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A NOVEL REARRANGEMENT OF 2,2'-BIPYRIDINE N,N'-DIOXIDES

THE CHARACTERISATION OF DIPYRIDO[1,2-b:2,3-d] ISOXAZOLINIUM SALTS AS INTERMEDIATES IN THE FORMATION OF 3-HYDROXY-2,2'-BIPYRIDINES

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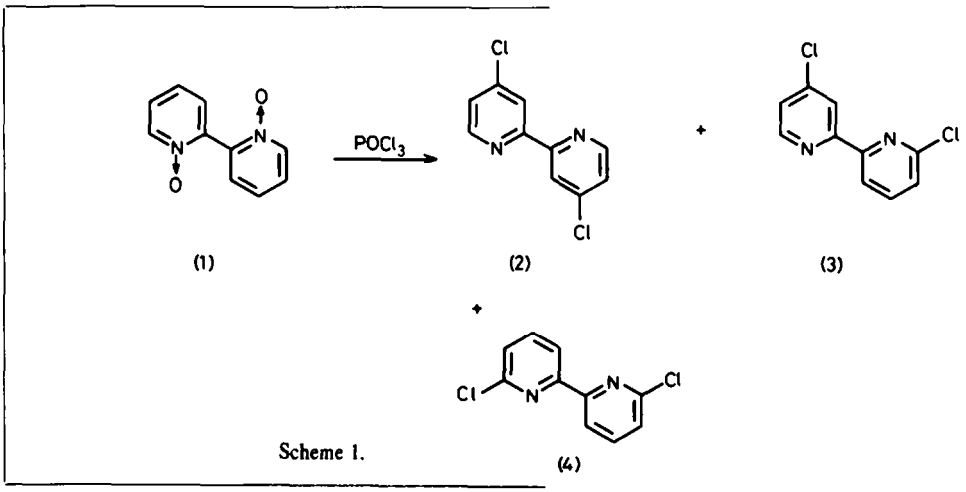
Abstract—The reactions of 2,2'-bipyridine N,N'-dioxides with $POCl_3$ and SO_2Cl_2 have been investigated, and the products shown to be synthetically useful halogenated derivatives. The presence of substituents in the 4 position favours an intramolecular cyclisation to form dipyrido[1,2-b:2,3-d]-isoxazolinium salts, which have been characterised for the first time.

INTRODUCTION

Transition metal diimine complexes have been widely investigated as photocatalysts for the decomposition of water,[1-3] and we are currently interested in the application of ruthenium(II) complexes to such systems. As a part of this study we have investigated the effect of small variations in ligand structure on the properties (redox, photochemical, etc.) of the complexes, and accordingly required a range of substituted 2,2'-bipyridines.

RESULTS AND DISCUSSION

2,2'-bipyridine N,N'-dioxide (**1**) reacted smoothly with either $POCl_3$ or SO_2Cl_2 to give a good yield of a mixture of 6,6'-dichloro-2,2'-bipyridine, (**4**), 4,6'-dichloro-2,2'-bipyridine (**3**) and 4,4'-dichloro-2,2'-bipyridine (**2**). No other products could be isolated from this reaction, although the examination of the crude product by TLC indicated the presence of trace amounts of 2,2'-bipyridine.[5]

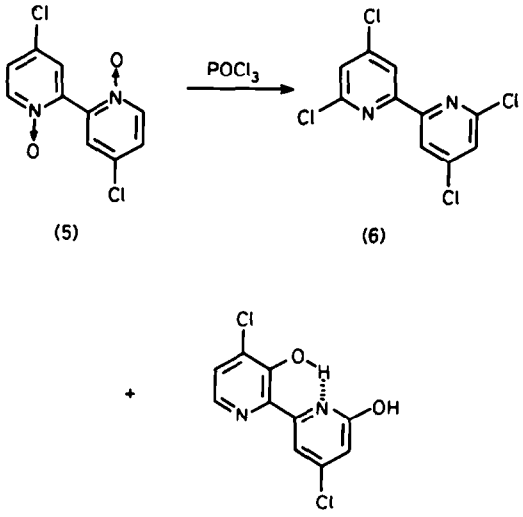


Scheme 1.

We considered that the reaction of 2,2'-bipyridine N,N'-dioxides with inorganic acid halides might provide a suitable route to halogen substituted 2,2'-bipyridines,[4] and it is the results of this investigation which are described. In particular, we wish to report the anomalous formation of 3-hydroxy-2,2'-bipyridines, which we have shown to arise via an isoxazolinium intermediate, which is formed in an intramolecular cyclisation.

4,4'-dichloro-2,2-bipyridine N,N'-dioxide (**5**) also reacted cleanly with either $POCl_3$ or SO_2Cl_2 to give 92% of the expected product, 4,4',6,6'-tetrachloro-2,2'-bipyridine (**6**), obtained as a white solid after hydrolysis of the crude mixture of salts obtained upon evaporation of the excess acid halide. However, alkaline hydrolysis of the strongly acidic solution obtained after the separation of **6**, led to the precipitation of an intensely fluorescent

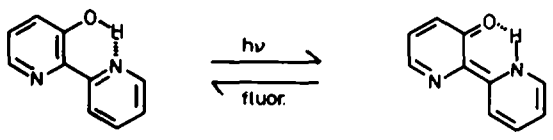
yellow solid, identified as 4,4'-dichloro-3,6'-dihydroxy-2,2'-bipyridine (7) in 8% yield. The identification of 7 will be discussed in greater detail later.



Scheme 2.

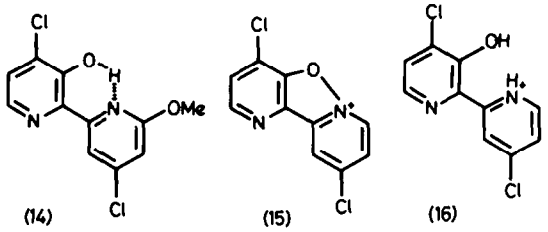
4,4'-dinitro-2,2'-bipyridine N,N'-dioxide (8) reacted with either $POCl_3$ or SO_2Cl_2, with the evolution of brown nitrogen oxides, to give, after the removal of excess acid halide *in vacuo*, a pale yellow mixture of salts. Hydrolysis of the crude reaction mixture led to the precipitation of a mixture of the expected products, **6**, **9** and **10**, and left a strongly acidic pale yellow solution. Treatment of this solution with aqueous potassium hydroxide led to the formation of 4,6'-dichloro-4'-nitro-2,2'-bipyridine (**11**) and **7**, the yield of **7** now amounting to 30%. The yield and distribution of products in this reaction was unaffected by changes in the reaction time (2-24 h), by conducting the reaction under an inert atmosphere, or by the passage of a stream of N_2 through the mixture to remove nitrogen oxides as they were formed.[6]

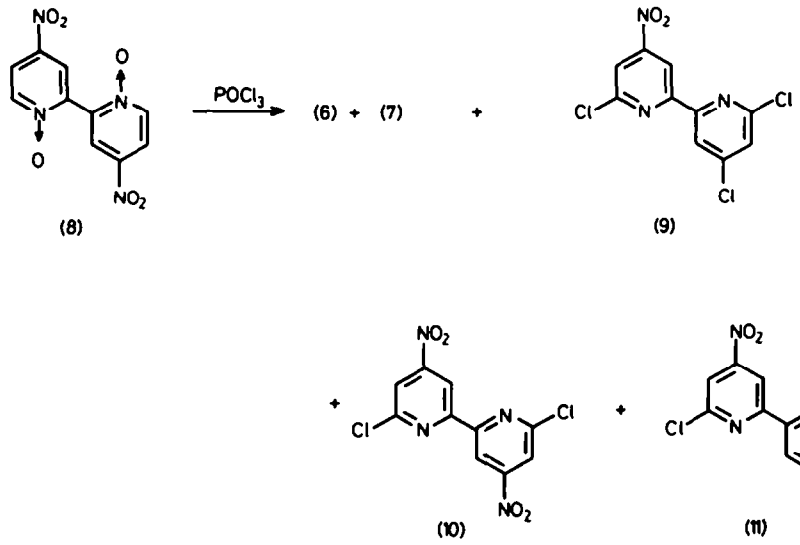
The structure of the unexpected product **7** was assigned on the basis of the ^1H and ^{13}C NMR spectra, the mass spectrum, and the vibrational and electronic spectra, all of which were fully consistent with the proposed structure. The ^1H NMR spectrum showed two AM patterns (Experimental), which is fully consistent with the proposed 3,4,4',6'-tetrasubstituted 2,2'-bipyridine structure, and the mass spectrum showed a parent ion at *m/z* 256, 258, 260. The fluorescence of 3-hydroxy-2,2'-bipyridines has been previously commented upon, and may be explained in terms of the keto-enol phototautomerisation 12↔13.[7]



Scheme 4.

In order to elucidate the mode of formation of the products **7** and **11**, the crude mixture was concentrated *in vacuo* until no further acid halide could be removed, and then treated with methanolic solium methoxide, when the same product distribution was obtained, with the exception that 4,4'-dichloro-3-hydroxy-6'-methoxy-2,2'-bipyridine (**14**) was formed instead of **7**. On the basis of this observation we considered the intermediacy of an isoxazolinium cation of type **15**, which might be expected to undergo nucleophilic attack at C_6, with concommitant ring-opening to give **7** or **14**.[8]





Scheme 3.

Accordingly, the methnolic solvolysate was treated with methanolic ammonium hexafluorophosphate, when a white precipitate of the hexafluorophosphate salt of **15** was obtained. The ^1H NMR spectrum of this compound (Fig. 1) showed an AB quartet and an ABM multiplet, the chemical shifts and coupling constants all being consistent with the proposed structure. It was interesting to note that although the continuous wave ^1H NMR spectrum of the compound was as expected, the intensity of the peaks due to H_3 were much reduced in intensity in Fourier Transform spectra unless long delays between pulses were introduced. This prompted us to investigate the relaxation behaviour of this resonance, and a T_1 of 10.5 sec (20 mg in 1.0 cm^3 of dmso-d_6) was measured. This is extraordinarily long, all the other resonances in the molecule, and in 4,4'-dichloro-2,2'-bipyridine, being in the region of 3,5 sec. We explain this in terms of the "locking" of the 2,2'-bipyridine structure on the introduction of the isoxazolinium ring in **15**, which prevents H_3, relaxing through the Van der Waals interactions resulting from rotation about the C_2-$C_{2'}$ bond. The ^{13}C NMR spectrum of **15** is described in Table 1, and is also fully consistent with the structure we propose for **15**. Finally, the field desorption mass spectrum of the compound was obtained, and showed peaks at *m/z* 239–245, showing exactly the pattern expected for a cation of formula $C_{10}H_5N_2Cl_2O$. We consider this to be very strong support for the isoxazolinium structure, and, in particular, to eliminate structures such as **16**. The salt was completely stable to water and oxygen, melted at 210°, and gave satisfactory elemental analyses for C,H,N,P and F.

Treatment of the purified [PF_6] salt of **15** with aqueous alkali or methanolic Na[OMe] led to the quantitative formation of **7** and **14** respectively. Whilst it is possible

Table 1. ^{13}C NMR data for di (4-chloropyrido)[1,2-b:2,3-d] isoxazolinium hexafluorophosphate (400 MHz, $(CD_3)_2SO$, 5000 transients, 5 sec pulse delay, 30° pulse, 30°).

Chemical shift	Multiplicity
151.68	d
149.28	s
148.66	s
140.57	s
135.82	s
133.72	d
129.19	d
126.71	d
124.98	s
121.53	d

that **7** and **14** arise from the oxidative dehydrogenation of pseudobases of compounds such as **16**, we could find no evidence for attack at C_6 of either 4,4'-dichloro-2,2'-bipyridine or 3,3'-dihydroxy-2,2'-bipyridine, or at C_3 of 2,2'-bipyridine-6(1*H*), 6'(1'*H*)-dione, under the conditions employed above.

The reaction of pyridine N-oxides with inorganic acid halides has been widely investigated, and most authors agree that the first step is electrophilic attack at the N-oxide O atom, followed by nucleophilic attack of halide at C_2 or C_4. In the absence of nitro groups in the

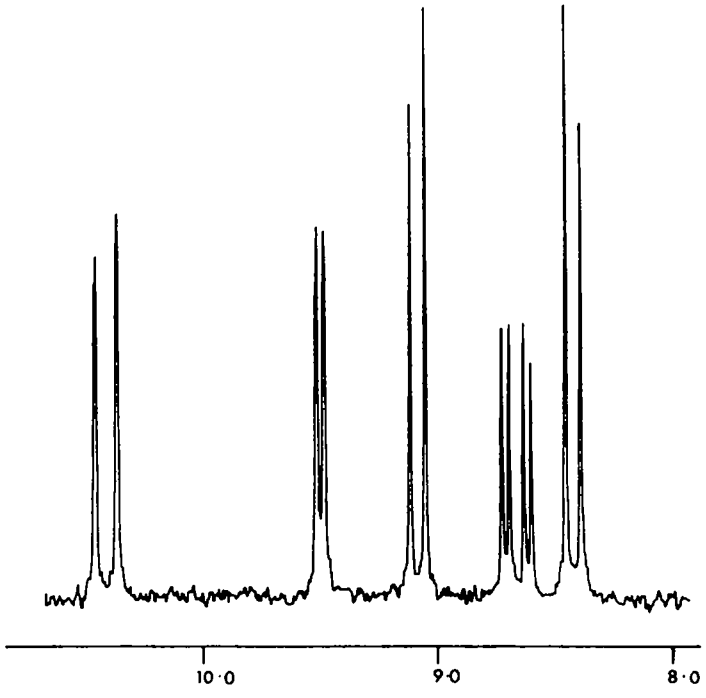
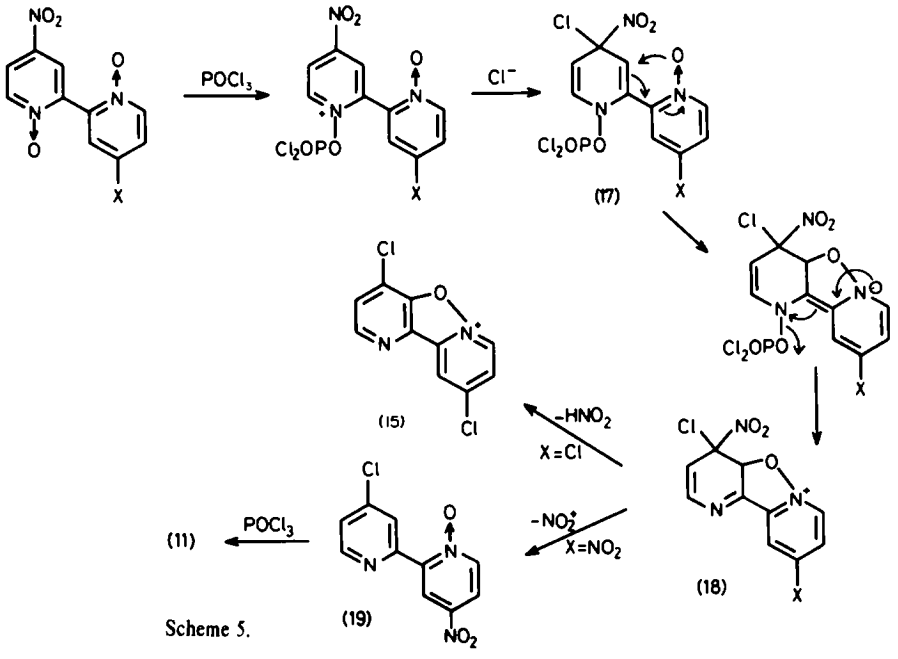


Fig. 1. ^1H NMR spectrum of di(4-chloropyrido)[1,2-b:2,3-d]isoxazolinium hexafluorophosphate (80 MHz, $(CD_3)_2SO$, 30 transients, 10-sec pulse delay, 90° pulse, 35°).



Scheme 5.

4-position, the 2- or 4-chloro derivatives are formed directly, by loss of H^+ and $[PO_2Cl_2]^-$, and this satisfactorily explains the formation of **2**, **3** and **4** from **1**, and also of **6** from **5** and **10** from **8**. The loss of nitrite from 4-chloro-4-nitro-1,4-dihydropyridinium salts is also well documented, and is followed by attack of halide at C_2, and this explains the formation of **6** and **9** from **8**.[4]

We propose that the key step in the formation of the anomalous products in the reaction of **8** and **5** with inorganic acid halides is an intramolecular cyclisation, involving nucleophilic attack of N-oxide oxygen upon C_3 of the 1,4-dihydro intermediate, **17**. A similar mechanism has been invoked to explain the formation of 3-hydroxy derivatives in the reaction of pyridine N-oxides with tosyl chloride, a reaction in which the tosylate ion acts as the nucleophile.[10] The presence of the N-oxide group on a directly bonded ring renders such a reaction pathway very favourable, and it is possible to write the reaction as a concerted 2+4 cycloaddition, although we have no evidence to substantiate this mechanism.[11]

The intermediate so produced may then rearomatise, to produce the key intermediate, **18**, the fate of which depends upon the group X. If X is a nitro group, it is expected to destabilise the pyridinium ion so produced, and the cation undergoes opening of the isoxazolinium ring, with the loss of $[NO_2]^+$ to give an N-oxide, **19**. This then reacts with $POCl_3$ in the expected manner to produce the chloro species **11**. In the event of X being a chloro group, the ion is not so strongly destabilised, and the isoxazolinium ion **15** is formed by the loss of H^+ and $[NO_2]^-$.

This mechanism satisfactorily explains the formation of the anomalous products, and explains why these, and only these, are obtained. We consider the formation of the isoxazolinium cation to be evidence for the electrophilic nature of C_3 in 1-acyloxy-1,4-dihydropyridines, and to provide supportive evidence for the mechanisms proposed for the formation of 3-hydroxypyridines in the reaction of pyridine N-oxides with tosyl chloride. We are at present investigating further examples of intramolecular cyclisations of this type.

EXPERIMENTAL

NMR spectra were recorded on JEOL PMX-60, Varian CFT-20 or Bruker WH-400 spectrometers. Mass spectra were recorded on MSS 501 or ZAP 4F spectrometers. All m.ps are uncorrected. 2,2'-bipyridine N,N'-dioxide,[12] 4,4'-dinitro-2,2'-bipyridine N,N'-dioxide[13] and 4,4'-dichloro-2,2'-bipyridine N,N'-dioxide were[13] prepared by the literature methods.

Reaction of 2,2'-bipyridine N,N'-dioxide with phosphoryl chloride. 2,2'-bipyridine N,N-dioxide dihydrate (2.00g, 0.009 mol) was heated to reflux with $POCl_3$ (25 ml) for 5h. After the initial violent reaction had subsided, a pale yellow suspension was obtained, which darkened upon continued heating. Excess $POCl_3$ was removed *in vacuo* to give a sticky yellow residue, which was cautiously hydrolysed with water (0°, 30 ml): the white insoluble residue was collected by filtration. Recrystallisation from EtOH gave 6,6'-dichloro-2,2'-bipyridine as white needles, m.p. 219–221° (0.26 g, 11.5%). (Found: C, 53.6; H, 2.8; N, 12.4. $C_{10}H_6Cl_2N_2$ requires: C, 53.3; H, 2.7; N, 12.4%); δ[$CDCl_3$, 60 MHz] 8.30 (1H, d, J = 7.5 Hz), 7.75 (1H, t) 7.22 (1H, d, J = 7.5 Hz). The acidic filtrate was neutralised with NaOH(aq), and the white solid ppt filtered off, dissolved in $CHCl_3$ and chromatographed (Al_2O_3:$CHCl_3$). The first band to be eluted gave 4,6'-dichloro-2,2'-bipyridine as a colourless oil, which solidified on standing. Recrystallisation from petroleum ether (b.p. 60–80°) gave white plates, m.p. 87.5–89° (0.45 g, 20%). (Found: 53.2; H, 2.7; N, 12.7. $C_{10}H_6Cl_2N_2$ requires: C, 53.3; H, 2.7; N, 12.4%); δ [$CDCl_3$, 60 MHz] 8.30 (1H, d, J = 1.5 Hz), 8.31 (1H, d, J = 7.5 Hz), 7.70 (1H, t), 7.30 (1H, dd, J_1 = 5.0 Hz, J_2 = 1.5 Hz), 7.20 (1H, d, J = 7.5 Hz), 8.49 (1H, d, J = 5.0 Hz). The second band gave 4,4'-dichloro-2,2'-bipyridine as a white solid, m.p. 133–134° (lit.[13] 131–132°) (0.15 g, 6.7%). (Found: 53.3; H, 2.7; N, 12.3. $C_{10}H_6Cl_2N_2$ requires: C, 53.3; H, 2.7; N, 12.4%); δ [$CDCl_3$, 60 MHz] 8.35 (1H, d, J = 1.5 Hz), 8.48 (1H, d, J = 5.0 Hz) 7.25 (1H, dd, J_1 = 1.5 Hz, J_2 = 5.0 Hz). Extraction of the neutralised aqueous soln with $CHCl_3$ (3 × 100 ml) gave a dark coloured material (0.18 g) which appeared from its ^{1}H NMR spectrum to be mainly unreacted **1**.

Reaction of 1 with sulphuryl chloride. **1** (1.00 g, 0.0045 mol) was heated to reflux with SO_2Cl_2 (25 ml) for 5 hr. and worked up as described above. Essentially the same product distribution was obtained.

Reaction of 5 with phosphoryl chloride. 4,4'-dichloro-2,2'-bipyridine N,N'-dioxide (1.3 g, 0.005 mol) was heated to reflux with $POCl_3$ (25 ml) for 4 hr. Excess $POCl_3$ was removed *in vacuo* and the sticky residue treated with water (50 ml). The white solid

was collected by filtration and recrystallised from EtOH to give 4,4',6,6'-tetrachloro-2,2'-bipyridine as white needles, m.p. 199–201° (1.36 g, 92%) (Found: C, 40.4; H, 1.3; N, 9.2. $C_{10}H_4Cl_4N_2$ requires: C, 40.8; H, 1.4; N, 9.5%) δ [$CDCl_3$, 60 MHz] 8.35 (1H, d, J = 1.5 Hz), 7.40 (1H, d, J = 1.5 Hz). The aqueous filtrate was neutralised with NaOH(aq) and the pale yellow solid collected by filtration, and recrystallised from aqueous MeOH to give yellow microprisms of 4,4'-dichloro-3,6'-dihydroxy-2,2'-bipyridine, m.p. 236–240° (dec) (0.1 g, 8%) (Found: C, 46.7; H, 2.5; N, 11.4. $C_{10}H_6Cl_2N_2O_2$ requires: C, 46.7; H, 2.3; N, 10.9%) δ [$(CD_3)_2SO$, 60 MHz] 7.05 (1H, d, J = 1.5 Hz), 7.70 (1H, d, J = 6.0 Hz), 7.98 (1H, d, J = 1.5 Hz), 8.27 (1H, d, J = 6.0 Hz).

Reaction of **8** *with phosphoryl chloride.* 4,4'dinitro-2,2'-bipyridine N,N'-dioxide (0.65 g, 0.0023 mol) was heated to reflux with $POCl_3$ (15 ml) for 5 hr, after which period the evolution of brown nitrogen oxides had ceased. Excess $POCl_3$ was removed *in vacuo* and the residue was treated with water (25 ml). The pale yellow solid was collected by filtration and washed well with hot MeOH (50 ml) to give a white solid, which was recrystallised from DMF to give white plates of 4,4'-dinitro-6,6'-dichloro-2,2'-bipyridine, m.p. 302.5–303° (dec) (0.20 g, 27.5%) (Found: C, 38.1; H, 1.5; N, 17.3. $C_{10}H_4Cl_2N_4O_4$ requires: C, 38.1; H, 1.3; N, 17.8%) δ [$CDCl_3$, 60 MHz] 7.91 (1H, d, J = 1.5 Hz), 8.90 (1H, d, J = 1.5 Hz). The pale yellow methanolic extract deposited, on standing, colourless crystals crystals of 4,4',6,6'-tetrachloro-2,2'-bipyridine, m.p. 199–200° (0.15 g, 22%). The remaining mother liquor was chromatographed to give 4,6'-dichloro 4'-nitro-2,2'-bipyridine as pale yellow needles from MeOH, m.p. 101–103° (0.075 g, 12%) (Found: C, 44.5; H, 1.85; N, 15.6. $C_{10}H_5Cl_2N_3O_2$ requires: C, 44.4; H, 1.85; N, 15.5%) δ[$CDCl_3$, 60 MHz] 7.47 (1H, d, J = 1.5 Hz), 7.97 (1H, d, J = 1.5 Hz), 8.40 (1H, d, J = 6.0 Hz), 8.92 (1H, d, J = 1.5 Hz), 8.50 (1H, d, J = 6.0 Hz). A very small amount of material identified by ^{1}H NMR as 4,6,6'-trichloro-4'-nitro-2,2'-bipyridine was also obtained δ [$CDCl_3$, 60 MHz] 8.45 (1H, d, J = 1.5 Hz), 8.17 (1H, d, J = 1.5 Hz), 7.50 (1H, d, J = 1.5 Hz), 9.10 (1H, d, J = 1.5 Hz). Neutralisation of the aqueous filtrate with NaOH resulted in the precipitation of **7** as a yellow solid, m.p. 240–245° (dec) (0.17 g, 30%).

Isolation of **15** *and its reaction with sodium methoxide.* The evaporated residue from the reaction between **8** and $POCl_3$ was treated with MeOH (10 ml) instead of water, and the pale yellow ppt removed by filtration. The filtrate was treated with saturated ammonium hexafluorophosphate soln (5 ml) when white cubic crystals of di(4-chloropyrido)[1,2-b:2,3-d]isoxazolinium hexafluorophosphate, m.p. 210–215° were obtained (Found: C, 31.3; H, 1.4; N, 7.3; Cl, 18.3; P, 8.2. $C_{10}H_5Cl_2F_6N_2OP$ requires C, 31.2; H, 1.3; N, 7.3; Cl, 18.4; P, 8.1%) δ[$(CD_3)_2SO$, 80 MHz] 10.42 (1H, d, J = 7.5 Hz), 9.55 (1H, d, J = 2.3 Hz), 9.08 (1H, d, J = 5.1 Hz), 8.66 1H, dd, J_1 = 2.3 Hz, J_2 = 7.5 Hz), 8.41 (1H, d, J = 5.1 Hz). Treatment of either a soln of the hexafluorophosphate salt, or the crude methanolic solution of **15**, with methanolic NaOMe gave a pale yellow soln of 4,4'-dichloro-3-hydroxy-6'-methoxy-2,2'-bipyridine. Evaporation to dryness *in vacuo* gave a pale yellow solid, which was recrystallised from MeOH to give pale yellow needles, m.p. 185–187° (Found: C, 49.1; H, 3.1; N, 10.4. $C_{11}H_8N_2Cl_2O_2$ requires: C, 48.7; H, 2.95; N, 10.3%) δ [$CDCl_3$, 60 MHz] 6.71 (1H, d, J = 1.5 Hz), 7.21 (1H, d, J = 6.0 Hz), 7.91 (1H, d, J = 6.0 Hz), 8.00 (1H, d, J = 1.5 Hz), 3.9 (3H, s).

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