Imidazopyridinium and Pyridopyrimidium Bromides: Synthesis and Hydrolysis

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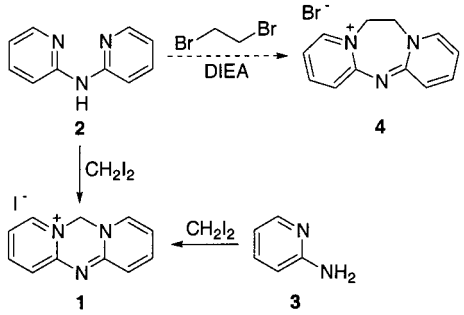
Abstract: The reactions of symmetrical and unsymmetrical 2,2′-dipyridylamines with 1,2-dibromoethane and 1,3-dibromopropane give imidazopyridinium and pyridopyrimidium bromides, respectively. These acetone/CH_2Cl_2-insoluble, highly fluorescent quaternary ammonium salts undergo addition/ring opening upon treatment with methanolic KOH to give pyridin-2-one derivatives. A sequential *N*,*N*-dialkylation/ring-opening hydrolysis/*N*,*N*-dialkylation/ring-opening hydrolysis strategy was developed for the construction of unsymmetrical bis(pyridin-2-ones).

As recently reported by us[1] and by others,[2] various heterocyclic ammonium salts have been shown to activate the cystic fibrosis transmembrane conductance regulator protein CFTR.[3] Since it is generally believed that restoration of CFTR chloride permeability will be clinically beneficial, an important goal in cystic fibrosis research is the identification of small molecule activators of CFTR.

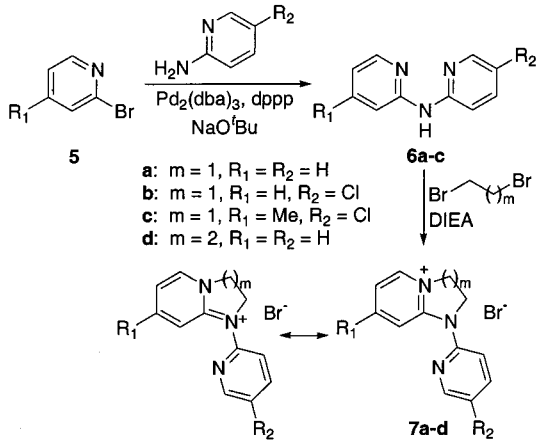
Azacyanine **1**, the parent compound in a novel class we reported capable of modulating chloride-selective ion channels, can be constructed[4] by either reaction of 2,2′-dipyridylamine **2** with diiodomethane or, more directly, by reaction of aminopyridine **3** with diiodomethane (Scheme 1). As part of an investigation of these and other transformations,[5] we wondered if the seven-membered analogue of **1** (**4**) would be available by reaction of **2** with 1,2-dibromoethane in the presence of a base such as DIEA (*N*,*N*-diisopropylethylamine).

The starting material for this study, 2,2′-dipyridylamine (**6**), was prepared by the Buchwald method of palladium-catalyzed carbon−nitrogen bond formation.[6] As outlined in Scheme 2, this method involves treating

Scheme 1. Azacyanines (1) from 2,2′-Dipyridylamines (2)



Scheme 2. Imidazo- (*m* = 1) and Pyridopyrimidium (*m* = 2) Bromides



a 2-bromopyridine (**5**) with Pd(II) in the presence of chelating bis(phosphine) ligand 1,3-bis(diphenylphosphino)propane (dppp) and a 2-aminopyridine to deliver the targeted 2,2′-dipyridylamine (**6**) in ca. 70−75% yield. Proper selection of 2-bromo- and 2-aminopyridine starting materials allows for the preparation of unsymmetrical 2,2′-dipyridylamines. Subsequent treatment of the resulting 2,2′-dipyridylamines **6a**−**c** with 1,2-dibromopropane (used also as solvent) and DIEA (2−3 equiv) at reflux (ca. 130 °C) under a nitrogen atmosphere for 18 h did produce a quaternary ammonium heterocycle, but not **4**. Rather, this *N*,*N*-dialkylation produced imidazopyridinium bromide[7] **7a**−**c** (*m* = 1) as the sole product. Intrigued by this transformation and the fact that imidazopyridium salts are reported to have hypoglycemic,[8] type I allergy,[9] and neuromuscular blocking[10] properties, we decided to further investigate the synthesis and hydrolysis reactions of these imidazopyridium salts.

After cooling to room temperature, the crude acetone- and CH_2Cl_2-insoluble solids from the reaction of **6** with

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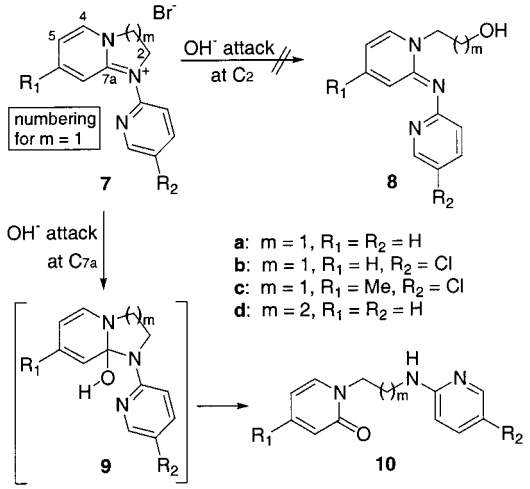
Scheme 3. Ring Opening of Imidazo- and Pyridopyrimidium Bromides

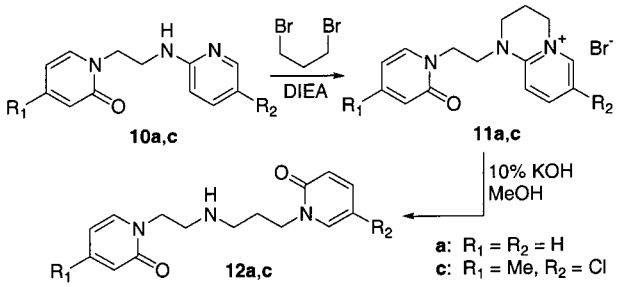


dibromoethane were washed with additional acetone and CH_2Cl_2 to remove the DIEA·HBr salts and then recrystallized from hot methanol to afford imidazopyridium bromides **7a**−**c** ($m = 1$) in excellent yields (80−100%). All of these quaternary ammonium bromides display signals for the ethylene group at δ 4.4 and 4.9 (t, $J = 10$ Hz) in the ^{1}H NMR and δ 47 and 51 in the ^{13}C NMR (DMSO-d_6). This ethylene nonequivalence provides unequivocal evidence that these products are imidazopyridium salts (**7**) and not azacyanine salts (**4**).

In the light of these results with 1,2-dibromoethane, we next investigated the reaction of 2,2′-dipyridylamine **6a** with 1,3-dibromopropane (again, as solvent) in the presence of DIEA (2 equiv). As with the imidazopyridinium system, this reaction proceeds cleanly to afford the pyridopyrimidium bromide (**7d**, $m = 2$) in high yield (88%). The propyl methylenes in this quaternary ammonium salt appear at δ 2.4, 4.0, and 4.5 in the ^{1}H NMR and δ 21, 48, and 52 in the ^{13}C NMR (DMSO-d_6).

We are aware of only one report of nucleophilic ring opening of the imidazopyridinium ring system. In that case, thiophenolate and selenophenolate nucleophiles were shown to attack at the C2 position ($m = 1$) of the imidazopyridinium analogue.[11] Although we expected an analogous attack by hydroxide to yield **8**, we were not surprised, in the light of our previous work,[5] to find that the reaction followed an alternative course to produce pyridin-2-ones in quantitative yield. In this reaction, the hydroxide ion is presumed to attack position C7a of the imidazopyridinium **7** to produce, via intermediate **9**, pyridin-2-ones (**10**). This reaction was easily monitored both by TLC and loss of fluorescence as **7** → **10**.The success of this **6** → **7** → **10** sequence prompted us to wonder if a second *N*,*N*-dialkylation/hydrolysis cycle, acting on the remaining 2-aminopyridine moiety, might be possible. To address this question, pyridones **10a** and **10c** were first reacted with dibromopropane in the presence of DIEA to give quaternary ammonium salt **11a** and **11c**, respectively, in high yields. Nucleophilic addition of KOH to these pyrido[1,2-*a*]pyrimidin-5-ylium salts led to ring opening and formation of the unsymmetrical dialkylamino bis(pyridin-2-ones) **12a** and **12c**, respectively.[12] In conclusion, we have demonstrated a viable synthesis of imidazopyridium and pyridopyrimidium bromides and have further shown that treatment of these salts with methanolic KOH leads, by addition/ring opening, to novel pyridin-2-one derivatives.

Scheme 4. Unsymmetrical Dialkylamino Bis(pyridin-2-ones)



Experimental Section

General Experimental. Unless otherwise noted, starting materials were obtained from commercial suppliers and used as received. Melting points were determined using an Electrothermal 9100 apparatus and are uncorrected. Infrared spectra were taken neat on a refractive spectrophotometer. ^{1}H NMR was measured in $CDCl_3$, MeOH-d_4, DMSO-d_6, or CD_3CO_2D at 400 or 300 MHz and ^{13}C NMR was measured at 100 or 75 MHz. Elemental analyses were performed by Midwest Microlabs (Indianapolis, IN). Silica gel chromatography was performed according to the method of Still.[13]

General Method for the Preparation of Unsymmetrical 2,2′-Dipyridylamine. A three-necked round-bottom flask equipped with a magnetic stir bar was charged with the specific 2-bromopyridine, aminopyridine (1.3 equiv), $Pd_2(dba)_3$ (0.2 equiv), dppp (0.5 equiv), sodium *tert*-butoxide (1.7 equiv), and dry toluene in this order. Under a nitrogen atmosphere, this solution was stirred at 80 °C for 1 day. Additional $Pd_2(dba)_3$ (0.2 equiv), dppp (0.5 equiv), and sodium *tert*-butoxide (1.7 equiv) were added, and the mixture was stirred under nitrogen atmosphere at 80 °C for an additional 24 h. After TLC showed complete consumption of bromopyridine, the mixture was cooled to room temperature and quenched with water. The aqueous layer was separated from the organic layer and extracted with diethyl ether. The combined organic layers were dried with $MgSO_4$, filtered, concentrated, and purified by column chromatography. Recrystallization afforded white crystals.

(5-Chloropyridin-2-yl)pyridin-2-ylamine (6b).[6] The general procedure for the preparation of unsymmetrical 2,2′-dipyridylamine was employed with the following reagents and quantities: 2-bromopyridine (1.9 g, 12 mmol), 4-chloro-2-aminopyridine (1.6 g, 12 mmol), $Pd_2(dba)_3$ (0.2 g, 0.2 mmol), dppp (0.2 g, 0.5 mmol), sodium *tert*-butoxide (2 g, 21 mmol), and dry toluene (90 mL); additional $Pd_2(dba)_3$ (0.2 g, 0.2 mmol), dppp (0.2 g, 0.5 mmol), and sodium-*tert*-butoxide (2 g, 21 mmol). Column chromatography (3:1 hexane/ethyl acetate) followed by recrystallization from hot methanol produced **6b** [1.7 g, 8.4 mmol, 70%; mp 102−3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.84 (m, 1H), 7.55 (m, 5H), 8.26 (m, 1H), 9.03 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 112.1, 112.9, 116.8, 123.3, 137.7, 138.1, 146.1, 147.7, 152.8, 154.1; IR (neat) 3262, 3025, 1602, 1588, 797 cm^{-1}].

(5-Chloropyridin-2-yl)(4-methylpyridin-2-yl)amine (6c).[6] The general procedure for the preparation of unsymmetrical 2,2′-dipyridylamine was employed with the following reagents and quantities: 4-methyl-2-bromopyridine (1.6 g, 12 mmol), 4-chloro-2-aminopyridine (1.6 g, 12 mmol), $Pd_2(dba)_3$ (0.2 g, 0.2 mmol), dppp (0.2 g, 0.5 mmol), sodium *tert*-butoxide (2 g, 21 mmol), and dry toluene (90 mL); additional $Pd_2(dba)_3$ (0.2 g, 0.2 mmol), dppp (0.2 g, 0.5 mmol), and sodium *tert*-butoxide (2 g, 21 mmol).

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Column chromatography (3:1 hexane/ethyl acetate) followed by recrystallization from hot methanol produced **6c** [1.5 g, 6.82 mmol, 75%; mp 85−6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 6.69 (dd, J = 1, 5 Hz, 1H), 7.25 (d, J = 1 Hz, 1H), 7.53 (dd, J = 3, 9 Hz, 1H), 7.60 (d, J = 9 Hz, 1H), 8.12 (d, J = 5 Hz, 1H), 8.20 (d, J = 3 Hz, 1H), 8.40 (br s, 1H; ^{13}C NMR (100 MHz, $CDCl_3$) δ_ 21.5, 112.1, 112.7, 118.4, 123.3, 137.7, 141.8, 146.4, 147.6, 149.3, 152.5; IR (neat) 3250, 3023, 1603, 1508, 788 cm^{-1}].

General Method for the Preparation of Quaternary Ammonium Bromides. The specific 2,2′-dipyridylamine was dissolved in the appropriate dibromoalkane (as solvent) containing DIEA (about 2 equiv). The mixture was refluxed for 18 h and monitored by TLC (disappearance of starting material and the appearance of a fluorescent product on the baseline). The product precipitated from the reaction mixture and, upon cooling, the precipitate was collected and washed with CH_2Cl_2 and acetone to remove DIEA·HBr salts. Recrystallization from hot methanol gave the product.

(1-Pyridin-2-yl)-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridinium Bromide (7a). The general procedure for the preparation of quaternary ammonium bromide was employed with the following reagents and quantities: dipyridin-2-ylamine **6a** (2.8 g, 16.4 mmol), 1,2-dibromoethane (20 mL, 232 mmol), and DIEA (6 mL, 34 mmol) gave **7a** [4.5 g, 16.4 mmol, 100%; mp 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.44 (t J = 10 Hz, 2H), 4.91 (t J = 10 Hz, 2H), 7.42 (m, 2H), 7.33 (m, 1H), 7.96 (m, 1H), 8.26 (m, 1H), 8.46 (m, 1H), 8.63 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.1, 50.9, 112.4, 114.0, 117.5, 120.4, 139.8, 140.1, 146.4, 148.5, 150.8, 152.0; IR (neat) IR (neat) 2969, 1638, 1560, 1336, 758 cm^{-1}].

1-(5-Chloropyridin-2-yl)-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridinium Bromide (7b). The general procedure for the preparation of quaternary ammonium bromide was employed with the following reagents and quantities: (5-chloropyridin-2-yl)pyridin-2-ylamine **6b** (1 g, 4.62 mmol), 1,2-dibromoethane (10 mL, 116 mmol), and DIEA (3 mL, 17 mmol) gave **7b** [1.2 g, 3.9 mmol, 86%; mp 230−233 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.43 (t J = 10 Hz, 2H), 4.91 (t J = 10 Hz, 2H), 7.29 (d, J = 9 Hz, 1H), 7.37 (m, 1H), 8.09 (dd, J = 1, 9 Hz, 1H), 8.29 (m, 1H), 8.52 (d, J = 1 Hz, 1H), 8.56 (dd, J = 1, 9 Hz, 1H), 8.63 (d, J = 6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 47.3, 51.0, 113.9, 114.0, 118.0, 126.3, 139.8, 140.0, 146.6, 146.8, 150.6; IR (neat) 3006, 1635, 1540, 1315, 760 cm^{-1}. Anal. Calcd for $C_{12}H_{11}BrClN_3$**.**H_2O; C, 46.11; H, 3.55; N, 13.44. Found: C, 43.94; H, 3.38; N, 13.78].

1-(5-Chloropyridin-2-yl)-7-methyl-2,3-dihydro-1*H*-imidazo[1,2-*a*]pyridinium Bromide (7c). The general procedure for the preparation of quaternary ammonium bromide was employed with the following reagents and quantities: (5-chloropyridin-2-yl)(4-methylpyridin-2-yl)amine **6c** (1.5, 6.96 mmol), 1,2-dibromoethane (22 g, 117.3 mmol), and DIEA (2.5 mL, 14.3 mmol) gave **7c** [2 g, 6.12 mmol, 88%; mp 320 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.52 (s, 3H), 4.43 (t J = 9 Hz, 2H), 4.86 (t J = 9 Hz, 2H), 7.25 (dd, J = 1, 7 Hz, 1H), 7.31 (d, J = 9 Hz, 1H), 8.10 (dd, J = 2, 9 Hz, 1H), 8.41 (d, J = 1 Hz, 1H), 8.53 (d, J = 7 Hz, 1H), 8.54 (d, J = 2 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.9, 47.7, 50.5, 113.0, 114.0, 119.3, 126.5, 138.8, 139.6, 146.8, 150.1, 150.5, 159.4; IR (neat) 2996, 1622, 1539, 1300, 750 cm^{-1}. Anal. Calcd for $C_{13}H_{13}BrClN_3$; C, 47.81; H, 4.01; N, 12.86. Found: C, 47.75; H, 4.19; N, 12.33].

1-(Pyridin-2-yl)-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidium Bromide (7d). The general procedure for the preparation of quaternary ammonium bromide was employed with the following reagents and quantities: (dipyridin-2-ylamine **6a** (1 g, 5.84 mmol), 1,3-dibromopropane (30 mL, 290 mmol), and DIEA (2.5 mL, 14.3 mmol) gave **7d** [1.5 g, 5.12 mmol, 88%; mp 290 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.35 (m, 2H), 3.95 (t, J = 6 Hz, 2H), 4.52 (t, J = 6 Hz, 2H), 7.05 (d, J = 9 Hz, 1H), 7.14 (m, 1H), 7.47 (m, 1H), 7.61 (d, J = 8 Hz, 1H), 7.89 (m, 1H), 8.05 (dt, J = 2, 8 Hz, 1H), 8.33 (dd, J = 1, 6 Hz, 1H), 8.56 (dd, J = 1, 4 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 20.8, 48.2, 52.5, 115.7, 116.4, 120.4, 124.2, 140.8, 141.7, 143.2, 150.2, 151.5, 154.4; IR (neat) 2981, 1600, 1533, 1322, 720 cm^{-1}].

General Method for the Reaction of Quaternary Ammonium Salts with Methanolic KOH. The quaternary ammonium salt was mixed with 10% methanolic KOH (and water to dissolve if necessary) and magnetically stirred at 80 °C. The reaction was monitored by the disappearance of the highly fluorescent starting material (12−24 h). The mixture was then poured into a separatory funnel containing a 1:1 water/CH_2Cl_2 mixture. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine and saturated $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated via rotatory evaporation. Column chromatography (gradient from EtOAc to a MeOH/EtOAc ratio depending on the compound) afforded the desired pyridin-2-one.

1-[2-(Pyridin-2-ylamino)ethyl]-1*H*-pyridin-2-one (10a). The general procedure for the reaction of quaternary ammonium salts with methanolic KOH was employed with the following reagents and quantities: pyridinium bromide **7a** (1 g, 3.6 mmol) and 50 mL of 10% methanolic KOH gave **10a** [640 mg, 3 mmol, 86 %; mp 108−109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (q, J = 6 Hz, 2H), 4.16 (t, J = 6 Hz, 2H), 5.22 (t, J = 6 Hz, 1H), 6.06 (dt, J = 2, 7 Hz, 1H), 6.39 (d, J = 8 Hz, 1H), 6.51 (m, 2H), 7.17 (dd, J = 2, 7 Hz, 1H), 7.29 (m, 2H), 8.02 (dd, J = 1, 5 Hz, 1H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.5, 49.7, 106.2, 108.3, 113.1, 120.9, 137.4, 138.6, 139.9, 148.0. 158.3, 163.2; IR (neat) 3298, 1644, 1589 cm^{-1}. Anal. Calcd for $C_{12}H_{13}N_3O$; C, 66.96; H, 6.09; N, 19.52. Found: C, 66.93; H, 6.20; N, 19.50].

1-[2-(5-Chloropyridin-2-ylamino)ethyl]-1*H*-pyridin-2-one (10b). The general procedure for the reaction of quaternary ammonium salts with methanolic KOH was employed with the following reagents and quantities: pyridinium bromide **7b** (1 g, 3.2 mmol) and 50 mL of 10% methanolic KOH gave **10b** [643 mg, 2.6 mmol, 80%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (q, J = 6 Hz, 2H), 4.18 (t, J = 6 Hz, 2H), 5.29 (br s, 1H), 6.12 (dt, J = 2, 7 Hz, 1H), 6.38 (d, J = 9 Hz, 1H), 6.56 (dd, J = 1, 9 Hz, 1H), 7.20 (dd, J = 2, 7 Hz, 1H), 7.31 (m, 2H), 7.99 (d, J = 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.9, 49.6, 106.4, 109.3, 121.0, 126.1, 137.3, 138.4, 140.0, 146.2, 156.6, 163.4; IR (neat) 3308, 2996, 1651, 1579, 760 cm^{-1}].

1-[2-(5-Chloropyridin-2-ylamino)ethyl]-4-methyl-1*H*-pyridin-2-one (10c). The general procedure for the reaction of quaternary ammonium salts with methanolic KOH was employed with the following reagents and quantities: pyridinium bromide **7c** (1 g, 3.06 mmol) and 50 mL of 10% methanolic KOH gave **10c** [660 mg, 2.5 mmol, 82%; mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.63 (dt, J = 6 Hz, 2H), 4.12 (t, J = 6 Hz, 2H), 5.49 (br s, 1H), 5.95 (dd, J = 2, 7 Hz, 1H), 6.31 (d, J = 2 Hz, 1H), 6.37 (d, J = 9 Hz, 1H), 7.06 (d, J = 7 Hz, 1H), 7.28 (dd, J = 3, 9 Hz, 1H), 7.96 (d, J = 3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 42.0, 49.1, 109.0, 109.4, 119.3, 119.9, 137.1, 137.3, 146.2, 151.8, 156.8, 163.3; IR (neat) 3308, 3308, 1645, 1530, 720 cm^{-1}. Anal. Calcd for $C_{13}H_{14}ClN_3O$; C, 59.21; H, 5.35; N, 15.91. Found: C, 59.29; H, 5.41; N, 15.72].

1-[3-(Pyridin-2-ylamino)propyl]-1*H*-pyridin-2-one (10d). The general procedure for the reaction of quaternary ammonium salts with methanolic KOH was employed with the following reagents and quantities: pyridinium bromide **7d** (1 g, 3.4 mmol) and 50 mL of 10% methanolic KOH gave **10d** as a yellow oil [640 mg, 2.8 mmol, 82%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85 (quintet, J = 7 Hz, 2H), 3.17 (q, J = 7 Hz, 2H), 3.86 (t, J = 7 Hz, 2H), 5.47 (t, J = 7 Hz, 1H), 5.97 (dt, J = 1, 7 Hz, 1H), 6.24 (dd, J = 1, 9 Hz, 1H), 6.34 (m, 2H), 7.13 (m, 3H), 7.87 (dd, J = 1, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.4, 38.3, 47.1, 106.5, 108.2, 112.5, 120.7, 137.2, 137.9, 139.7, 147.8, 158.7, 162.9; IR (neat) 3311, 3001, 1649, 1506 cm^{-1}].

1-[2-(2-Oxo-2*H*-pyridin-1-yl)ethyl]-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (11a). The general procedure for the preparation of quaternary ammonium bromide was employed with the following reagents and quantities: pyridin-2-one **10a** (600 mg, 2.78 mmol), 1,2-dibromopropane (30 mL, 294 mmol), and DIEA (1.5 mL, 8.61 mmol) gave **11a** [930 mg, 2.78 mmol, 100%; mp 300 °C; ^{1}H NMR (300 MHz, CD_3CO_2D) δ 2.35 (m, 2H), 3.78 (t, J = 5 Hz, 2H), 4.28 (t, J = 6 Hz, 2H), 4.45 (t, J = 5 Hz, 2H), 4.82 (t, J = 6 Hz, 2H), 6.92 (m, 1H), 7.20 (m, 1H), 7.43 (m, 2H), 7.93 (m, 2H), 8.11 (m, 1H), 8.67 (d, J = 7 Hz, 1H); ^{13}C NMR (75 MHz, CD_3CO_2D) δ 48.2, 49.3, 50.1, 52.3, 54.9, 112.8, 113.2, 116.1, 116.4, 141.1, 141.8, 143.2, 146.3, 151.8, 161.54; IR (neat) 2998, 1632, 1555 cm^{-1}].

5-Chloro-1-[2-(4-methyl-2-oxo-2*H*-pyridin-1-yl)ethyl]-1,2,3,4-tetrahydropyrido[1,2-*a*]pyrimidin-5-ylium Bromide (11c). The general procedure for the preparation of quaternary ammonium bromide was employed with the following reagents and quantities: pyridin-2-one **10c** (600 mg, 2.28 mmol), 1,2-

dibromopropane (30 mL, 294 mmol), and DIEA (1.5 mL, 8.61 mmol) gave **11c** [880 mg, 2.28 mmol, 100%; mp 300 °C; ^{1}H NMR (300 MHz, MeOH-d_4) δ 2.25 (m, 2H), 3.63 (t J = 6 Hz, 2H), 3.98 (t, J = 6 Hz, 2H), 4.28 (t, J = 6 Hz, 2H), 4.32 (t, J = 6 Hz, 2H), 4.90 (s, 3H), 6.35 (d, J = 7 Hz, 1H), 6.37 (s, 1H), 7.45 (d, J = 10 Hz, 1H), 7.64 (d, J = 7 Hz, 1H), 7.89 (dd, J = 2, 10 Hz, 1H), 8.17 (d, J = 2 Hz, 1H); ^{13}C NMR (75 MHz, MeOH-d_4) δ 19.0, 20.4, 46.2, 47.0, 50.2, 52.2, 111.7, 114.0, 117.2, 119.3, 138.1, 138.5, 142.6, 150.8, 155.3, 163.2; IR (neat) 2998, 1632, 1555 cm^{-1}. Anal. Calcd for $C_{16}H_{19}BrClN_3O{\cdot}H_2O{\cdot}HBr$; C, 39.74; H, 4.59; N, 8.69. Found: C, 39.74; H, 4.40; N, 8.06].

1-[3-(1*H*-Pyridin-2-one)-2-ethylaminopropyl]-1*H*-pyridin-2-one (12a). The general procedure for the reaction of quaternary ammonium salts with methanolic KOH was employed with the following reagents and quantities: pyridinium bromide **11a** (500 mg, 1.48 mmol) and 40 mL of 10% methanolic KOH gave **12a** [360 mg, 1.3 mmol, 88%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (br s, 1H), 1.89 (quintet, J = 7 Hz, 2H), 2.61 (t, J = 7 Hz, 2H), 2.96 (t, J = 6 Hz, 2H), 3.97 (t, J = 7 Hz, 2H), 4.03 (t, J = 6 Hz, 2H), 6.14 (m, 2H), 6.55 (m, 2H), 7.29 (m, 4H); 13C NMR (75 MHz, $CDCl_3$) δ 29.5, 46.1, 47.5, 48.3, 50.4, 105.9, 106.2, 121.0, 121.1, 138.0, 138.5, 139.6, 139.8, 162.8, 162.9; IR (neat) 3258, 1653, 1580 cm^{-1}].

5-Chloro-1-[3-(4-methyl-1*H*-pyridin-2-one)-2-ethylaminopropyl]-1*H*-pyridin-2-one (12c). The general procedure for the reaction of quaternary ammonium salts with methanolic KOH was employed with the following reagents and quantities: pyridium bromide **11c** (500 mg, 1.3 mmol) with 40 mL of 10% methanolic KOH gave **12c** [420 mg, 1.3 mmol, 100%; mp 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (br s, 1H), 1.87 (m, 2H), 2.15 (s, 3H), 2.60 (t, J = 7 Hz, 2H), 2.92 (t, J = 6 Hz, 2H), 3.93 (t, J = 7 Hz, 2H), 3.98 (t, J = 6 Hz, 2H), 6.00 (dd, J = 2, 7 Hz, 1H), 6.35 (d, J = 2 Hz, 1H), 6.49 (d, J = 10 Hz, 1H), 7.19 (d, J = 7 Hz, 1H), 7.24 (dd, J = 2, 10 Hz, 1H), 7.28 (d, J = 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 29.2, 45.9, 47.9, 48.4, 49.7, 108.6, 112.2, 119.3, 121.8, 135.7, 137.3, 140.4, 151.4, 161.1, 162.8; IR (neat) 3299, 1630, 1590 cm^{-1}. Anal. Calcd for $C_{16}H_{20}ClN_3O_2$; C, 59.72; H, 6.26; N, 13.43. Found: C, 59.90; H, 6.38; N, 13.18].

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for **7a**, **7d**, **10b**, **10d**, **11a**, and **12a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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