New Symmetric and Unsymmetric Polyfunctionalized 2,2′-Bipyridines

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Recently, a large number of biheterocycles have been synthesized in order to build macrobicyclic cryptates. To pursue investigations in this field, we prepared new symmetric and unsymmetric functionalized bipyridines and we describe here two synthetic strategies leading to new tetrasubstituted **3** to **15** and trisubstituted **17** to **29** bipyridines. Modification at the α,α'-methyl groups and introduction of functionalities in the 4,4′-positions have been performed after N-O activation of the starting 6,6′-dimethyl-2,2′-bipyridine unit. In the case of cyano and hydroxymethyl groups, alkylation of the N-O function followed by a nucleophilic attack with the CN anion or an hydroxymethyl radical allowed us to obtain the dissymmetric species. To understand observed differencies between cyanation and hydroxymethylation processes, the unstable and hygroscopic *N*-methoxybipyridinium salt **30** has been isolated and characterized by nmr. Dibromomethyl compounds **8, 15, 29** were finally obtained in good to moderate yields by the Boekelheide rearrangement followed by a pseudohalogen exchange.

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The 2,2′-bipyridine group with parent and other -5 and -6 membered heterocycles have been extensively studied in recent years for their extensive coordination chemistry with metals ions [1]. Placing chemically active substituents at defined positions of the C-part of the heterocyclic ring allows the chemist to begin structural organization work and to prepare new compounds with properties for molecular recognition and light conversion by energy transfer [2]. Many recent publications indicate the diversity of structures thus prepared, for example, oligomers [3], polymers [4], coronands and podands [5-6], macrocycles [7] and cryptands [8,9,10], designed as supramolecular chelating agents.

In the field of polyheterocyclic macrobicyclic rare earth cryptates designed as light conversion devices [11], a large number of biheteroaryl species have been worked out in order to incorporate them into pathways of a foreseen synthetic strategy. In this sense, 2,2′-bipyridine (bpy) [6,9,10,12], 1,10-phenanthroline (phen) [9,13], 2,2′-biisoquinoline (biqi) [10,12], *N,N*-bipyrazoles [14], and more recently 2,2′-bithiazoles (btz), 2,2′-biimidazoles (biim) and 2,2′-bipyrimidines (bpym) [15,16], as well as 4,4′-disubstituted bipyridines (COOR [10]; NO_2, Br [16]) have been functionalized with the aim of placing the diimine chelating sites inside a cavity; the corresponding synthetic strategy requiring the preparation of biheteroaryl units bearing bromomethyl or aminomethyl groups in the α- and α'-positions.

To pursue the investigations in this last area, we desired to introduce novel electroactive substituents such as nitrile, amine and ether functionalities. Furthermore, as some of those substituents, *e.g.* -COOR, are required to anchor the final compound to its specific support, it seemed of great interest to create a dissymmetry leading to an unambiguous and stoichiometric binding site. Surprisingly, no reports have subsequently described the syntheses of such bipyridyl units; we hope this work will be helpful for the design of new series of ligands for numerous physicochemical approaches.

We report here the synthesis of new symmetrically 4,4′- and 6,6′-tetrasubstituted 2,2′-bipyridines and a new way to prepare dissymmetrically 4-(4′-) and 6,6′-trisubstituted-2,2′-bipyridines.

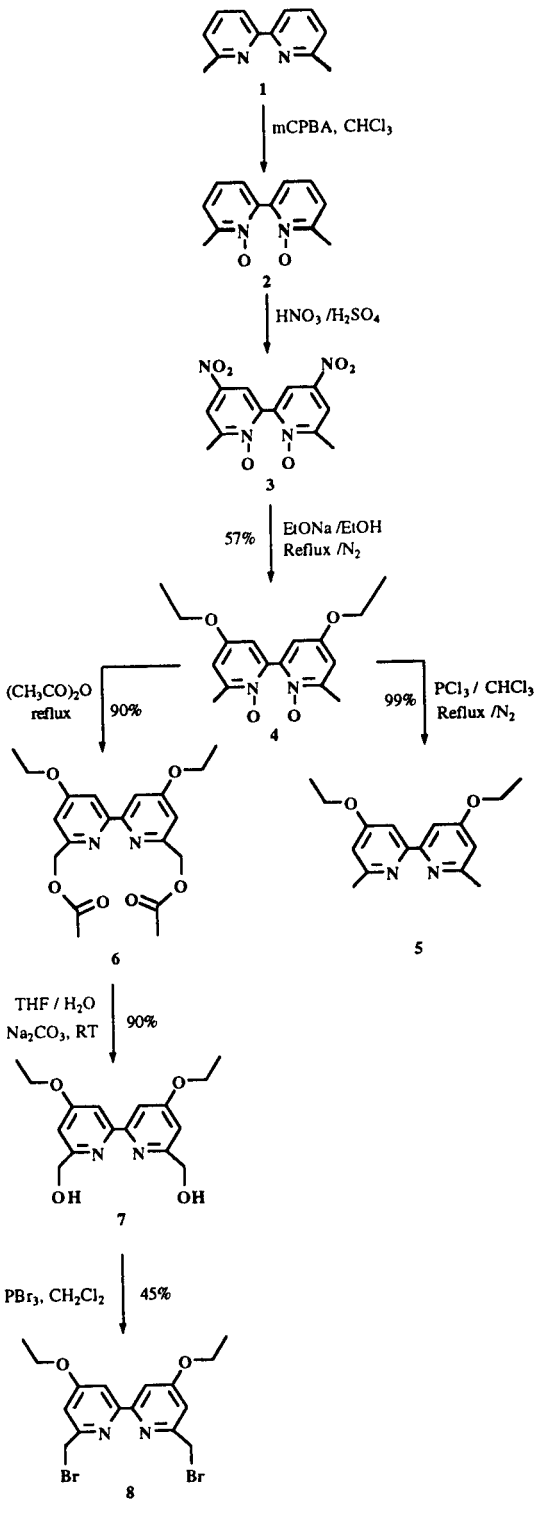
Synthetic Strategy for Tetrasubstituted Bipyridines.

The 4,4′ and 6,6′ symmetrically functionalized 2,2′-bipyridines have been built up from 6,6′-dimethyl-2,2′-bipyridine **1** (Scheme 1). Activation of the 4 and 4′ positions through the N_1 and $N_{1'}$ dioxide species in the case of 2,2′-bipyridine has been adequately reported [17]. It has also been demonstrated that the N-O function in such heterocycles is a very efficient activating group for introducing chemical activity at a methyl group when attached to the α-position [18,19,10].

We decided to combine these approaches around the di-*N*-oxide **2**. Such an approach has recently been employed with the 4,4′-dinitro-6,6′-dimethyl-2,2′-bipyridine [16].

Oxidation in acidic medium of **2** afforded **3**. Treatment with sodium ethoxide gave **4** which was then treated with acetic anhydride to give the bis-acetate **6**. No results were obtained when trifluoroacetic anhydride was employed. Hydrolysis of **6** in a basic water:tetrahydrofuran mixture

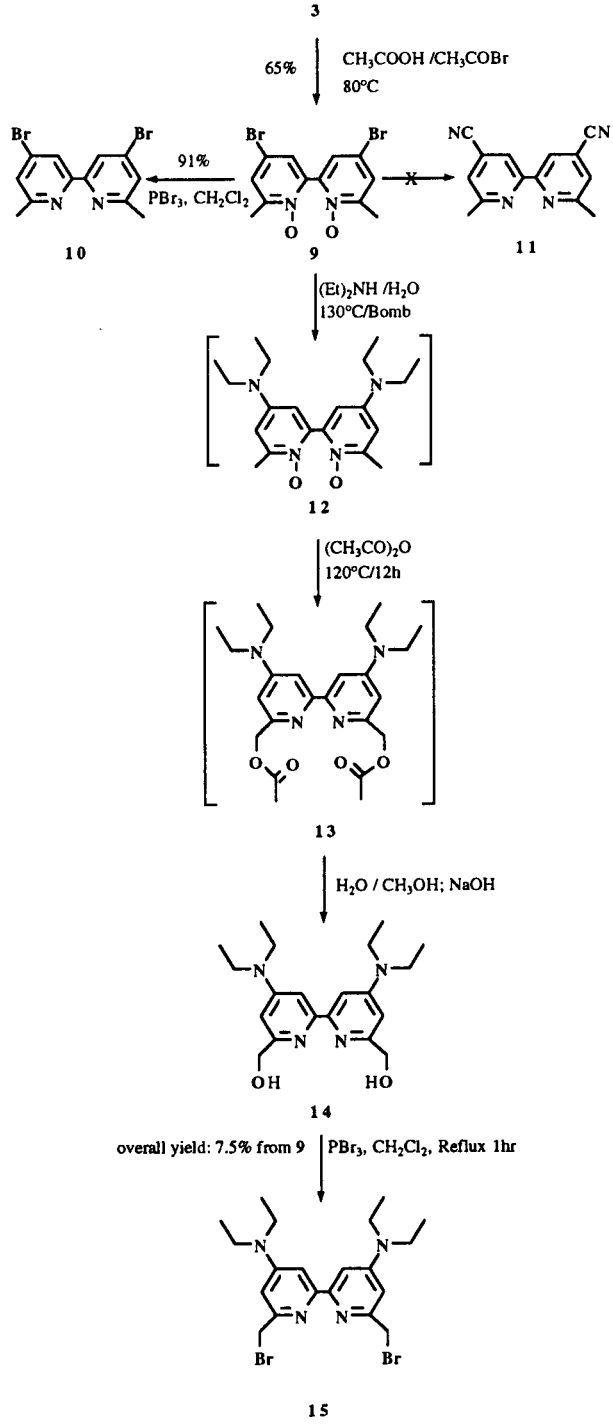
Scheme 1



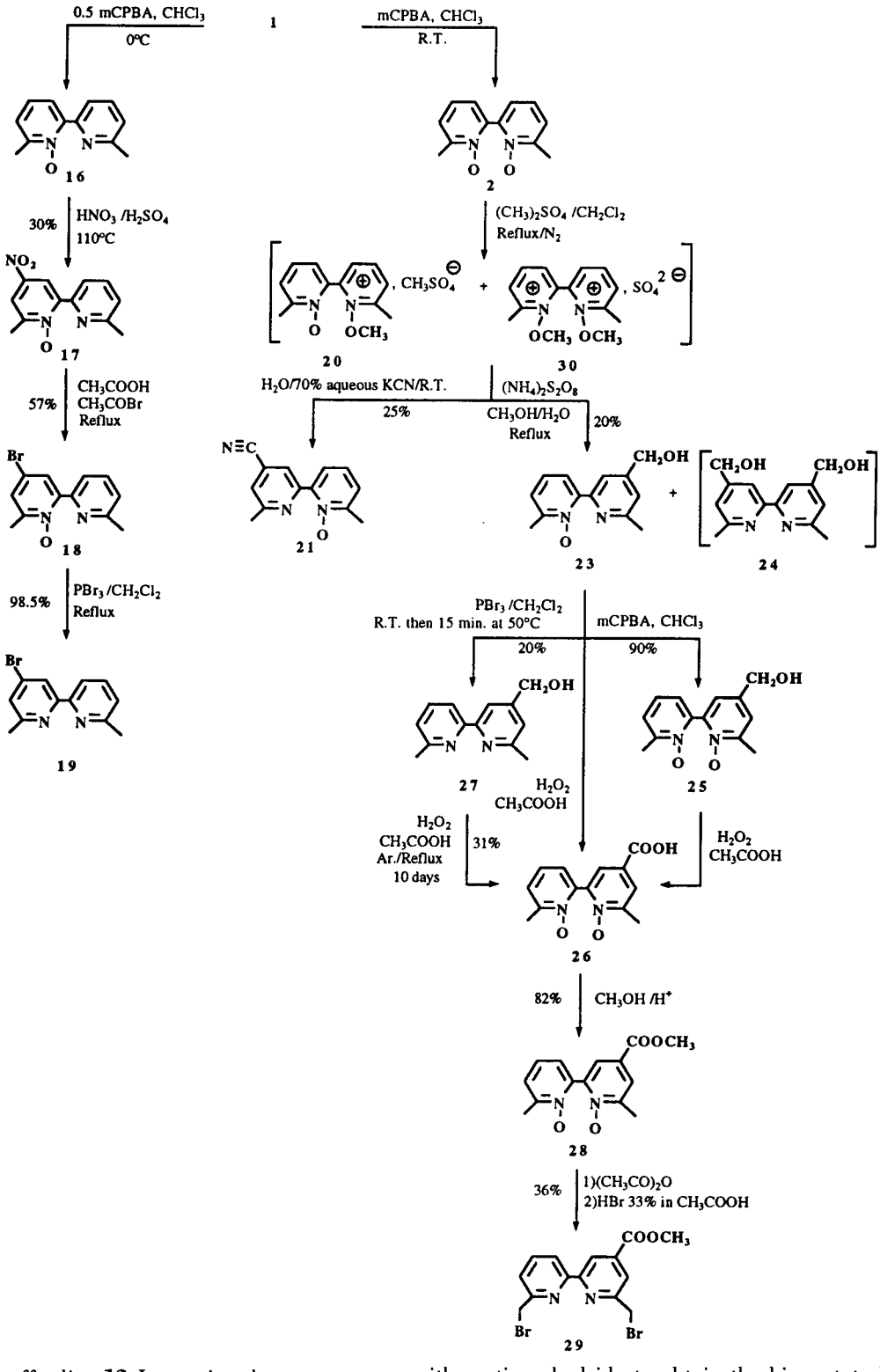
led to the diol **7** which was finally brominated with phosphorus tribromide to give **8**. Reacting phosphorus trichloride with **4** afforded the deoxidized analog **5**. Attempts to introduce methoxy or phenoxy groups in the 4- and 4'-positions did not give good results.

Reacting **3** with acetyl bromide in acetic acid afforded its 4,4'-dibromo analog **9**. Removal of the oxide was performed by means of phosphorus tribromide to give **10** (Scheme 2). As the 4,4'-dibromo-6,6'-bis(bromomethyl)-2,2'-bipyridine has been recently described [16], we did not try to obtain it by this new way. Replacement of bromine in **9** with a diethylamino group has been performed by means of medium pressure and temperature (130°) in a

Scheme 2



Scheme 3



stainless steel bomb, affording **12**. Increasing the temperature to 160° gave a large amount (*ca.* 50%) of the deoxidized equivalent of **12**. Attempts to purify **12** by classical methods failed because of its lability. We thus reacted it with acetic anhydride to obtain the bis-acetate **13** which had a great tendency to decompose on chromatography supports or under mild hydrophilic conditions. So, hydrolysis of **13** in a methanol:water basic medium afforded the

diol **14** which was also not easy to purify. Finally, reacting **14** with phosphorus tribromide gave the dibromide **15**. We tried as far as possible to isolate pure **12**, **13** and **14** for spectroscopic analysis. The synthesis of **15** will be described in the Experimental starting from **9**, with an overall yield of 7.5%. We tried unsuccessfully in **9** or **10** to replace bromine with cyano groups by means of copper cyanide in dimethylformamide or pyridine and various conditions of temperature and concentration. Such a function has been recently introduced onto a bipyridine through a dehydration process occurring between a carboxamide function and phosphorus oxychloride under ultrasonic conditions [20]. Looking for an elegant method to provide the dinitrile **11**, we found that introduction of a cyano group on a pyridine ring was performed through its *N*-oxide by means of alkylation of the N-O function followed by a nucleophilic attack by the cyanide anion, under aqueous conditions of the previously formed pyridinium salt [21], affording the corresponding cyanopyridine. We thought that starting from **2** may allow us to obtain **11** in this way. We found that in fact this reaction was an efficient way to introduce a dissymmetry in a 2,2'-bipyridine unit. We present these results in the following paragraph.

Synthetic Strategy for Trisubstituted Bipyridines (Scheme 3).

Reacting the dioxide **2** with dimethyl sulfate in methylene chloride might afford the symmetic $N_1,N_{1'}$-dimethoxy-2,2'-dipyridinium sulfate **30**. In fact, the white precipitate thus obtained gave after treatment with aqueous potassium cyanide a mixture containing the bipyridine **1**, its N_1-oxide **16** [19] and a small amount of 4'-cyano-6,6'-dimethyl-2,2'-bipyridine N_1-oxide **21**, without any dicyano derivative **11**. We encountered during the synthesis of **21** some difficulties, particularly at the step of nucleophilic attack of the cyanide anion, giving sometimes a red polar and uncharacterized compound mixed with **1** and without any **21**. The extraction step of excess dimethyl sulfate seems to play a role in the sense that residual alkylating agent may react with a potentially residual free pyridine nitrogen leading to a methylpyridinium salt.

Close to a positive result, we pursued our investigations towards the attaching a functionality easy to transform. We found that it was possible to introduce a hydroxymethyl group in the 2-, 4- or 6-position of a *N*-alkoxypyridinium methyl sulfate by means of a nucleophilic attack of an hydroxymethyl radical generated *in situ*. [22]. In this sense, **2** was treated with dimethyl sulfate in methylene chloride to give the pyridinium salt. The white solid was then reacted with ammonium persulfate in aqueous methanol to give a mixture of the desired 6,6'-dimethyl-4'-hydroxymethyl-N_1-oxo-2,2'-bipyridine **23** and the 4,4'-bishydroxymethylated analog **24** [23]. We tried at this step to understand the differences of the results between the cyanation and the hydroxymethylation reaction. Thinking that **21** and **23** were justified by the formation of the monomethylated species **20**, we isolated the salt for analysis. Even though very hygroscopic and unstable in solution, ^{1}H- and ^{13}C-nmr were performed and showed us that this salt was a symmetric unit corresponding to the dipyridinium **30**. Many hypotheses can thus be built up for the non-formation of **11** and will be subject of a future report. Through oxidation or reduction *plus* oxidation processes, we transformed the alcohol **23** into its di-*N*-oxide carboxylic acid analog **26**. At first, smooth oxidation with *m*-chloroperbenzoic acid gave the $N_1,N_{1'}$-dioxide **25** without attack of the alcoholic function. This last product was transformed in peracetic acid medium (acetic acid and hydrogen peroxide, 110 volume mixture) into **26**. Direct oxidation of **23** into **26** was also performed using the same medium. For purification, it has been found better to deoxidize **23** into **27** before oxidizing it into **26** with peracetic acid. It is interesting to note that in this, phosphorus tribromide does not react on the alcoholic function even with a 15 minute heating step. Classical esterification reaction with methanol afforded the methyl ester **28**. The latter was finally treated with acetic anhydride, then hydrobromic acid, 33% in acetic acid to give through the Boekelheide rearrangement followed by a pseudohalogen exchange the trisubstitued compound **29**.

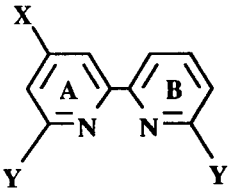
EXPERIMENTAL

All commercially available chemicals employed were reagent grade and used without further purification, unless stated otherwise. Melting points were obtained on a Büchi capillary apparatus and uncorrected. The uv spectra were recorded on Phillips PU 8710 or Beckmann DU-64 spectrometers (λ max in nm; ϵ in $mol^{-1}.l.cm^{-1}$). The ir spectra were recorded with Phillips PU 9700 or Perkin-Elmer 1310 spectrometers (region 4000-200 cm^{-1}; potassium bromide matrix). Nuclear magnetic resonance (nmr) spectra were obtained on Bruker AC 250, AC 200 or AM 400 spectrometers and all spectra were referenced to TMS as an internal standard (δ 0.0 ppm). Mass spectra (ms), Fast-Atom-Bombardment positive mode, Electron Impact (70 eV) or Chemical Ionization were obtained on a Nermag R-1010-C spectrometer and the elemental analyses were performed at the Service Commun d'Analyse, Université des Sciences et Techniques du Languedoc, Montpellier and at the Service Central de Microanalyse (CNRS), Vernaison, Lyon. Fractions of solvent molecules in the C, H, N, datas are employed consistently with nmr analysis. For ^{1}H- and ^{13}C-nmr shifts attributed to the dissymmetrically substituted bipyridines, we chose according to Scheme 4 to represent the 4-substituted ring, ring A, the other one ring B and to separate them as single pyridines units.

4,4'-Diethoxy-6,6'-dimethyl-2,2'-bipyridine $N_1,N_{1'}$-Dioxide (**4**).

A suspension of **3** (0.5 g, 1.59 mmoles) [16] in a sodium ethoxide solution (from sodium, 0.128 g and anhydrous ethanol, 17 ml) was refluxed under nitrogen during 80 minutes, then filtered

Scheme 4



while warm. The cooled filtrate was neutralized with concentrated hydrochloric acid, then evaporated to give a residue which was chromatographed (silica gel, 70% methylene chloride/30% methanol) to give **4**, 0.276 g (57%), mp dec 230°; ir (potassium bromide): ν 1237, 1174 (N-O) cm^{-1}; uv (chloroform): λ max (ϵ) 329 (10100); ^{1}H-nmr (deuteriochloroform): δ 1.40 (t, 6, J = 7.0, CH_3-CH_2-O), 2.54 (s, 6, CH_3), 4.05 (q, 4, J = 7.0, CH_3-CH_2-O), 6.86 (d, 2, J = 3.0, H ar), 6.93 (d, 2, J = 3.0, H ar); ^{13}C-nmr (deuteriochloroform): δ 14.9 (CH_3-CH_2-O), 18.8 (CH_3), 65.0 (CH_3-CH_2-O), 111.9, 113.5 (C_3, C_5), 144.0, 150.7, 156.1 (C_2, C_4, C_6); ms: (fast atom bombardment positive mode, thioglycerol) m/z 305 $(M+H)^+$, 289 $(M-O+H)^+$.

Anal. Calcd. for $C_{16}H_{20}N_2O_4 \cdot 0.25H_2O$: C, 62.22; H, 6.69; N, 9.07. Found: C, 62.15; H, 6.60; N, 9.05.

4,4'-Diethoxy-6,6'-dimethyl-2,2'-bipyridine (**5**).

A mixture of **4** (0.076 g, 0.25 mmole) and phosphorus trichloride (0.3 ml) in chloroform (3 ml) was refluxed under nitrogen during 2 hours. The cooled mixture was then added carefully to ice-water and the chloroform evaporated. The resulting aqueous solution was basified with sodium hydroxide then extracted with methylene chloride (4 x 10 ml). The organic phase was dried (magnesium sulfate) and evaporated to give **5**, 0.07 g (99%), mp 147°; uv (chloroform): λ max (ϵ) 330 (10950); ^{1}H-nmr (deuteriochloroform): δ 1.44 (t, 6, J = 7.0, CH_3-CH_2-O), 2.55 (s, 6, CH_3), 4.18 (q, 4, J = 7.0, CH_3-CH_2-O), 6.66 (d, 2, J = 2.2, H ar), 7.73 (d, 2, J = 2.2 H ar); ^{13}C-nmr (deuteriochloroform): δ 15.0 (CH_3-CH_2-O), 25.1 (CH_3), 63.8 (CH_3-CH_2-O), 104.9, 110.3 (C_3, C_5), 157.9, 159.5, 166.6 (C_2, C_4, C_6); ms: (fast atom bombardment positive mode) m/z 273 $(M+H)^+$.

Anal. Calcd. for $C_{16}H_{20}N_2O_2 \cdot H_2O$: C, 66.19; H, 7.63; N, 9.63. Found: C, 66.69; H, 7.50; N, 9.36.

4,4'-Diethoxy-6,6'-diacetoxymethyl-2,2'-bipyridine (**6**).

A mixture of **4** (1 g, 3.67 mmoles) and acetic anhydride (15 ml) was heated at 115° under nitrogen during 1 hour. After evaporation, the residue was chromatographed (alumina, 100% chloroform) to give **6**, 1.2 g (90%), mp 145-146°; ir (potassium bromide): ν 1730 (C=O), 1598, 1251 cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.47 (t, 6, J = 7.0, CH_3-CH_2-O), 2.19 (s, 6, CH_3-CO), 4.21 (q, 4, J = 7.0, CH_3-CH_2-O), 5.24 (s, 4, -COOCH_2-), 6.87 (d, 2, J = 2.2, H ar), 7.88 (d, 2, J = 2.2, H ar); ^{13}C-nmr (deuteriochloroform): δ 14.9 (CH_3-CH_2-O), 21.4 (CH_3-CO), 64.2, 67.3 (-COOCH_2- and CH_3-CH_2-O), 106.2, 109.3 (C_3, C_5), 157.0, 157.7, 167.0 (C_2, C_4, C_6), 171.1 (-COO^-); ms: (fast atom bombardment positive mode) m/z 389 $(M+H)^+$.

Anal. Calcd. for $C_{20}H_{24}N_2O_6 \cdot 0.2CHCl_3$: C, 58.84; H, 5.92; N, 6.79. Found: C, 58.82; H, 6.08; N, 6.97.

4,4'-Diethoxy-6,6'-bis(hydroxymethyl)-2,2'-bipyridine (**7**).

A solution of **4** (0.3 g, 0.986 mmole) in acetic anhydride (3 ml), was heated at 115° under nitrogen during 1 hour. Excess of anhydride was then evaporated under vacuum and the residue dissolved in tetrahydrofuran (10 ml). Aqueous sodium carbonate was then added (*ca.* 3 ml) and the resulting mixture was stirred overnight. Solvents were then evaporated and the residue chromatographed (alumina, 100% tetrahydrofuran) to give **7**, 0.24 g (80%), mp 134-135°; ir (potassium bromide): ν 1295, 1052 (CH_2OH) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 1.47 (t, 6, J = 7.0, CH_3-CH_2-O), 4.18 (q, 4, J = 7.0, CH_3-CH_2-O), 4.75 (s, 4, -CH_2-OH), 6.74 (d, 2, J = 2.3, H ar), 7.85 (d, 2, J = 2.3, H ar); ^{13}C-nmr (deuteriochloroform): δ 14.9 (CH_3-CH_2-O), 64.3 (-CH_2-OH and CH_3-CH_2-O), 106.9, 107.1 (C_3, C_5), 156.1, 160.3, 167.0 (C_2, C_4, C_6); ms: (fast atom bombardment positive mode, nitrobenzyl alcohol) m/z 305 $(M+H)^+$.

Anal. Calcd. for $C_{16}H_{20}N_2O_4 \cdot 0.25H_2O$: C, 62.22; H, 6.61; N, 9.07. Found: C, 62.35; H, 6.68; N, 9.14.

4,4'-Diethoxy-6,6'-bis(bromomethyl)-2,2'-bipyridine (**8**).

Diol **7** (0.12 g, 0.394 mmole) was dissolved in methylene chloride, phosphorus tribromide (0.17 ml, 0.5 g, 1.8 mmoles) was slowly added at room temperature. The mixture was then heated at reflux during 30 minutes and methylene chloride was evaporated. Crushed ice was added to the residue, the aqueous solution was neutralized with concentrated potassium hydroxide then extracted with methylene chloride (3 x 15 ml). The organic phase was dried (magnesium sulfate), evaporated, and the residue chromatographed (silica gel, 100% methylene chloride) to give **8**, 0.076 g (45%), mp 145-146°; uv (chloroform): λ max (ϵ) 273 (11300), 328 (shoulder); ^{1}H-nmr (deuteriochloroform): δ 1.46 (t, 6, J = 7.0, CH_3-CH_2-O), 4.20 (q, 4, J = 7.0, CH_3-CH_2-O), 4.55 (s, 4, CH_2Br), 6.96 (d, 2, J = 2.2, H ar), 7.89 (d, 2, J = 2.2, H ar); ^{13}C-nmr (deuteriochloroform): δ 14.9 (CH_3-CH_2-O), 34.7 (CH_2Br), 64.3 (CH_3-CH_2-O), 107.0, 110.9 (C_3, C_5), 157.5, 157.9, 167.1 (C_2, C_4, C_6); ms: (fast atom bombardment positive mode) m/z 429/431/433 (1/2/1) $(M+H)^+$.

Anal. Calcd. for $C_{16}H_{18}Br_2N_2O_2 \cdot 0.2CH_2Cl_2$: C, 43.51; H, 4.14; N, 6.26. Found: C, 43.88; H, 4.30; N, 5.82.

4,4'-Dibromo-6,6'-dimethyl-2,2'-bipyridine N_1,N_1-Dioxide (**9**).

To a suspension of **3** (0.3 g, 0.95 mmole) [16], in glacial acetic acid (4 ml) was added acetyl bromide (2.3 ml). The resulting mixture was heated at 80° during 2.5 hours. After cooling it was added cautiously to crushed ice and the resulting yellow precipitate was filtered and rinsed with water. The aqueous phase was neutralized with sodium carbonate then extracted with methylene chloride. The organic phases were added to the precipitate and the solution dried with magnesium sulfate, filtered and concentrated. Addition of ether gave **9** as a white precipitate 0.23 g (65%), mp >250°; ir (potassium bromide): ν 1258 (N-O) cm^{-1}; ^{1}H-nmr (methanol-d_4 + deuteriochloroform): δ 2.53 (s, 6, CH_3), 7.53 (d, 2, J = 2.7, H ar), 7.60 (d, 2, J = 2.7, H ar); ^{13}C-nmr (methanol-d_4 + deuteriochloroform): δ 17.8 (CH_3), 118.9 (C_4), 128.7, 130.6 (C_3, C_5), 143.3, 151.4 (C_2, C_6); ms: (fast atom bombardment positive mode) m/z 373/375/377 (1/2/1) $(M+H)^+$.

Anal. Calcd. for $C_{12}H_{10}Br_2N_2O_2$: C, 38.53; H, 2.69; N, 7.49. Found: C, 38.32; H, 2.43; N, 7.41.

4,4'-Dibromo-6,6'-dimethyl-2,2'-bipyridine (**10**).

Phosphorus tribromide (1 ml) and **9** (0.2 g, 0.535 mmole) were mixed in methylene chloride (5 ml) at reflux for 1.5 hours, methylene chloride was evaporated and the residue added to crushed ice. The resulting solution was basified at 0° with sodium hydroxide and extracted with methylene chloride (3 x 100 ml). The

organic phase was dried (magnesium sulfate) then chromatographed (alumina, 100% methylene chloride) to give **10**, 0.19 g (91%), mp 192-194°; uv (chloroform): λ max (ε) 278.4 (19000), 325 (3300); ^{1}H-nmr (deuteriochloroform): δ 2.60 (s, 6, CH_3), 7.36 (d, 2, J = 1.4, H ar), 8.40 (d, 2, J = 1.4, H ar); ^{13}C-nmr (deuteriochloroform): δ 24.7 (CH_3), 122.2, 127.0, 134.3 (C_3, C_5, C_4), 156.0, 159.7 (C_2, C_6); ms: (fast atom bombardment positive mode) m/z 341/343/345 (1/2/1) $(M+H)^+$.

Anal. Calcd. for $C_{12}H_{10}Br_2N_2 \cdot 0.1CH_2Cl_2$: C, 41.45; H, 2.93; N, 7.99. Found: C, 41.24; H, 2.67; N, 7.99.

4,4'-[*N,N*-(Diethyl)amino]-6,6'-bis(bromomethyl)-2,2'-bipyridine (**15**).

From Dibromide **9** Through 4,4'-[*N,N*-(Diethyl)amino]-6,6'-dimethyl-2,2'-bipyridine N_1,N_1'-Dioxide **12**, 4,4'-[*N,N*-(Diethyl)-amino]-6,6'-dimethyl Bis(acetate)-2,2'-bipyridine **13** and its 6,6'-Dimethanol Analog **14**.

Compound **9** (1 g, 2.67 mmoles), diethylamine (8 ml) and water (8 ml) were heated at 130° in a stainless steel bomb during 18 hours. After cooling, the resulting mixture was recovered and the bomb rinsed with acetone. Liquids were evaporated to dryness (1 mm Hg, 60°) and the brown residue dissolved in dry acetone (10 ml). The insoluble material **9** (0.15 g) was filtered off and the filtrate evaporated to dryness to give crude **12** which was then treated at 120° with acetic anhydride (40 ml) during 12 hours (thin layer chromatography monitoring on alumina 99% methylene chloride/methanol). After evaporation to dryness, the residue was dissolved in methylene chloride, treated with solid sodium carbonate and filtered on a short alumina column (99% methylene chloride/methanol) to give crude **13** (decomposes rapidly). The "diacetate" was then hydrolysed in a basic medium (water:methanol, sodium hydroxide) during 20 hours at room temperature. Methanol was evaporated and the resulting aqueous mixture extracted with methylene chloride (4 x 100 ml), affording after evaporation the crude diol **14**. This last diol was finally dissolved in dry methylene chloride (10 ml) and phosphorus tribromide (1 ml) was added slowly. The solution was refluxed during 1 hour and methylene chloride evaporated. Crushed ice was added to the residue, the resulting solution carefully basified at 0° with concentrated sodium hydroxide and extracted with methylene chloride (2 x 100 ml). The organic layer was dried (magnesium sulfate), evaporated then chromatographed (alumina 100% methylene chloride) to give (**15**) as an oil 0.082 g (7.5% from reacted **9**).

Compound **12** ($C_{20}H_{30}N_4O_2$) was recovered as a crystalline precipitate by adding a concentrated acetone solution of crude **12** in ether, followed by chromatography on a preparative thin layer chromatography plate (alumina 98% methylene chloride/methanol then 95% methylene chloride/methanol); **12** was then extracted from alumina by 70% methylene chloride/methanol; ^{1}H-nmr (deuteriochloroform): δ 1.25 (t, 12, CH_3-CH_2N), 2.55 (s, 6, CH_3), 3.48 (q, 8, CH_3-CH_2-N), 6.63 (s, 4, H ar); ms: (fast atom bombardment positive mode) m/z 359 $(M+H)^+$.

Compound **13** ($C_{24}H_{34}N_4O_4$) as the crude material was chromatographed on a preparative thin layer chromatography plate (alumina 99% methylene chloride/methanol), but decomposed very rapidly on this support; ^{1}H-nmr (deuteriochloroform): δ 1.25 (t, 12, CH_3-CH_2-N), 2.22 (s, 6, CH_3), 3.51 (q, 8, CH_3-CH_2-N), 5.23 (s, 4, CH_2O-CO), 6.60 (s, 2, H ar), 7.62 (s, 2, H ar); ms: (fast atom bombardment positive mode) m/z 443 $(M+H)^+$.

Compound **14** ($C_{20}H_{30}N_4O_2$) as the crude material was chromatographed on a preparative scale thin layer chromatography plate (alumina, multielution methylene chloride, then 98% methylene chloride/methanol). Extraction of **14** from alumina was performed with 90% methylene chloride/methanol, mp 134-135°; ^{1}H-nmr (methanol-d_4 + deuteriochloroform): δ 1.38 (t, 12, J = 7.0, CH_3-CH_2-N), 3.63 (q, 8, J = 7.0, CH_3-CH_2-N), 4.81 (s, 4, CH_2OH), 6.82 (d, 2, J = 2.4, H ar), 7.29 (d, 2, J = 2.4, H ar); ^{13}C-nmr (methanol-d_4 + deuteriochloroform): δ 14.4 (CH_3-CH_2-N), 48.2 (CH_3-CH_2-N), 68.9 (CH_2OH), 106.0, 108.5 (C_3, C_5), 158.1, 161.1, 164.2 (C_2, C_4, C_6); ms: (fast atom bombardment positive mode) m/z 359 $(M+H)^+$.

Compound **15** had uv (chloroform): λ max (ε) 288.0 (shoulder, 9000); ^{1}H-nmr (deuteriochloroform): δ 1.25 (t, 12, J = 7.1, CH_3-CH_2-N), 3.55 (q, 8, J = 7.1, CH_3-CH_2-N), 4.71 (s, 4, CH_2Br), 6.68 (d, 2, J = 1.4, H ar), 7.64 (d, 2, J = 1.4, H ar); ^{13}C-nmr (deuteriochloroform): δ 12.8 (CH_3), 33.5 (CH_2Br), 45.0 (CH_2N), 105.1, 106.5 (C_3, C_5), 154.9, 155.4, 157.0 (C_2, C_4, C_6); ms: (fast atom bombardment positive mode, thioglycerol): m/z 483/485/487 (1/2/1) $(M+H)^+$, 326 $(M-2Br+H)^+$.

Anal. Calcd. for $C_{20}H_{28}Br_2N_4 \cdot 0.2CH_2Cl_2$: C, 48.40; H, 5.71; N, 11.18. Found: C, 48.15; H, 5.64; N, 11.50.

4-Nitro-6,6'-dimethyl-2,2'-bipyridine N_1-Oxide (**17**).

Compound **16** (2.2 g, 11 mmoles) [19] was dissolved in 95% sulfuric acid (15 ml). Ten ml of fuming nitric acid was carefully added and the mixture was heated at 110° during 2 hours. It was then cooled at 0° and added carefully to crushed ice. The resulting aqueous solution was basified at 0° with concentrated sodium hydroxide affording a yellow precipitate. Extraction with methylene chloride (3 x 100 ml) gave after drying over magnesium sulfate a yellow powder which was finally chromatographed (silica gel, 100% methylene chloride then 99% methylene chloride/methanol) to give **17** 0.82 g (30%), mp 159-160°; ir (potassium bromide): ν 1525, 1335 (NO_2), 1275 (N-O) cm^{-1}; uv (chloroform): λ max (ε) 264.6 (5250), 346.0 (5300); ^{1}H-nmr (deuteriochloroform): δ 2.60 (s, 3, CH_3 A), 2.63 (s, 3, CH_3 B), 7.25 (d, 1, J = 7.8, H ar B), 7.72 (t, 1, J = 7.8, H ar B), 8.08 (d, 1, J = 3.2, H ar A), 8.55 (d, 1, J = 7.8, H ar B), 8.92 (d, 1, J = 3.2, H ar A); ^{13}C-nmr (deuteriochloroform): δ 19.1 (CH_3 A), 25.0 (CH_3 B), 119.0 (C_3 B), 120.4 (C_3 A), 122.5 (C_5 B), 125.1 (C_5 A), 137.0 (C_4 B), 141.7 (C_2 A), 148.0 (C_6 A), 148.9 (C_4 A), 152.0 (C_2 B), 159.1 (C_6 B); ms: (70 eV electron impact): m/z 245 (M^+), 229 (M^+-O), 199 (M^+-NO_2).

Anal. Calcd. for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.13. Found: C, 58.71; H, 4.74; N, 16.99.

4-Bromo-6,6'-dimethyl-2,2-bipyridine N_1-Oxide (**18**).

To a solution of **17** (0.5 g, 2 mmoles) in glacial acetic acid (10 ml) at room temperature was added acetyl bromide (5 ml). The solution was refluxed during 2 hours, then cooled and added to crushed ice (100 g). The resulting mixture was basified at 0° with sodium carbonate and washed with methylene chloride (4 x 100 ml). The organic phase was dried (magnesium sulfate) and evaporated. The residue was finally chromatographed (alumina, 100% methylene chlorlide) to give **18** 0.32 g (57%), mp 117-118°; ir (potassium bromide): ν 1259 (N-O) cm^{-1}; uv (chloroform) λ max (ε) 273.0 (17500), 323.0 (shoulder, 3300); ^{1}H-nmr (deuteriochloroform): δ 2.54 (s, 3, CH_3 B), 2.61 (s, 3, CH_3 A), 7.21 (d, 1, J = 7.8, H ar B), 7.41 (d, 1, J = 3.0, H ar A), 7.70 (t, 1, J = 8.0, H ar B), 8.18 (d, 1, J = 3.0, H ar A), 8.60 (d, 1, J = 8.0, H ar B); ^{13}C-nmr (deuteriochloroform): δ 18.7 (CH_3 A), 25.0 (CH_3 B), 118.6 (C_4 A), 122.9 (C_5 B), 124.5 (C_3 B), 128.7 (C_3 A), 128.8 (C_5 A), 136.9 (C_4 B), 148.7 (C_2 A), 148.8 (C_2 B), 151.4 (C_6 A), 158.6 (C_6 B); ms: (fast atom bom-

bardment positive mode, nitrobenzyl alcohol) m/z 279 ($M_{79}+H^+$), 281 ($M_{81}+H^+$).

Anal. Calcd. for $C_{12}H_{11}BrN_2O\cdot 0.1CH_2Cl_2$: C, 50.52; H, 3.92; N, 9.73. Found: C, 50.78; H, 3.70; N, 9.90.

4-Bromo-6,6'-dimethyl-2,2-bipyridine (**19**).

A solution of **18** (0.1 g, 0.36 mmole) and phosphorus tribromide (0.3 ml, 3 mmoles) in chloroform (4 ml) was refluxed under nitrogen during 45 minutes. After cooling, the solvent was evaporated and the residue added carefully to crushed ice. The solution was basified to *p*H 9-10 with 20% aqueous sodium hydroxide. The resulting white precipitate was extracted with methylene chloride (3 x 50 ml) to give after drying (magnesium sulfate) and evaporation pure **19**, 0.92 g (99%), mp 56-57°; ^{1}H-nmr (deuteriochloroform): δ 2.49 (s, 3, CH_3 B), 2.54 (s, 3, CH_3 A), 7.06 (d, 1, J = 7.8, H ar B), 7.21 (d, 1, J = 1.2, H ar A), 7.57 (t, 1, J = 7.8, H ar B), 8.11 (d, 1, J = 7.8, H ar B), 8.36 (d, 1, J = 1.2, H ar A); ^{13}C-nmr (deuteriochloroform): δ 24.7 and 24.9 (CH_3 A and CH_3 B), 118.8 (C_3 B), 121.8 (C_3 A), 124.0 (C_5 B), 126.3 (C_4 A), 134.2 (C_5 A), 137.4 (C_4 B), 154.6 (C_2 A), 157.2 (C_2 B), 158.2 (C_6 B), 159.4 (C_6 A); ms: (fast atom bombardment positive mode) m/z 263 ($M_{79}+H^+$), 265 ($M_{81}+H^+$).

Anal. Calcd. for $C_{12}H_{11}BrN_2\cdot 0.2CH_2Cl_2$: C, 52.30; H, 4.10; N, 10.00. Found: C, 52.50; H, 4.06; N, 10.29.

4-Cyano-6,6'-dimethyl-2,2'-bipyridine N_1-Oxide (**21**).

Dimethyl sulfate (0.9 ml, 9.2 mmoles) was added to a solution of **2** (1 g, 4.6 mmoles) [19] in methylene chloride (3 ml). The mixture was refluxed under nitrogen during 2 hours (thin layer chromatography monitoring alumina, 95% methylene chloride/methanol). Evaporation of the solvent and residual dimethyl sulfate, afforded a vitrious residue which was dissolved in dry acetone, then added to an excess of dry ether to take off residual dimethyl sulfate. The resulting oily precipitate containing **20** and/or **30** was rinsed with ether (3 x 10 ml), then dissolved in the minimum of water. This solution was finally dropped into a 70% aqueous potassium cyanide (10 ml) at room temperature affording a precipitate which was filtered then chromatographed (alumina, 100% methylene chloride then 95% methylene chloride/ethanol) to give **21** 0.26 g, (25%) free of bipyridine **1**, mp dec 230°; ir (potassium bromide): ν 2240 (CN) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.58 (s, 3, CH_3 B), 2.66 (s, 3, CH_3 A), 7.25-7.33 (m, 2, H ar B), 7.39 (s, 1, H ar A), 8.08 (d, 1, J = 7.3, H ar B), 9.07 (s, 1, H ar B); ^{13}C-nmr (deuteriochloroform): δ 18.7 (CH_3 B), 24.9 (CH_3 A), 117.1 (CN), 121.3 (C_4 A), 124.7 (C_3 A), 125.4 (C_5 A), 125.2 (C_5 B), 126.1 (C_3 B), 127.0 (C_4 B), 146.2 (C_2 B), 150.5 (C_6 B), 151.3 (C_6 A), 159.7 (C_2 A); ms: (fast atom bombardment positive mode, thioglycerol) m/z 226 ($M+H^+$), 210 ($M-O+H^+$).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.65. Found: C, 69.29; H, 5.20; N, 18.46.

4-Hydroxymethyl-6,6'-dimethyl-2,2'-bipyridine (**27**).

Dimethyl sulfate (4.8 ml, 49 mmoles) was added dropwise to a solution of **2** (4.8 g, 22 mmoles) in methylene chloride (48 ml) at room temperature and the resulting mixture was refluxed during 2 hours. After cooling and removal of the solvent, acetone (100 ml) was added to the residual oil. The crude product was triturated leaving a white powder which was filtered, washed with ether (100 ml), then dissolved in a 50% methanol/water medium. Ammonium persulfate (1.6 g, 7 mmoles) was then slowly added and the resulting mixture was refluxed during 5 hours. After cooling, the solvents were removed *in vacuo* and the residue containing crude **23** was dried overnight over phosphorus pentoxide. It was then dissolved in methylene chloride (20 ml), treated with phosphorus tribromide (2.2 ml, 5.5 mmoles) at room temperature, then gently warmed to 50° during 15 minutes. Evaporation of the solvent afforded the crude alcohol which was chromatographed (silica gel, 100% methylene chloride then 99% methylene chloride/methanol) to give pure **27**, 0.94 g (20%); ir (potassium bromide): ν 3300 (OH), 3080 (CH, aromatic), 2920, 2960 (CH_3), cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.51 (s, 3, CH_3 B), 2.54 (s, 3, CH_3 A), 4.66 (s, 2, CH_2OH), 3.87 (s, 1, OH), 7.23-7.34 (m, 3, H ar B), 8.06 (s, 1, H ar A), 8.51 (s, 1, H ar A); ^{13}C-nmr (deuteriochloroform): δ 18.4 (CH_3 B), 23.8 (CH_3 A), 63.3 (CH_2-OH), 120.4, 122.3, 125.9, 126.4 (C_3, C_4, C_5 A and B); ms: (70 eV electron impact) m/z 213 (M^+).

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.89; H, 6.54; N, 13.08. Found: C, 73.10; H, 6.48; N, 13.17.

4-Hydroxymethyl-6,6'-dimethyl-2,2'-bipyridine N_1-Oxide (**23**).

Instead of adding phosphorus tribromide in the last procedure, the solubilized crude alcohol was deposited over alumina, dried under vacuum then chromatographed (alumina, 97% methylene chloride/methanol) to give **23** (20% yield), mp 118-119°; ir (potassium bromide): ν 1076, 1203 (CH_2OH), 1220 (N-O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.51 (s, 3, CH_3 B), 2.54 (s, 3, CH_3 A), 4.51 (s, 2, CH_2OH), 7.12 (s, 1, H ar A), 7.25 (d, 2, J = 6.0, H ar B), 7.85 (t, 1, J = 6.0, H ar B), 8.19 (s, 1, H ar A); ^{13}C-nmr (deuteriochloroform): δ 18.8 (CH_3 B), 24.5 (CH_3 A), 63.2 (CH_2OH), 120.2 (C_4 A), 121.3 (C_5 B), 126.1 (C_4 B), 126.5 (C_3 B), 141.3 (C_2 B), 148.5 (C_3 A), 149.5 (C_6 B), 150.3 (C_5 A), 152.0 (C_2 A), 158.6 (C_6 A); ms: (fast atom bombardment positive mode, thioglycerol) m/z 231 ($M+H^+$), 215 ($M-O+H^+$).

Anal. Calcd. for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.16. Found: C, 67.92; H, 5.98; N, 12.34.

4,4'-Bis(hydroxymethyl)-6,6'-dimethyl-2,2'-bipyridine (**24**) [23].

After elution of **23**, the solvent was modified from 97% methylene chloride/methanol to 90% methylene chloride/methanol then 85% methylene chloride/methanol, affording a small amount of the diol **24**; ^{1}H-nmr (deuteriochloroform): δ 2.53 (s, 6, CH_3), 4.57 (s, 4, CH_2OH), 7.03 (s, 2, H ar), 7.86 (s, 2, H ar); ms: (fast atom bombardment positive mode, nitrobenzyl alcohol) m/z 245 ($M+H^+$).

Anal. Calcd. for $C_{14}H_{16}N_2O_2\cdot 0.1H_2O$: C, 68.33; H, 6.64; N, 11.38. Found: C, 68.14; H, 6.41; N, 11.56.

4-Hydroxymethyl-6,6'-dimethyl-2,2'-bipyridine N_1,N_1-Dioxide (**25**).

A solution of **23** (0.06 g, 0.26 mmole) and *m*-chloroperbenzoic acid 80% (0.1 g, 0.46 mmole) in chloroform (10 ml) was stirred under nitrogen at room temperature during 14 hours. Evaporation of the solvent afforded a gummy precipitate which was triturated with ether (3 x 5 ml) to give a white powder containing **25**. Chromatography (silica gel, 88% methylene chloride/methanol) afforded pure **25**, 0.05 g (90%), mp dec 195°; ir (potassium bromide): ν 1242, 1072 (CH_2OH), 1265 (N-O) cm^{-1}; ^{1}H-nmr (deuteriochloroform + methanol-d_4): δ 2.49 (s, 3, CH_3 A), 2.52 (s, 3, CH_3 B), 4.55 (s, 2, CH_2OH), 7.26-7.40 (m, 5, H ar A and B); ^{13}C-nmr (deuteriochloroform + methanol-d_4): δ 18.2 and 18.2 (CH_3 A and B), 62.39 (CH_2OH), 123.33, 123.13, 125.89, 126.65, 127.62, 141.74, 143.01, 144.0, 149.7, 150.3 (C_2, C_3, C_4, C_5, C_6 A and B); ms: (fast atom bombardment positive mode, nitrobenzyl alcohol)

m/z 247 ($M+H^+$).

Anal. Calcd. for $C_{13}H_{14}N_2O_3 \cdot 0.1H_2O$: C, 62.89; H, 5.76; N, 11.28. Found: C, 63.01; H, 5.89; N, 11.14.

4-Carboxy-6,6'-dimethyl-2,2'-bipyridine $N_1,N_{1'}$-Dioxide (**26**).

A mixture of **27** (296 mg, 1.38 mmoles), hydrogen peroxide (5 ml, vol 110) and acetic acid (11 ml) was refluxed under argon (105°) during 10 days. After 3 days, a complement of hydrogen peroxide (3 ml) was added and such an addition was repeated daily until consumption of **27** (thin layer chromatography monitoring, silica gel methylene chloride 90/methanol). The solvent and excess of reagent were removed under high vacuum and the resulting **26** was dried overnight over phosphorous pentoxide (112.5 mg, 31%); ir (potassium bromide): ν 3400 (OH), 1700 (C=O), 1250 (N-O) cm^{-1}; ^{1}H-nmr (dimethyl sulfoxide-d_6): δ 2.39 (s, 3, CH_3 B), 2.40 (s, 3, CH_3 A), 7.12 (s, 1, OH), 7.23 (t, 1, J = 6.0, H ar B), 7.52 (d, 1, J = 6.0, H ar B), 7.60 (d, 1, J = 6.0, H ar B), 7.85 (s, 1, H ar A), 8.06 (s, 1, H ar A); ^{13}C-nmr (dimethyl sulfoxide-d_6): δ 17.2 (CH_3 B), 17.2 (CH_3 A), 123.7 (C_5 B), 125.5 (C_4 B), 125.8 (C_3 B), 126.4 (C_5 A), 127.1 (C_3 A), 124.8 (C_4 A), 142.2 (C_2 B), 143.3 (C_2 A), 148.0 (C_6 B), 148.6 (C_6 A), 164.8 (C=O); ms: (70 eV electron impact) m/z 260 (M^+), 243 (M^+-O).

Anal. Calcd. for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.77. Found: C, 59.70; H, 4.70; N, 11.11.

4-Carbomethoxy-6,6'-dimethyl-2,2'-bipyridine $N_1,N_{1'}$-Dioxide (**28**).

A solution of **26** (100 mg, 0.38 mmole) in methanol (30 ml) was stirred with a catalytic amount of sulfuric acid (0.75 ml) under reflux during 24 hours. The solution was then neutralized with saturated aqueous sodium bicarbonate and extracted two times with 20 ml of methylene chloride. The organic phase was dried (magnesium sulfate) and evaporated to dryness to give **28**, 86 mg (82%); ir (potassium bromide): ν 3090 (CH aromatic), 2960-2920 (CH_3), 1720 ($COOCH_3$), 1260 (N-O) cm^{-1}; ^{1}H-nmr (deuteriochloroform): δ 2.62 (s, 6, CH_3 A and B), 4.00 (s, 3, $COOCH_3$), 7.31 (t, 1, J = 8.0, H ar B), 7.40 (d, 1, J = 8.0, H ar B), 7.44 (d, 1, J = 8.0, H ar B), 8.00 (s, 1, H ar A), 8.02 (s, 1, H ar A); ^{13}C-nmr (deuteriochloroform): δ 17.8 (CH_3 A and B), 52.6 ($COOCH_3$), 124.4 (C_4B), 125.4 (C_5 B), 125.6 (C_3 B), 126.6 (C_5 A), 127.1 (C_3 A), 124.6 (C_4 A), 143.0 (C_2 A), 143.7 (C_2 B), 149.8 (C_6 A and B), 164.1 (C=O); ms: (70 eV, electron impact) m/z 274 (M^+), 257 (M^+-O).

Anal. Calcd. for $C_{14}H_{14}N_2O_4 \cdot 0.1CH_2Cl_2$: C, 59.88; H, 5.06; N, 9.90. Found: C, 59.58; H, 5.38; N, 9.56.

4-Carbomethoxy-6,6'-bis(bromomethyl)-2,2'-bipyridine (**29**).

A solution of **28** (83.5 mg, 0.3 mmole) in acetic anhydride (1.35 g, 13.2 mmoles) was heated at 120° during 1.5 hours. Excess of anhydride was removed *in vacuo* and hydrobromic acid 33% in acetic acid (2.5 ml) was added. The resulting solution was heated 7 hours at 70°, then cooled and diluted with water (25 ml), before neutralization with saturated aqueous sodium bicarbonate and extraction with methylene chloride (3 x 10 ml). The combined organic phases were washed with water, dried (magnesium sulfate), then evaporated to dryness. The resulting crude material was chromatographed (silica gel, 50% petroleum ether/methylene chloride) to give after recrystallization from petroleum ether pure **29**, 44.2 mg (36%); ir (potassium bromide): ν 3080 (CH, aromatic), 1725 (C=O) cm^{-1}; ^{1}H-nmr (deuteriochloroform), δ 3.90 (s, 3, $COOCH_3$), 4.65 (2 s, 4, CH_2Br), 7.45 (d, 1, J = 7.0, H ar B), 7.80 (t, 1, J = 7.0, H ar B), 7.95 (s, 1, H ar A), 8.35 (d, 1, J = 7.0, H ar B), 8.85 (s, 1, H ar A); ^{13}C-nmr (deuteriochloroform): δ 33.4 (CH_2Br, B), 33.9 (CH_2Br, A), 52.8 ($COOCH_3$), 119.9 (C_4 B), 120.6 (C_5 B), 122.8 (C_3 B), 124.1 (C_5 A), 138.0 (C_3 A), 139.6 (C_4 A), 154.6 (C_2 B), 156.5 (C_2 A), 156.7 (C_6 B), 157.3 (C_6 A), 165.4 ($COOCH_3$); ms: (CI, NH_3/isobutan) m/z 401 (MH^+), 321 (MH^+-Br).

Anal. Calcd. for $C_{14}H_{12}N_2O_2Br_2$: C, 42.00; H, 3.00; N, 7.00. Found: C, 42.03; H, 3.12; N, 6.75.

$N_1,N_{1'}$-Dimethoxy-6,6'-dimethyl-2,2'-bipyridinium Sulfate (**30**).

This salt was prepared as the synthesis of **21** or **23** and isolated under anhydrous conditions for spectroscopic analysis; ^{1}H-nmr (methanol-d_4): δ 3.10 (s, 6, CH_3), 4.16 (s, 6, N-OCH_3), 8.45 (d, 2, J = 7.0, H ar), 8.53 (d, 2, J = 7.0, H ar), 8.76 (t, 2, J = 7.0, H ar), ^{13}C-nmr (methanol-d_4): δ 18.5 (CH_3), 70.3 (N-OCH_3), 132.0 (C_4), 135.8 (C_5), 140.9 (C_6), 147.1 (C_3), 159.4 (C_2).

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