}C NMR δ 21.9, 31.4, 50.5, 55.8, 95.2, 112.5, 116.1, 124.1, 125.2, 143.1, 147.3, 165.3, 170.3; UV 252, 263, 305, 321 nm; IR 1627, 1614 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.41; H, 5.79; N, 5.99.

2,3-Dihydro-8-hydroxy-1-methyl[1]benzopyrano[2,3-*b*]pyrrol-4(1*H*)-one (2g) was prepared according to the procedure for **2a**: yield (method B) 1.12 g (61%); mp >300 °C (MeOH/CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 2.66 (t, J = 9 Hz, 2), 2.86 (s, 3), 3.45 (t, J = 9 Hz, 2), 6.91 (m, 1), 7.00 (m, 1), 7.22 (m, 1); IR 1612, 1558, 1198 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 65.98; H, 4.97; N, 6.38.

1-Methyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (3a). Method A. A solution of **8a** (1.7 g, 7.3 mmol) in 24 mL of PPE/$CHCl_3$ (124 g/250 mL) under N_2 was heated to reflux for 3.5 h. The volatiles were removed *in vacuo*, and the residue was added to 150 mL of saturated Na_2CO_3 at 0 °C. The mixture was stirred 20 min at rt and extracted with 4 × 50 mL of CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The crude solid was chromatographed over 50 g of silica gel (4% MeOH/CH_2Cl_2) to afford 1.0 g (64%) of **3a** along with 134 mg (8.5%) of **10a**. Method B. A solution of **8a** (1.20 g, 5.1 mmol) in 15 mL of CH_2Cl_2 was treated with Tf_2O (3.0 mL, 18.4 mmol) (Caution: exotherm) and stirred for 23 h at rt. The mixture was concentrated *in vacuo*, and the solid was partitioned between 25 mL of saturated $NaHCO_3$ and 25 mL of CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated (1.15 g). ^{1}H NMR revealed a 4:1 mixture of product/starting material. The crude material was chromatographed over 30 g of silica gel (3% MeOH/CH_2Cl_2) to afford 720 mg (66%) of **3a**: mp 137–139 °C; ^{1}H NMR δ 1.93 (m, 2), 2.70 (d, J = 6.4 Hz, 2), 3.16 (s, 3), 3.38 (d, J = 6.4 Hz, 2), 7.27 (m, 2), 7.47 (m, 1), 8.16 (m, 1); ^{13}C NMR δ 19.4, 20.6, 35.7, 50.4, 94.9, 116.0, 122.9, 124.3, 125.5, 131.0, 152.9, 173.3; UV 244, 253, 283, 294, 323 nm; IR 1617, 1554 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.48; H, 6.09; N, 6.47.

1,9-Dimethyl-8-hydroxy-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (3b). A solution of **8b** (2.28 g, 8.7 mmol) in 32 mL of PPE/$CHCl_3$ (124 g /250 mL) under N_2 was heated to reflux for 3 h. The volatiles were removed *in vacuo*, and the residue was added to 150 mL of 2 N NaOH at 0 °C. The pH was adjusted to 5 with 10% HCl, and the precipitate was collected, washed with H_2O, and dried. The solid was recrystallized from MeOH/CH_2Cl_2 to give 1.22 g (58%) of **3b**; mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 1.82 (m, 2), 2.21 (s, 3), 2.47 (t, J = 6 Hz, 2), 3.13 (s, 3), 3.37 (m, 2), 6.85 (m, 1), 7.61 (m, 1), 8.60 (s, 1); UV 249, 282, 293, 321 nm; IR 1627, 1589 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_3$ (0.52% H_2O found): C, 68.20; H, 6.19; N, 5.68. Found: C, 67.96; H, 6.26; N, 5.60.

8-Methoxy-1-methyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (3c) was prepared according to the procedures for **3a**: yield (method A) 1.1 g (60%), (method B) 1.63 g (87%); mp 149–150 °C (EtOAc); ^{1}H NMR δ 1.92 (m, 2), 2.67 (t, J = 6 Hz, 2), 3.14 (s, 3), 3.36 (t, J = 6 Hz, 2), 3.86 (s, 3), 6.70 (m, 1), 6.86 (m, 1), 8.05 (m, 1); ^{13}C NMR δ 19.3, 20.7, 35.7, 50.4, 55.6, 94.0, 99.7, 112.3, 116.5, 126.7, 154.2, 159.7, 162.2, 173.4; UV 251, 282, 291, 323 nm; IR 1631, 1612, 1601 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.52; H, 6.25; N, 5.70.

8-Chloro-1-methyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (3d) was prepared according to the procedure for **3a**: yield (method B) 1.39 g (75%); mp 159–160 °C (EtOAc); ^{1}H NMR δ 1.93 (m, 2), 2.68 (t, J = 6 Hz, 2), 3.15 (s, 3), 3.39 (t, J = 6 Hz, 2), 7.27 (m, 2), 8.07 (m, 1); ^{13}C NMR δ 19.2, 20.4, 35.6, 50.3, 94.8, 116.1, 121.4, 124.8, 126.7, 136.5, 152.8, 159.5, 172.3; UV 251, 286, 296, 329 nm; IR 1602, 1547 cm^{-1}. Anal. Calcd for $C_{13}H_{12}ClNO_2$: C, 62.53; H, 4.84; N, 5.61. Found: C, 62.35; H, 4.88; N, 5.66.

***N*-(1-Methyl-1,3,4,5-tetrahydro-5-oxo-2*H*-[1]benzopyrano[2,3-*b*]pyridin-7-yl)acetamide (3e)** was prepared according to the procedure for **3a**: yield (method A) 1.2 g (64%); mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 1.62 (m, 2), 1.89 (s, 3), 2.27 (t, J = 6 Hz, 2), 2.92 (s, 3), 3.20 (t, J = 6 Hz, 2), 7.05 (m, 1), 7.60 (m, 1), 7.76 (m, 1), 10.10 (m, 1); ^{13}C NMR (DMSO-d_6) δ 19.1, 20.1, 24.1, 35.3, 49.6, 93.0, 105.3, 115.2, 117.6, 125.0, 141.9, 152.9, 159.2, 168.9, 171.4; UV 261, 286, 297, 331 nm; IR 1690, 1632, 1617 cm^{-1}; HRMS calcd for $C_{15}H_{16}N_2O_4$: 272.1161, found 272.1160.

9-Methoxy-1-methyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (3f) was prepared according to the procedure for **3a**: yield (method B) 1.63 g (56%); mp 165–166 °C (EtOAc); ^{1}H NMR δ 1.92 (m, 2), 2.69 (t, J = 6 Hz, 2), 3.19 (s, 3), 3.37 (t, J = 6 Hz, 2), 3.93 (s, 3), 7.02 (m, 1), 7.20 (m, 1), 7.73 (m, 1); ^{13}C NMR δ 19.3, 20.5, 35.5, 50.1, 56.1, 94.7, 112.5, 116.5, 123.6, 123.9, 142.8, 147.5, 159.3, 173.2; UV 251, 260, 319 nm; IR 1624, 1604 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.38; H, 6.05; N, 5.60.

9-Hydroxy-1-methyl-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (3g) was prepared according to the procedure for **3a**: yield (method B) 950 mg (51%); mp 299–301 °C (MeOH/CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ 1.92 (m, 2), 2.58 (m, 2), 3.23 (s, 3), 3.47 (m, 2), 7.17 (m, 2), 7.40 (m, 1), 10.17 (bs, 1); ^{13}C NMR (DMSO-d_6) δ 19.4, 20.3, 35.2, 49.6, 93.6, 114.3, 117.6, 124.0, 124.1, 142.0, 145.5, 159.1, 172.0; UV 253, 318 nm; IR 1612, 1607 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.40; H, 5.78; N, 6.06.

3-(2-Hydroxybenzoyl)-1-(4-methoxybenzyl)-2-piperidone (12). A solution of *N*-(4-Methoxybenzyl)-δ-valerolactam (12.1 g, 56 mmol) in 50 mL of dry THF at 0 °C under N_2 was treated with a solution of LDA (28 mL, 56 mmol) and stirred for 30 min. The mixture was treated with methyl salicylate (2.33 mL, 18 mmol), and the reaction was stirred for 30 min at 0 °C and for 4 h at rt. The mixture was recooled to 0 °C and quenched with 10 mL of H_2O, and the pH was adjusted to 6.5 with 10% HCl. The aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The oil was chromatographed over 200 g of silica gel (60% EtOAc/hexanes) to afford 4.81 g (82%) of **12**; mp 107 °C; ^{1}H NMR δ 1.72–2.24 (m, 4), 3.30 (m, 2), 3.80 (s, 3), 4.46 (d, J = 14 Hz, 1), 4.50 (m, 1), 4.70 (d, J = 14 Hz, 1), 6.80–6.94 (m, 4), 7.15 (m, 2), 7.47 (m, 1), 7.78 (m, 1), 12.18 (bs, 1); ^{13}C NMR ($CDCl_3$) δ 20.8, 25.8, 46.8, 49.8, 50.0, 55.3, 114.0, 118.7, 118.9, 119.1, 128.8, 129.5, 131.0, 136.7, 159.0, 163.1, 166.3, 204.4; IR 1630 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.52; H, 6.22; N, 4.12.

1-(4-Methoxybenzyl)-1,2,3,4-tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (13). A solution of **12** (2.0 g, 5.9 mmol) in 35 mL of PPE/$CHCl_3$ (124 g/250 mL) under N_2 was heated at reflux for 2 h. The volatiles were removed *in vacuo*, and the residue was added to 150 mL of 2 N NaOH at 0 °C and stirred for 30 min. The mixture was extracted with 3 × 50 mL of CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The oil was chromatographed over 60 g of silica gel (3% MeOH/CH_2Cl_2) to afford 1.02 g (54%) of **13**: mp 114–115 °C; ^{1}H NMR δ 1.88 (m, 2), 2.71 (t, J = 6 Hz, 2), 3.36 (t, J = 6 Hz, 2), 3.80 (s, 3), 4.66 (s, 2), 6.88 (m, 2), 7.20–7.34 (m, 4), 7.48 (m, 1), 8.20 (m, 1); ^{13}C NMR δ 19.5, 20.7, 47.9, 51.2, 55.3, 95.0, 114.3, 116.0, 123.0, 124.4, 125.6, 128.5, 128.8, 131.2, 152.9, 159.1, 159.2, 173.7; UV 253, 277, 283, 295, 324 nm; IR 1603 cm^{-1}. Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.63; H, 6.10; N, 4.32.

1,2,3,4-Tetrahydro-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-one (14). A solution of **13** (450 mg, 1.38 mmol) in 3 mL of trifluoroacetic under N_2 at 0 °C was treated with H_2SO_4 (1.2 mL, 43 mmol) and stirred for 20 min as it warmed to rt. The reaction was poured into 150 mL of saturated $NaHCO_3$ and extracted with 3 × 50 mL of CH_2Cl_2. The combined organics were dried over $MgSO_4$ and concentrated *in vacuo*. The solid was recrystallized from EtOAc/CH_2Cl_2 to afford 243 mg (88%) of **14**: mp 235–237 °C (lit.[4b] mp 232 °C); ^{1}H NMR (DMSO-d_6) δ 1.92 (m, 2), 2.66 (t, J = 6 Hz, 2), 3.47 (t, J = 6 Hz, 2), 7.45 (m, 2), 7.72 (m, 1), 8.08 (m, 1); ^{13}C NMR (DMSO-d_6) δ 18.7, 20.0, 92.1, 116.1, 122.7, 124.0, 124.5, 131.4, 152.6, 160.1, 171.8; UV 243, 283, 295, 315 nm; IR 1634, 1606 cm^{-1}. Anal. Calcd for $C_{12}H_{11}NO_2$ (0.08% H_2O found): C, 71.57; H, 5.52; N, 6.96. Found: C, 71.14; H, 5.39; N, 6.86.

Supplementary Material Available: Experimental details for **7c-g**, **8c-g**, **2h**, and **3h**, ^{1}H and ^{13}C NMR spectra for **7e**, **8f**, **2e**, **3e**, and **2h**, and COLOC spectra for **9h**, **10h**, **2h**, and **3h** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.