the reaction mixture was analyzed by GC. The structural assignment of the products was carried out by the comparison of authentic samples or by spectral analyses of the isolated products.

2-Pyridyl triflate (6): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1 H, d, J = 8.2 Hz, 3-H), 7.41 (1 H, dd, J = 7.4, 4.8 Hz, 5-H), 7.92 (1 H, dd, J = 8.2, 4.8 Hz, 4-H), 8.40 (1 H, d, J = 4.8 Hz, 6-H); ^{19}F NMR ($CDCl_3$) 73.13 (s); IR (neat) 1420 (SO_2), 1210, 1135 cm^{-1}; mass spectrum, m/e 227 (M^+). Anal. Found C, 31.47; H, 1.88; N, 6.03. Calcd for $C_6H_4F_3O_3S$: C, 31.73; H, 1.77; N, 6.17.

2-Chloro-6-[[(trifluoromethyl)sulfonyl]oxy]pyridine (10): oil; ^{1}H NMR ($CDCl_3$) δ 7.15 (1 H, d, J = 7.8 Hz, 3-H), 7.49 (1 H, d, J = 7.8 Hz, 5-H), 7.89 (1 H, dd, J = 7.8, 7.8 Hz, 4-H); ^{19}F NMR ($CDCl_3$) 73.0 (s, CF_3); IR (neat) 1423 (SO_2), 1215, 1135 cm^{-1}; mass spectrum, m/e 263, 261 (M^+). Anal. Found: C, 27.42; H, 1.16; N, 5.26. Calcd for $C_6H_3ClF_3NO_3S$: C, 27.53; H, 1.15; N, 5.35.

2-Fluoro-6-[[(trifluoromethyl)sulfonyl]oxy]pyridine (13): oil; ^{1}H NMR ($CDCl_3$) δ 7.10 (1 H, dd, J = 7.8, 2.3 Hz, 3-H), 7.17 (1 H, d, J = 7.8 Hz, 5-H), 8.04 (1 H, ddd, J = 7.8, 7.8, 7.8 Hz, 4-H); ^{19}F NMR ($CDCl_3$) 67.0 (1 F, bs, 2-F), 74.6 (3 F, s, CF_3); IR (neat) 1430 (SO_2), 1220, 1140 cm^{-1}; mass spectrum, m/e 245 (M^+). Anal. Found: C, 29.16; H, 1.27; N, 5.55. Calcd for $C_6H_3F_4NO_3S$: C, 29.39; H, 1.22; N, 5.71.

3,5-Bis(trifluoromethyl)-2-[[(trifluoromethyl)sulfonyl]oxy]pyridine (17): oil; ^{1}H NMR ($CDCl_3$) δ 8.83 (1 H, bs, 6-H), 8.37 (1 H, bs, 4-H); ^{19}F NMR ($CDCl_3$) 62.8 (3 F, s, CF_3), 63.3 (3 F, s, CF_3), 73.4 (3 F, s, SO_2CF_3); IR (in $CDCl_3$) 1425 (SO_2), 1350, 1220, 1160, 1130 cm^{-1}; mass m/e 363.9660 (M^+) (calcd for $C_8H_2NF_9O_3S$ 363.9645).

Reaction of Pyridine-F_2 with Sodium Triflate or BF_3·OEt_2. With Sodium Triflate. A 10% F_2/N_2 mixture was introduced at a flow rate of 30 mL/min just above the surface of a solution of pyridine (3 mmol) in 6 mL of $CFCl_3$ on a cooling bath of -78 °C under stirring. As the fluorine was introduced, a white or creamy solid formed. Total amount of F_2 used was 4.5 mmol. After nitrogen was flowed at a rate of 15 mL/min for 30 min, a solution of 0.518 g of sodium triflate in 12 mL of dry CH_3CN was added carefully, the temperature being kept below -40 °C, and the reaction mixture was stirred for 2 h on a cooling bath of -40 °C. The mixture was warmed to room temperature, filtered through Celite to remove sodium fluoride, and evaporated up to dryness without heating. The resulting solid was sufficiently washed with 2 mL of dry tetrahydrofuran to give 0.235 g (32%) of **5**.

With BF_3·OEt_2. Pyridine (3 mmol) was fluorinated with 10% F_2/N_2 in 6 mL of dry CH_3CN in the same manner as above. F_2 used was 9 mmol. After the fluorination, the homogeneous reaction solution was warmed to room temperature and left for 1 h. The NMR spectra of this acetonitrile solution are discussed in Results and Discussion section. Then the solution was cooled on a bath of -40 °C and BF_3·OEt_2 (3 mmol) was added into it under stirring. After stirring for 1 h at -40 °C, 50 mL of diethyl ether was added into the solution at -40 °C. The resulting solid was collected by filtration and washed with 2 mL of dry tetrahydrofuran to give 0.203 g of the solid, which was recrystallized from dry CH_3CN-Et_2O to give 0.172 g (31%) of **1** (X = BF_4, R = H).

Registry No. **1** (X = BF_4, R = 3-CO_2Et), 116241-52-2; **1a**, 107264-09-5; **1b**, 107264-12-0; **1c**, 107264-10-8; **1d**, 116241-53-3; **1e**, 116241-63-5; **1f**, 116241-55-5; **1g**, 116241-56-6; **1h**, 119071-51-1; **1i**, 109705-15-9; **1j**, 116241-51-1; **1k**, 119071-53-3; **1l**, 119071-53-3; **1m**, 119071-55-5; **1n**, 116241-58-8; **2** (R = 3,5-Me_2), 111887-71-9; **2** (R = 4-*t*-Bu), 116241-60-2; **2** (R = 6-OMe), 116241-61-3; **2** (R = 4-Ph), 116241-62-4; **2** (R = 4-CO_2Me), 455-69-6; **2** (R = 3-CO_2Et), 113898-56-9; **2** (R = 3,5-$(Cl)_2$), 823-56-3; **2** (R = 3-CN), 3939-13-7; **2** (R = 2-cyano-6-fluoro), 3939-15-9; **2** (R = 4-NO_2), 18614-46-5; **2** (R = 4-Me), 461-87-0; **2** (R = 5-CO_2Et), 116241-59-9; **2a**, 372-48-5; **5**, 107263-95-6; **6**, 65007-00-3; **7**, 109-09-1; **8** (R = H), 110-86-1; **8** (R = 4-Me), 108-89-4; **8** (R = 3,5-$(Me)_2$), 591-22-0; **8** (R = 4-*t*-Bu), 3978-81-2; **8** (R = 2-OMe), 1628-89-3; **8** (R = 4-Ph), 939-23-1; **8** (R = 4-CO_2Me), 2459-09-8; **8** (R = 3,5-$(Cl)_2$), 2457-47-8; **8** (R = 3,5-bis(CF_3)), 20857-47-0; **8** (R = 3-Cn), 100-54-9; **8** (R = 2-CN), 100-70-9; **8** (R = 4-NO_2), 1122-61-8; **8** (R = 3-CO_2Et), 614-18-6; **9**, 119071-56-6; **10**, 119071-57-7; **11**, 20885-12-5; **12**, 2402-78-0; **13**, 119071-58-8; **14**, 1513-65-1; **16**, 119071-59-9; **17**, 119071-60-2; **18**, 119071-61-3; **19**, 70158-60-0.

Synthesis of Side-Chain Derivatives of 2,2′-Bipyridine

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General and versatile synthetic methods have been developed for the preparation of a large variety of 2,2′-bipyridines bearing a single functionalized side chain in the 4-position.

Introduction

Few organic ligands have received more attention than 2,2′-bipyridine (bpy) and its analogues (e.g. 1,10-phenanthroline).[1] A large proportion of the recent interest in this ligand stems from the very interesting photophysical and photochemical properties exhibited by several of its transition metal complexes, in particular those of ruthenium,[2] osmium,[3] and rhenium.[4] As more elaborate systems exploiting such properties have started to emerge, especially in redox electrocatalysis and solar energy conversion, it has become increasingly desirable to find ways to link the metal complexes covalently to a variety of auxiliary molecules and/or to polymeric substrates.[5] Regarding the former, one of the currently most active areas of research involves the synthesis of chromophore-quencher systems, where an attempt at achieving improved charge separation is made by attaching suitable electron-transfer acceptors (such as 4,4′-bipyridinium ion) and/or donors (such as phenothiazine) to $Ru(bpy)_3^{2+}$ and related species.[6] Another area of growing interest is to be found

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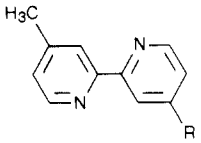
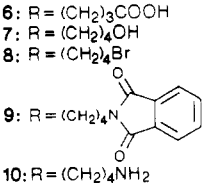
in the use of bpy complexes of transition and lanthanide metals as probes of interfacial systems and biomolecules.[7,8] Unfortunately, only one compound suitable for these applications is commercially available (5-amino-1,10-phenanthroline), while the known chemistry of 2,2′-bipyridines bearing a single functionalized side chain has been confined to a few examples.[9] In this study, we report reliable routes to substituted bipyridines. In general, they appear to be capable of being generalized to any desired length of the spacer between the functional group and the ring.

Results and Discussion

The most versatile, inexpensive, and easily available source of 2,2′-bipyridine derivatives, is 4,4′-dimethyl-2,2′-bipyridine (1). As first shown by Ghosh and Spiro,[9a] 1 is lithiated with *n*-butyllithium at the methyl substituents by analogy to 4-methylpyridine. The resulting equilibrium mixture of mono-, di-, and unlithiated 1 can be allowed to react with a wide variety of electrophiles. In order to minimize the amount of symmetrical bipyridines produced, which are often difficult to separate from the desired unsymmetrical compounds, about 0.92 equiv of *n*-butyllithium were employed in the lithiation of 1.



1: R = CH_3
2: R = CH_2COOH
3: R = CH_2COOCH_3
4: R = $(CH_2)_3$-(2-dioxolanyl)
5: R = $(CH_2)_3CHO$



6: R = $(CH_2)_3COOH$
7: R = $(CH_2)_4OH$
8: R = $(CH_2)_4Br$
9: R = $(CH_2)_4$-N(phthalimido)
10: R = $(CH_2)_4NH_2$

With carbon dioxide (as dry ice), lithiated 1 gave 4′-methyl-2,2′-bipyridine-4-acetic acid (**2**) in 66% yield. Although compound **2** is stable indefinitely at room temperature, it is easily decarboxylated upon heating. For this reason, its methyl ester **3** was best prepared by reaction with boron trifluoride–methanol complex at 0 °C. The exchangeability of the methylene hdyrogens of **2** is shown by the broad peak at δ 4.0–5.5 in its ^1H NMR spectrum in DMSO-d_6 solution. The peak is absent when the spectrum is recorded in D_2O.

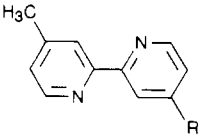
A very flexible way of introducing a functionalized side chain into 2,2′-bipyridine utilizes the reaction of lithiated 1 with 2-(2-bromoethyl)-1,3-dioxolane. The product, 4-[3-(1,3-dioxolan-2-yl)propyl]-4′-methyl-2,2′-bipyridine (**4**), obtained in 58% yield, was efficiently deprotected (95%) by acid hydrolysis to aldehyde **5**. The aldehyde functionality, with its intermediate oxidation level, could then be easily subjected to a variety of transformations under mild conditions.

Oxidation of **5** with potassium permanganate in acetone gave the corresponding carboxylic acid **6** in 52% yield, while reduction with sodium borohydride in ethanol afforded alcohol **7** (48% from 1). Treatment of **7** with 62% hydrobromic acid at reflux effected its conversion to the bromobutyl derivative **8**. Although the latter compound could also be obtained by direct reaction of lithiated 1 with an excess of 1,3-dibromopropane, the resulting product mixture is difficult to purify and yields tend to be variable. We found the more lengthy route described above far more reliable, largely because the critical purification step is performed at the alcohol stage. At that stage chromatography of the crude product mixture is facile due to the very different retention times of the various components in the reaction mixture. The standard Gabriel synthesis was carried out on **8**, resulting in its conversion to amine **10** in high yield (90%). Preliminary experiments also indicate that other alkylations with **8** can be equally successful (e.g. of CN^-, thiourea, diethyl malonate, etc.), allowing further scope for functional modifications.

The synthetic strategy outlined above should be easily applicable to lower and higher homologues of 2-(2-bromomethyl)-1,3-dioxolane in combination with the use of one- and two-carbon electrophiles, such as formaldehyde,[9a] carbon dioxide, or ethylene oxide.[10] It is capable of providing the wide range of functionalized 2,2′-bipyridines that may be needed in a particular application or study. Only when the functional group is near or directly attached to the ring is a different approach required. An attractive starting material for the synthesis of such derivatives would be 4-bromo-2,2′-bipyridine. However, its use is not practical because of the lengthy reaction sequence needed to prepare it from 2,2′-bipyridine.

Oxidation of 1 to aldehyde **16** was recently reported;[11] unfortunately, no reaction conditions or yield were given. In our hands, the action of *N*-chlorosuccinimide (NCS) and *N*-bromosuccinimide (NBS) on 1 generated only a complex mixture of halogenated products, all in low yield and difficult to separate. Attempts to react lithiated 1 with NBS or bromine were likewise unsuccessful.

γ-Methyl functionalization of 1 was achieved by employing the well-known rearrangement of 2- and 4-methylpyridines *N*-oxide with acetic anhydride.[12] 4,4′-Dimethyl-2,2′-bipyridine *N*-oxide (**11**) was readily prepared (83%) by oxidation of 1 with 3-chloroperoxybenzoic acid in chloroform at 0 °C. The ^1H NMR spectrum of **11** was easily interpreted by comparison with those of 1, 2,2′-bipyridine, and 2,2′-bipyridine *N*-oxide.[13] The large upfield ($\Delta\delta$ = 0.6 ppm) shift observed for the H_3, ring hydrogen, with respect to its position in 1, is due to the proximity of the *N*-oxide group.



11: N → O, R = CH_3
12: R = CH_2OAc
13: R = CH_2OH
14: R = CH_3; 3-OH
15: R = CH_3; 5-OH
16: R = CHO
17: R = CH=NOH
18: R = CH_2NH_2
19: R = CH_2Br

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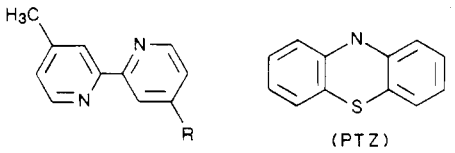
When **11** is heated at reflux with acetic anhydride, ester **12** is generated, together with several ring-substituted products. The crude mixture was not purified at this point, but was instead hydrolyzed with ethanolic sodium hydroxide. Chromatography on silica then allowed the isolation of alcohol **13** (41%), 4,4'-dimethyl-3-hydroxy-2,2'-bipyridine (**14**) (6%), and 4,4'-dimethyl-5-hydroxy-2,2'-bipyridine (**15**) (5.5%).

Oxidation of **13** with activated manganese dioxide gave aldehyde **16**, which upon treatment with hydroxylamine hydrochloride in methanol afforded the corresponding oxime **17** in 90% yield. Hydrogenation of **17** over Pd/C then yielded (73%) amine dihydrochloride **18**.

Finally, **13** could be transformed (92%) into the bromoethyl dihydrobromide derivative **19** by the action of 62% hydrobromic acid at reflux. As the free base of **19** quickly polymerizes by quaternization, this compound is best stored as a salt and then neutralized in situ when used as a reagent. Via this approach, **19** was added to an excess of phenothiazine anion. Displacement of bromide led to the desired 10-[(4'-methyl-2,2'-bipyridin-4-yl)methyl]-phenothiazine (**20**) in 45% yield.

The synthesis of another bipyridine–phenothiazine compound, 10-[3-(4'-methyl-2,2'-bipyridin-4-yl)propyl]-phenothiazine (**21**) was first attempted by treating 10-(2-chloroethyl)phenothiazine (**22**) with lithiated **1**. As no reaction took place, the Cl in **22** was exchanged for Br with ethyl bromide, 1-methyl-2-pyrrolidinone, and a catalytic amount of sodium bromide. The resulting 10-(2-bromoethyl)phenothiazine (**23**) proved more reactive, giving **21** in 43% yield.



20: R = CH_2PTZ
21: R = $CH_2CH_2CH_2PTZ$
22: R = CH_2CH_2Cl
23: R = CH_2CH_2Br

Experimental Section

General. Melting points were taken in Kimax soft glass capillary tubes on a Melt-Temp melting point apparatus equipped with a calibrated thermometer. Nuclear magnetic resonance spectra (^1H NMR and ^{13}C NMR) were obtained on a Varian XL-100 or IBM/Bruker AC-200 spectrometer. Infrared spectra were recorded on a Nicolet 11-DX FT-IR instrument. The high-resolution mass spectrum (HRMS) was recorded at the Research Triangle Institute mass spectrometry laboratory, NC. Elemental analyses were determined by Galbraith Laboratories, Knoxville, TN. Thin-layer chromatography was performed on Merck Kieselgel 60 F_{254} precoated silica gel plates. Spots were visualized by irradiation with ultraviolet light (254 and 365 nm) and/or by dipping the plate in a freshly prepared aqueous solution of ammonium iron(II) sulfate hexahydrate; 2,2'-bipyridines produce various colors with Fe^{2+}, mostly red to purple. Column chromatography was performed on silica gel (Merck SG-60, 70–230 and 230–400 mesh ASTM) or neutral alumina (Merck aluminum oxide 90).

Argon was purified by passage through a BTS catalyst column, followed by a Drierite column. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl prior to use. Methylene chloride and chloroform were distilled from phosphorus pentoxide. Acetone was first distilled from potassium permanganate and then from anhydrous potassium carbonate. *N,N*-Dimethylformamide (DMF) and 1-methyl-2-pyrrolidinone were distilled from 4-Å molecular sieves under reduced pressure. 4,4'-Dimethyl-2,2'-bipyridine (Reilly Tar) was purified by sublimation and then ground to a fine powder. 2-Chloroethyl *p*-toluenesulfonate (Aldrich) was distilled under reduced pressure prior to use. Phenothiazine (Aldrich) was recrystallized from toluene and stored in a dark bottle under argon. Analytical grade Celite (Manville) was used, since general purpose grades contain too much iron impurities, which react with 2,2'-bipyridines. All other reagents were used as received from commercial sources. Reactions involving organometallic compounds were carried out under argon, in glassware that had been dried in an oven for at least 6 h at 150 °C and assembled while hot.

^{13}C and ^1H NMR spectra were recorded in $CDCl_3$ unless otherwise noted and are reported in ppm vs TMS.

Lithiation of 4,4'-Dimethyl-2,2'-bipyridine. A 3000-mL three-necked reaction kettle, equipped with a $2 \times {}^3/_4$ in. stir bar, a gas inlet adaptor, and a rubber septum (connected to an oil bubbler by needle) was flushed with argon, and dry THF (50 mL) was introduced by syringe through the septum, followed by dry diisopropylamine (35 mL, 250 mmol), also added by syringe. The reaction vessel was cooled to −78 °C and 2.5 M *n*-butyllithium in hexanes (100 mL, 250 mmol) was added by a stainless steel cannula. The mixture was stirred for 15 min, and a solution of 4,4'-dimethyl-2,2'-bipyridine (**1**) (50.0 g, 271 mmol) in 1200 mL of dry THF was cannulated dropwise (Teflon cannula). The resulting dark brown suspension was stirred for 2 h at −78 °C and was then ready for subsequent steps.

4'-Methyl-2,2'-bipyridine-4-acetic Acid (2). The lithiated 4,4'-dimethyl-2,2'-bipyridine was quickly poured into a 4000-mL Erlenmeyer flask containing a slush made from 1000 g of dry ice and 500 mL of anhydrous ether. A large amount of pale yellow precipitate formed immediately. The excess CO_2 was allowed to sublime overnight. Ether (500 mL) was added to the resulting semisolid white mass, and the mixture was extracted with 3 M NaOH (3 × 500 mL).

The alkaline layer was acidified, with cooling, to pH 1 with concentrated HCl and then extracted with ether (500 mL). The acidic solution was buffered to pH 5 with solid sodium acetate and addition of a saturated aqueous solution of cupric acetate precipitated a blue copper complex of **2**. This complex was washed with water, ethanol, and ether and air-dried. It was suspended in water (1000 mL), and H_2S was bubbled through the mixture for 20 min. The resulting dark brown suspension was filtered through Celite, the filtrate was concentrated to 150 mL and filtered again. The solution was evaporated under reduced pressure to a yellow, viscous oil, which crystallized after placement under vacuum. Two recrystallizations from ethanol–hexanes provided 36.3 g (66%) of white crystalline **2**: mp 198.0–200.0 °C; IR (KBr, cm^{-1}) 3000 (br, OH), 1712 (C=O); ^1H NMR (DMSO-d_6, ppm) δ 2.60 (s, CH_3), 4.0–5.5 (very br s, CH_2), 7.69–7.76 (m, H_5 + $H_{5'}$), 8.56 (s, $H_{3'}$), 8.58 (s, H_3), 8.73 (d, $H_{6'}$), 8.80 (d, H_6) [$J_{3,5} = J_{3',5'} = 5.0$ Hz]; ^{13}C NMR (DMSO-d_6, ppm) δ 21.28, 39.95, 124.05, 124.19, 127.15, 127.58, 144.85, 147.53, 147.87, 148.01, 155.68, 170.72; HRMS calcd for $C_{13}H_{12}O_2N_2$ m/z 228.0899, found 228.0894.

Methyl 4'-Methyl-2,2'-bipyridine-4-acetate (3). A suspension of 4'-methyl-2,2'-bipyridine-4-acetic acid (**2**) (400 mg, 1.75 mmol) in 2.0 mL of dry methanol was cooled to 0 °C in a 10-mL flask, and boron trifluoride–methanol complex (50% BF_3; 0.80 mL, 7.0 mmol) was added dropwise by syringe through a septum, with stirring. The resulting solution was refluxed for 6 h under argon, cooled, made alkaline with Na_2CO_3, and extracted with CH_2Cl_2 (3 × 15 mL). The combined CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated under reduced pressure to a colorless residual oil, which crystallized after a day. Recrystallization from toluene yielded 280 mg (66%) of ester **3** as a white crystalline solid: mp 62–64 °C; IR (KBr, cm^{-1}) 1736 (C=O); ^1H NMR ($CDCl_3$, ppm) δ 2.44 (s, CH_3), 3.72 (s, OCH_3), 3.73 (s, CH_2CO), 7.14 (dd, $H_{5'}$), 7.27 (dd, H_5), 8.23 (d, $H_{3'}$), 8.31 (d, H_3), 8.62 (dd, $H_{6'}$), 8.65 (dd, H_6) [$J_{3,5} = J_{3',5'} = 1.6$ Hz, $J_{3,6} = J_{3',6'} = 0.6$ Hz, $J_{5,6} = J_{5',6'} = 5.0$ Hz]. Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.25; H, 5.71; N, 11.59.

4-[3-(1,3-Dioxolan-2-yl)propyl]-4'-methyl-2,2'-bipyridine (4). 2-(2-Bromoethyl)-1,3-dioxolane (70.0 g, 387 mmol) was quickly added to lithiated 4,4'-dimethyl-2,2-bipyridine, and the resulting mixture was stirred at −78 °C for 1 h. It was allowed to warm to room temperature and was stirred overnight. The reaction mixture was poured into 600 mL of brine, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to a yellow, viscous oil. The oil was placed under vacuum for a week. The

crystals of 4,4′-dimethyl-2,2′-bipyridine that had separated were collected on a coarse fritted funnel and washed with a small amount of ether. The washings and the filtrate were diluted with 100 mL of ether, and the resulting solution was adsorbed onto neutral alumina (activity III) by mixing in a rotoevaporator. The excess solvent was evaporated under reduced pressure, and the adsorbed product mixture was carefully placed onto a 8 × 70 cm column (alumina activity III; hexanes–ether 2:1). 4,4′-Dimethyl-2,2′-bipyridine eluted first. Continued elution with hexanes–ether, 1:1, gave the product **4** as a colorless oil. Placement in vacuo produced crystallization within a few days (overnight if a seed crystal is available): yield 45.0 g (58%) of white crystals of mp 48–50 °C; ^{1}H NMR ($CDCl_3$, ppm) δ 1.73 (m, C_3H_2), 1.83 (m, C_2H_2), 2.42 (s, CH_3), 2.74 (t, C_1H_2, J = 9.5 Hz) 3.81–3.97 (m, OCH_2CH_2O), 4.87 (t, CH, J = 5.5 Hz), 7.11–7.14 (m, H_5 and $H_{5'}$), 8.20–8.22 (m, H_3 and $H_{3'}$), 8.51–8.55 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.75; H, 7.05; N, 9.90.

10-(2-Chloroethyl)phenothiazine (22) was prepared in 57% yield from phenothiazine and 2-chloroethyl *p*-toluenesulfonate according to a literature procedure:[14] mp 97–98 °C [lit.[14] mp 96–97 °C]; ^{1}H NMR ($CDCl_3$, ppm) δ 3.75 (distorted t, CH_2Cl, J = 7.0 Hz), 4.20 (distorted t, NCH_2, J = 7.0 Hz), 6.80–7.35 (m, 8H, phenothiazine hydrogens). Anal. Calcd for $C_{14}H_{12}NSCl$: C, 64.24; H, 4.62; N, 5.35. Found: C, 64.29; H, 4.68; N, 5.31.

10-(2-Bromoethyl)phenothiazine (23). A mixture of 10-(2-chloroethyl)phenothiazine (**22**) (5.25 g, 20.0 mmol), NaBr (400 mg), ethyl bromide (20 mL), and 22 mL of 1-methyl-2-pyrrolidinone was stirred at 65 °C for 3 days. The solvent and the volatile components of the mixture were removed under reduced pressure, and the residue was extracted into ether. The ethereal extracts were evaporated, and the residue was recrystallized from ethanol–acetone to give 3.14 g (51%) of 10-(2-bromoethyl)phenothiazine (**23**) as white needles: mp 81–82 °C [lit.[15] mp 83 °C]; ^{1}H NMR ($CDCl_3$, ppm) δ 3.60 (t, CH_2Br, J = 7.0 Hz), 4.28 (t, NCH_2, J = 7.0 Hz), 6.80–7.34 (m, 8 H, phenothiazine hydrogens). Anal. Calcd for $C_{14}H_{12}NSBr$: C, 54.91; H, 3.95; N, 4.57. Found: C, 54.86; H, 3.91; N, 4.56.

10-[3-(4′-Methyl-2,2′-bipyridin-4-yl)propyl]phenothiazine (21). 10-(2-Bromoethyl)phenothiazine (**23**) (2.82 g, 9.20 mmol) in 10 mL of dry THF was added dropwise to lithiated 4,4′-dimethyl-2,2′-bipyridine (1.69 g, 9.20 mmol) at −78 °C. The mixture was stirred for 2 h, allowed to reach room temperature, and then stirred overnight. It was quenched with 20 mL of water and extracted with ether (3 × 50 mL). The combined ethereal extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed on silica (toluene to chloroform gradient). The crude product was recrystallized twice from ethanol affording 1.63 g (43%) of **21** as white crystals: mp 124–125 °C; ^{1}H NMR ($CDCl_3$, ppm) δ 2.20 (m, C_2H_2), 2.43 (s, CH_3), 2.73 (t, C_3H_2, J = 6.8 Hz), 3.88 (t, C_1H_2, J = 7.0 Hz), 6.78–7.22 (m, H_5, $H_{5'}$ and 8 phenothiazine hydrogens), 8.18–8.22 (m, H_3 and $H_{3'}$), 8.43–8.55 (m, $_6$ and $H_{6'}$). Anal. Calcd for $C_{26}H_{23}N_3S$: C, 76.25; H, 5.66; N, 10.26. Found: C, 76.10; H, 5.60; N, 10.31.

4-(3-Formylpropyl)-4′-methyl-2,2′-bipyridine (5). The acetal **4** (12.0 g, 42.3 mmol) was dissolved in 250 mL of 1 M HCl and heated for 2 h at 50–60 °C. The solution was cooled to room temperature, neutralized with saturated aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (3 × 250 mL). The combined CH_2Cl_2 layers were washed with 100 mL of water, dried (Na_2SO_4), and evaporated under reduced pressure to a pale yellow oil: yield of **5** 9.6 g (95%); IR (neat, cm^{-1}) 2825, 2724 (H—CO), 1724 (C=O); ^{1}H NMR ($CDCl_3$, ppm) δ 2.03 (m, C_2H_2), 2.43 (s, CH_3), 2.50 (t, C_3H_2, J = 6.7 Hz), 2.74 (t, C_1H_2, J = 7.5 Hz), 7.12–7.14 (m, H_5 and $H_{5'}$), 8.17–8.21 (m, H_3 and $H_{3'}$), 8.52–8.58 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.98; H, 6.71; N, 11.66. Found: C, 74.81; H, 6.63; N, 11.62.

4-(3-Carboxypropyl)-4′-methyl-2,2′-bipyridine (6). The aldehyde **5** (9.00 g, 37.4 mmol) was dissolved in 150 mL of acetone, and finely powdered $KMnO_4$ was added in small portions. The reaction could be conveniently followed by TLC (silica; ethyl acetate–toluene, 1:1). A small additional amount of permanganate was required to completely oxidize the aldehyde. The acetone was then removed under reduced pressure, and the residue was suspended in 50 mL of water. The mixture was heated to boiling and then slowly cooled overnight in the refrigerator. The black manganese dioxide precipitate was removed by filtration through Celite and washed with two portions of saturated aqueous $NaHCO_3$. The washings and the filtrate were washed with CH_2Cl_2 (2 × 100 mL). The pH of the aqueous layer was adjusted to pH 4.8 (pH meter) with 1 M HCl prior to exhaustive extraction with CH_2Cl_2. The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and evaporated under reduced pressure to a yellow oil, which crystallized after 1–2 h. Recrystallization from $CHCl_3$–hexanes afforded 4.95 g (52%) of the acid **6** as white crystals: mp 107–109 °C; IR (KBr, cm^{-1}) ~2500 (br, OH), 1704 (C=O); ^{1}H NMR ($CDCl_3$, ppm) δ 2.10 (m, C_2H_2), 2.42–2.49 (m, CH_3 and C_3H_2), 2.74 (t, C_1H_2, J = 7.3 Hz), 7.12–7.14 (m, H_5 and $H_{5'}$), 8.19–8.21 (m, H_3 and $H_{3'}$), 8.52–8.58 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.01; H, 6.35; N, 10.87.

4-(4-Hydroxybutyl)-4′-methyl-2,2′-bipyridine (7). The crude acetal mixture obtained in the reaction between lithiated 4,4′-dimethyl-2,2′-bipyridine and 2-(2-bromoethyl)-1,3-dioxolane was not purified by chromatography as previously described but was instead hydrolyzed to 60–65 g of crude aldehyde, which was then dissolved in 200 mL of absolute ethanol. Sodium borohydride (3.15 g, 83.3 mmol) was added to the stirred solution in one portion. After 30 min the mixture was poured into 500 mL of brine and extracted with CH_2Cl_2 (3 × 500 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to a yellow oil. Purification by flash chromatography (silica; ethyl acetate) yielded 31.5 g (48% from 4,4′-dimethyl-2,2′-bipyridine) of **7** as a white, waxy solid: mp 32–35 °C; IR (KBr, cm^{-1}) ~3300 (br, OH), 1058 (C–O); ^{1}H NMR δ 1.60 (m, C_2H_2), 1.73 (m, C_3H_2), 2.41 (s, CH_3), 2.61 (t, C_1H_2, J = 7.5 Hz), 3.51 (br s, OH), 3.62 (t, C_4H_2, J = 6.3 Hz), 7.08–7.13 (m, H_5 and $H_{5'}$), 8.19 (m, H_3 and $H_{3'}$), 8.49–8.53 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.10; H, 7.55; N, 11.40.

4-(4-Bromobutyl)-4′-methyl-2,2′-bipyridine (8). The bipyridine alcohol **7** (30.0 g, 124 mmol) was dissolved in 250 mL of 62% HBr, and the resulting solution was refluxed for 6 h. It was then cooled to room temperature, poured into 500 g of crushed ice, made basic with a saturated aqueous solution of Na_2CO_3, and extracted with CH_2Cl_2 (3 × 500 mL). The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure to about 100 mL, and filtered through a 6-in. column (230–400 mesh silica; CH_2Cl_2 elution) to remove polymeric impurities. The resulting almost colorless oil crystallized after placement in vacuo, yielding **8** (29.5 g, 78%) as a waxy white solid: mp 50–52 °C; ^{1}H NMR ($CDCl_3$, ppm) δ 1.79–1.83 (m, C_2H_2 and C_3H_2), 2.41 (s, CH_3), 2.70 (t, C_1H_2, J = 7.5 Hz), 3.40 (t, C_4H_2, J = 6.5 Hz), 7.07–7.14 (m, H_5 and $H_{5'}$), 8.23–8.25 (m, H_3 and $H_{3'}$), 8.51–8.59 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{15}H_{17}N_2Br$: C, 59.03; H, 5.61; N, 9.18. Found: C, 59.09; H, 5.66; N, 9.08.

4-(4-Phthalimidobutyl)-4′-methyl-2,2′-bipyridine (9). 4-(4-Bromobutyl)-4′-methyl-2,2′-bipyridine (**8**) (10.0 g, 32.8 mmol) in 50 mL of DMF was added to a suspension of potassium phthalimide (6.07 g, 32.8 mmol) in 100 mL of DMF. The mixture was stirred at 50–60 °C for 2 h and then allowed to cool to room temperature. Water (300 mL) was added, and the mixture was extracted with $CHCl_3$ (3 × 200 mL). The organic layers were combined, washed with 150 mL of 0.2 M NaOH and then with 100 mL of water, and finally dried over Na_2SO_4. Removal of the solvent under reduced pressure left a yellow oil, which was purified by chromatography (silica; toluene–ethyl acetate, 1:1). Recrystallization from acetone containing a small amount of ethanol gave **9** (11.32, 92%) as a white crystalline solid: mp 116–118 °C; IR (KBr, cm^{-1}) 1771, 1704 (CONRCO); ^{1}H NMR ($CDCl_3$, ppm) δ 1.71–1.90 (m, C_2H_2 and C_3H_2), 2.44 (s, CH_3), 2.76 (t, C_1H_2, J = 7.3 Hz), 3.76 (t, C_4H_2, J = 6.6 Hz), 7.10–7.16 (m, H_5 and $H_{5'}$), 8.22–8.24 (m, H_3 and $H_{3'}$), 8.53–8.58 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.29; H, 5.76; N, 11.38.

4-(4-Aminobutyl)-4′-methyl-2,2′-bipyridine (10). The phthalimide **9** (1.00 g, 2.69 mmol) was slurried in 30 mL of ethanol

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and treated with 200 μL of hydrazine hydrate (206 mg, 4.12 mmol). The mixture was refluxed for 6 h, allowed to cool to room temperature, poured into 100 mL of brine, and basified with 50% w/w NaOH to pH 12. It was then extracted with CH_2Cl_2; the extracts were combined (Na_2SO_4) and evaporated under reduced pressure to a slightly yellow oil; yield of **10** 638 mg (98%); ^1H NMR ($CDCl_3$, ppm) δ 1.52–87 (m, C_2H_2 and C_3H_2), 2.01 (s, NH_2), 2.43 (s, CH_3), 2.63–2.78 (m, C_1H_2 and C_4H_2), 7.09–7.16 (m, H_5 and $H_{5'}$), 8.20–8.22 (m, H_3 and $H_{3'}$), 8.53–8.58 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{15}H_{19}N_3$: C, 74.66; H, 7.94; N, 17.41. Found: C, 74.59; H, 7.93; N, 17.37.

4,4'-Dimethyl-2,2'-bipyridine *N*-Oxide (11). 3-Chloroperoxybenzoic acid (200.0 g of 80–85%, 0.93–0.99 mmol) in 1200 mL of $CHCl_3$ was added dropwise to a mechanically stirred suspension of 4,4'-dimethyl-2,2'-bipyridine (168.0 g, 0.912 mol) in 600 mL of $CHCl_3$ at 0 °C, over a 3-h period. The mixture was then allowed to warm to room temperature, and stirring was continued for 2 days. The chloroform was removed under reduced pressure, and 4000 mL of 1 M aqueous K_2CO_3 was added to the residue. The mixture was heated at 90–95 °C for 30 min, cooled, and filtered to remove any unreacted 4,4'-dimethyl-2,2'-bipyridine. The filtrate was extracted with CH_2Cl_2 (4 × 1000 mL). The combined CH_2Cl_2 extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil, which crystallized upon standing: yield of **11** 151.0 g (83%) as a waxy, light yellow solid; mp 83–85 °C, after two recrystallizations from ether; ^1H NMR ($CDCl_3$, ppm) δ 2.36 (s, CH_3), 2.41 (s, CH_3), 6.98–7.20 (m, H_5 and $H_{5'}$), 7.96 (m, H_3), 8.22 (d, H_6, $J_{5,6}$ = 7.0/ Hz), 8.58 (d, $H_{6'}$, $J_{5',6'}$ = 5.0 Hz), 8.78 (m, $H_{3'}$). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.88; H, 6.01; N, 14.03.

4-(Hydroxymethyl)-4'-methyl-2,2'-bipyridine (13). Acetic anhydride (750 mL) was added dropwise to 4,4'-dimethyl-2,2'-bipyridine *N*-oxide (**11**) (74.0 g, 0.370 mol), and the mixture was stirred at 60–65 °C for 24 h. The volatile components of the mixture were removed under reduced pressure, and 750 mL of water was added to the dark brown residue. The resulting mixture was made alkaline with solid K_2CO_3 and extracted with ethyl acetate (3 × 500 mL). The combined extracts were dried (Na_2SO_4) and evaporated under reduced pressure to 76 g of a dark oil. Next, the oil was dissolved in 700 mL of 95% ethanol, and 1000 mL of a 10% aqueous solution of NaOH was added. The mixture was refluxed for 30 min, and the ethanol was removed under reduced pressure. The residue was acidified with concentrated HCl to pH 3, washed with 1000 mL of ethyl acetate, made alkaline with solid K_2CO_3, and extracted with ethyl acetate (2 × 600 mL). The extracts were combined, dried (Na_2SO_4), and evaporated under reduced pressure to a brown, viscous oil, which was chromatographed on silica. Elution with chloroform–methanol, 98:2, gave as first fraction (purple color with Fe^{2+}) 4.5 g (6%) of 4,4'-dimethyl-3-hydroxy-2,2'-bipyridine (**14**) as pale yellow crystals (methanol): mp 89–91 °C; ^1H NMR ($CDCl_3$, ppm) δ 2.31 (s, $CH_{3'}$), 2.45 (s, CH_3), 7.07–7.13 (m, H_5 and $H_{5'}$), 8.05 (d, H_6 or $H_{6'}$, J = 5.3 Hz), 8.33 (d, H_6 or $H_{6'}$, J = 5.3 Hz), 8.40 (d, $H_{3'}$, J = 1.6 Hz), 14.68 (s, OH). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.99; H, 6.07; N, 13.92. A small amount of another substituted 2,2'-bipyridine (blue color with Fe^{2+}) eluted next, followed by the major fraction, 4-(hydroxymethyl)-4'-methyl-2,2'-bipyridine (**13**), which gave a red color with Fe^{2+}. Recrystallization from benzene afforded 30.5 g (41%) of **14** as a white crystalline solid: mp 110–112 °C; ^1H NMR ($CDCl_3$, ppm) δ 2.45 (s, CH_3), 4.75 (s, CH_2), 4.95 (br s, OH), 7.10–7.35 (m, H_5 and $H_{5'}$), 8.23 (m, $H_{3'}$), 8.34 (m, H_3), 8.48–8.64 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.05; H, 5.99; N, 13.91. Further elution with chloroform–methanol, 95:5, gave as final fraction (orange color with Fe^{2+}) 4,4'-dimethyl-5-hydroxy-2,2'-bipyridine (**15**), 4.1 g (5.5%), after recrystallization from benzene: white crystals; mp 149–150 °C; ^1H NMR ($CDCl_3$, ppm) δ 2.29 (s, $CH_{3'}$), 2.39 (s, CH_3), 7.09 (d, $H_{5'}$), singlets at 8.00, 8.04, and 8.07 (H_3 and $H_{3'}$ and H_6), 8.49 (d, $H_{6'}$) [$J_{5',6'}$ = 5.0 Hz]. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.10; H, 5.98; N, 13.93.

4-Formyl-4'-methyl-2,2'-bipyridine (16). The bipyridine alcohol **13** (5.00 g, 35.0 mmol) was dissolved in CH_2Cl_2 (100 mL), and activated MnO_2 (20.0 g) was added in 5-g portions at room temperature over a 4-h period. The suspension was stirred overnight and filtered twice through Celite, and the pale brown filtrate was evaporated under reduced presure to yield 3.92 g of crude product. Purification by column chromatography (silica; ethyl acetate–toluene, 1:1) provided 2.88 g (58%) of **16** as white crystals: mp 131.9–132.9 °C; IR (KBr, ppm) 1708 (C=O); ^1H NMR ($CDCl_3$, ppm) δ 2.47 (s, CH_3), 7.21 (dd, $H_{5'}$), 7.72 (dd, H_5), 8.28 (br s, $H_{3'}$), 8.58 (dd, $H_{6'}$), 8.86 (br s, H_3), 8.89 (dd, H_6), 10.17 (s, HCO) [$J_{3,5}$ = 1.5 Hz, $J_{3',5'}$ = 1.0 Hz, $J_{5,6}$ = 5.1 Hz, $J_{5',6'}$ = 4.6 Hz]. Anal. Calcd for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.09; N, 14.13. Found: C, 72.68; H, 5.18; N, 14.13.

4-[(Hydroxyimino)methyl]-4'-methyl-2,2'-bipyridine (17). The aldehyde **16** (1.00 g, 5.00 mmol) and hydroxylamine hydrochloride (2.30 g) were dissolved in 75 mL of methanol. Pyridine (40 mL) was added, and the mixture was refluxed for 2 h. The solvents were evaporated, and the residue was suspended in 5 mL of cold water, collected on a fritted funnel, and washed with 2 mL of cold water. Recrystallization from ethanol provided 0.96 g (90%) of **17** as a white crystalline solid: mp 171.0–172.5 °C; ^1H NMR (CD_3OD, ppm) δ 2.49 (s, CH_3), 7.35 (br dd, $H_{5'}$), 7.63 (dd, H_5), 8.18 (br s, $H_{3'}$ and CH=N), 8.44 (br s, H_3), 8.51 (br d, $H_{6'}$), 8.65 (dd, H_6) [$J_{3,5}$ = 1.5 Hz, $J_{3',5'}$ = 0.9 Hz, $J_{5,6}$ = 5.1 Hz, $J_{5',6'}$ = 4.6 Hz]. Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.64; H, 5.16; N, 19.68.

4-(Aminomethyl)-4'-methyl-2,2'-bipyridine Dihydrochloride Hydrate (18). A mixture of oxime **17** (900 mg, 4.22 mmol), 50 mL of water, 1 mL of concentrated HCl, and 300 mg of 10% Pd/C was hydrogenated at 3 atm of H_2 for 3 h. The catalyst was removed by filtration, and the filtrate was evaporated to dryness. The residue was washed with cold ethanol and ether, yielding 890 mg of **18** (73%) as white crystals: mp 257–259 °C; ^1H NMR ($CDCl_3$, ppm) of the free base (colorless oil) δ 2.44 (s, CH_3), 2.70 (s, NH_2), 4.05 (s, CH_2), 7.15 (m, $H_{5'}$), 7.26 (m, H_5), 8.22 (br s, $H_{3'}$), 8.31 (br s, H_3), 8.53–8.57 (m, $H_{6'}$ and H_6). Anal. Calcd for $C_{12}H_{17}N_3OCl_2$: C, 49.67; H, 5.90; N, 14.48; O, 5.51; Cl, 24.43. Found: C, 49.81; H, 5.82; N, 14.50; O, 5.69; Cl, 24.10.

4-(Bromomethyl)-4'-methyl-2,2'-bipyridine Dihydrobromide (19). 4-(Hydroxymethyl)-4'-methyl-2,2'-bipyridine (**13**) (1.00 g, 5.00 mmol) was added to 10 mL of 62% HBr (Alfa), and the mixture was refluxed for 6 h. The solution was cooled and evaporated to dryness. The light brown residue was recrystallized from ethanol–ether, yielding 1.95 g (92%) of **19** as a white crystalline solid: ^1H NMR (D_2O) δ 2.80 (s, CH_3), 4.76 (s, CH_2), 7.82 (br d, $H_{5'}$), 8.01 (br d, H_5), 8.34 (br s, $H_{3'}$), 8.44 (br s, H_3), 8.75–8.85 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{12}H_{13}N_2Br_3$: C, 33.92; H, 3.08; N, 6.59. Found: C, 33.69; H, 3.05; N, 6.65.

10-[(4'-Methyl-2',2-bipyridin-4-yl)methyl]phenothiazine (20). *n*-Butyllithium in hexanes (1.55 M, 11 mL, 17.1 mmol) was diluted with 40 mL of dry THF and cooled to 0 °C. Phenothiazine (3.41 g, 17.1 mmol) was added in one portion, and the resulting bright yellow suspension was stirred for 1 h. 4-(Bromomethyl)-4'-methyl-2,2'-bipyridine dihydrobromide (**19**) (1.85 g, 4.4 mmol) was added in portion over a 1-h period. The reaction mixture was allowed to reach room temperature and was stirred overnight. The solvent was evaporated under reduced pressure, and 20 mL of water was added to the residue. The resulting suspension was extracted with $CHCl_3$ (3 × 50 mL). The combined $CHCl_3$ layers were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (silica; toluene to chloroform gradient), yielding the product **20** (750 mg, 45%) as a white crystalline solid: mp 155.0–156.0 °C (ethanol); ^1H NMR ($CDCl_3$, ppm) δ 2.43 (s, CH_3), 5.13 (s, CH_2), 6.50–7.30 (m, H_5 and $H_{5'}$ and 8 phenothiazine hydrogens), 8.26 (br s, $H_{3'}$), 8.47 (br s, H_3), 8.54–8.57 (m, H_6 and $H_{6'}$). Anal. Calcd for $C_{26}H_{23}NS$: C, 76.25; H, 5.66; N, 10.26. Found: C, 76.15; H, 5.63; N, 10.30.

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Registry No. 1, 1134-35-6; **2**, 118724-25-7; **3**, 118724-26-8; **4**, 115008-00-9; **5**, 115008-01-0; **6**, 114527-28-5; **7**, 118724-27-9; **8**, 115008-03-2; **9**, 115008-02-1; **10**, 115021-71-1; **11**, 81998-03-0; **12**, 81998-08-5; **13**, 81998-04-1; **14**, 81998-07-4; **15**, 118724-28-0; **16**, 104704-09-8; **17**, 118724-29-1; **18**, 118724-30-4; **19**, 118724-31-5; **20**, 118724-32-6; **21**, 118724-33-7; **22**, 21786-08-3; **23**, 118724-34-8; 2-(2-bromoethyl)-1,3-dioxolane, 18742-02-4; phenothiazine, 92-84-2.