4-Alkyl- and 4-Benzyl-Substituted 3,3′-Oxybispyridines: An Efficient Synthesis at Room Temperature

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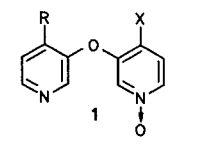
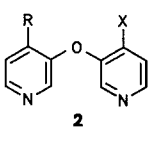
Several new 4-alkyl- and 4-benzyl-substituted 3,3′-oxybispyridines **1** are accessible at room temperature in high yields from 3-hydroxypyridine, potassium salt derivatives **7** and 3-bromo-4-nitropyridine 1-oxide (**5d**), which are readily available starting materials. The reactivity of **5d** depends on the solvent.

The hitherto unknown 4-benzyl-3,3′-oxybispyridines **2b, c** are convenient precursors for the synthesis of our novel 3,6-diazaxanthylium dyes with a previously unknown heterocyclic framework.[1] 3,3′-Oxybispyridines of type **2** and **3** have previously been prepared for pharmacological tests[2] and for a study of compounds related to the bipyridinium herbicides.[3]



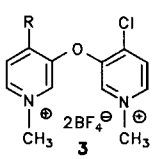
1

	R	X
a	Me	NO_2
b	CH_2Ph	NO_2
c	CH_2Ph-4-CF_3	NO_2
d	H	NO_2
e	H	H
f	H	CN



2

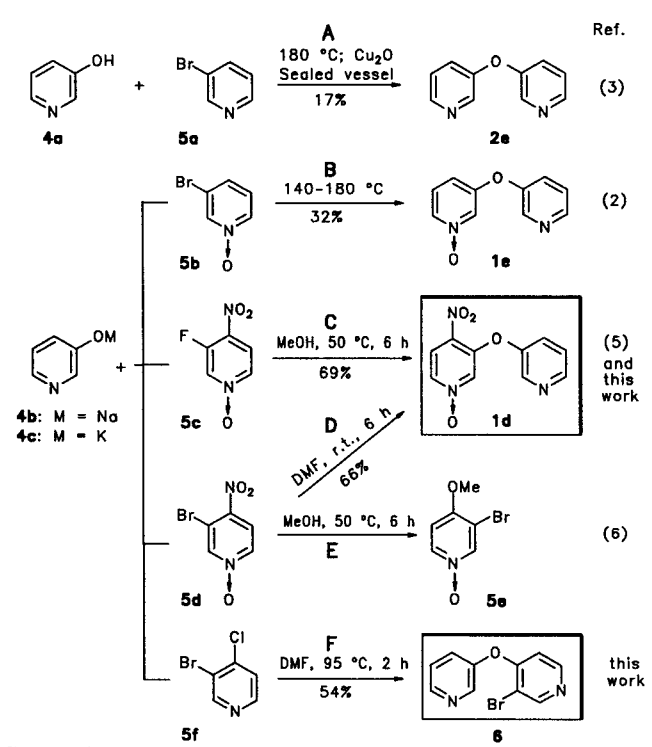
	R	X
a	Me	Cl
b	CH_2Ph	Cl
c	CH_2Ph-4-CF_3	Cl
d	Me	NO_2
e	H	H



3

	R
a	Me
b	CH_2Ph
c	CH_2Ph-4-CF_3

Scheme 1



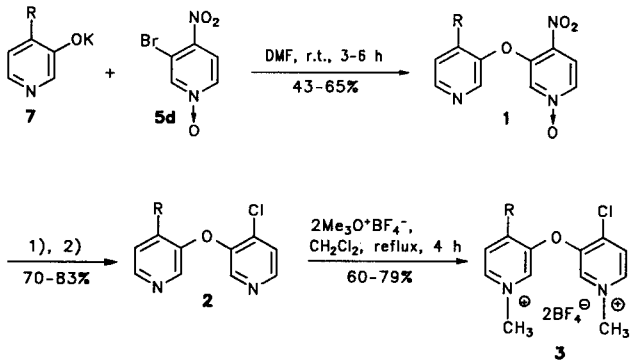
Scheme 2

Herein we report on the synthesis of the 3,3′-oxybispyridines **1–3** (Scheme 1). Three different synthetic methods are available for these compounds (Scheme 2).[4] The first two published methods (**A** and **B**) require high temperatures (140 or 180 °C) without using a solvent and the yields are low (up to 32%).[2,3] In 1984 Talik and Talik[5] described an efficient route (Scheme 2, method **C**) to the 3,3′-oxybispyridine **1d**: the reaction of 3-hydroxypyridine, sodium salt (**4b**) with 3-fluoro-4-nitropyridine 1-oxide (**5c**) in methanol at only 50 °C gave 4-nitro-3,3′-oxybispyridine (**1d**) in 69% yield.

We tested the cheaper and more readily available 3-bromo-4-nitropyridine 1-oxide (**5d**) so replacing the fluoro-substituted compound **5c** in this reaction. Heating of **5d** with 3-hydroxypyridine, potassium salt (**4c**) without solvent resulted in a violent reaction leading to a tarry residue only. Repeating this experiment in methanol (Scheme 2, Method **E**) gave 3-bromo-4-methoxypyridine 1-oxide (**5e**) according to similar findings of Johnson[6] and no trace of the desired oxybispyridine **1d** was detected. In contrast to these results we obtained 4-nitro-3,3′-oxybispyridine 1-oxide (**1d**) in 66% yield when using anhydrous DMF, a polar aprotic solvent at room temperature (Scheme 2, method **D**). The hydroxypyridine salt **4c** regioselectively attacks 3-bromo-4-nitropyridine 1-oxide (**5d**) and no substitution of the nitro group was observed.

According to experiments of Johnson,[6] S_N2-reactions of nitro- or halo-substituted pyridine 1-oxides in methanolic solution are faster in the *ortho* and *para* positions than those in the *meta* position. Furthermore the nitro function in the *para* position is a better leaving group than halogen. In contrast Talik and Talik[7] have found that the reactivity of 3-fluoro-4-nitropyridine 1-oxide (**5c**) is independent of the solvent: a fluoro group in the *meta* position is always substituted! When using methanol as solvent we confirmed the results of Johnson.[6] In DMF the nitro group activates substitution of the bromine atom in the *meta* position. Without the assistance of an electron-withdrawing group (EWG) (e.g. nitro) we obtained the following results in DMF: a) The reaction of 3-bromopyridine 1-oxide (**5b**) with the 3-hydroxypyridine salt **4c** required high temperatures (> 100 °C) and gave **1e** in less than 10% yield; b) the reaction of salt **4c** with 3-bromo-4-chloropyridine (**5f**) afforded the hitherto unknown 3′-bromo-3,4′-oxybispyridine (**6**) in 54% yield (Scheme 2, method **F**) providing the reaction temperature was kept at 100 °C. The attack of the nucleophile **4c** in the *para* position of **5f** corresponds to the results of Johnson.[6] In addition, reaction **F** is a very efficient method for preparing 3,4′-oxybispyridines. The only previously published procedure[4,8,9] gives 3,4′-oxybispyridine in 25% yield.

Treatment of 3-bromo-4-nitropyridine 1-oxide **(5d)** with the appropriate hydroxypyridine salt **7** affords the new 4-alkyl- or 4-benzyl-substituted 3,3′-oxybispyridines **1a**, **1b**, and **1c** (Scheme 3).

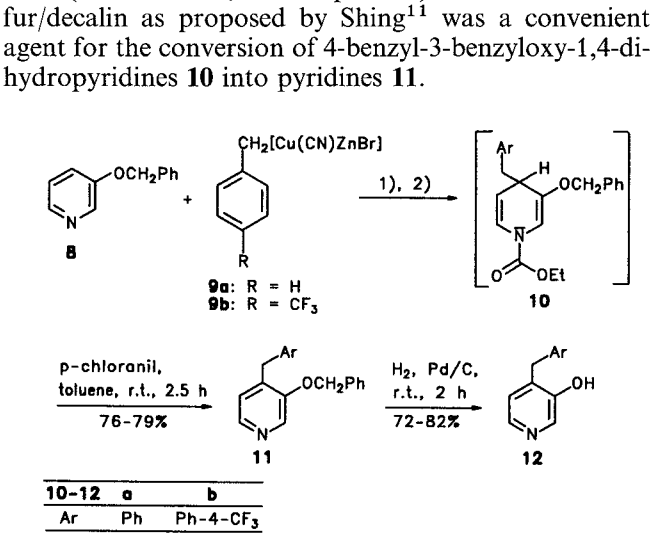


1-3, 7	a	b	c
R	Me	CH_2Ph	CH_2Ph-4-CF_3

[1] PCl_3, $CHCl_3$,* reflux, 1 h
[2] $POCl_3$, reflux, 0.5 h
* For R = Me different conditions were used

Scheme 3

The 4-methyl-3-hydroxypyridine was easily accessible by a three-step synthesis described by Snieckus.[10] The starting materials 4-benzyl-3-hydroxypyridine **(12a)** and 4-(*p*-trifluoromethyl)benzyl-3-hydroxypyridine **(12b)** were made according to a procedure of Shing et al.[11] (Scheme 4). The reaction of 3-benzyloxypyridine **(8)** with the organometallic compounds **9** gave 4-benzyl-3-benzyloxy-1,4-dihydropyridines **10**, which were not purified. *p*-Chloranil (tetrachloro-1,4-benzoquinone)[12] rather than sulfur/decalin as proposed by Shing[11] was a convenient agent for the conversion of 4-benzyl-3-benzyloxy-1,4-dihydropyridines **10** into pyridines **11**.



10-12	a	b
Ar	Ph	Ph-4-CF_3

[1] EtOC(O)Cl, THF, −25 °C, 0.5 h
[2] THF, −78 °C to r.t., 12 h

Scheme 4

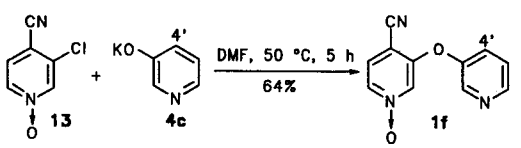
The 3-benzyloxy group can now easily be removed by hydrogenation with Pd/C as catalyst (Scheme 4).[13] The resulting hydroxypyridines **12a, b** were converted into their potassium salts **7**, as in the case of **4a**, according to an analogous procedure of Butler.[2] Then the anhydrous salts **7** were added to a solution of 3-bromo-4-nitropyridine 1-oxide **(5d)** in anhydrous DMF to produce the corresponding oxybispyridine **1b** (in situ generation of the 3-hydroxypyridine, sodium salt **(4b)** with the aid of NaH gave a lower yield of the oxybispyridine **1b**).

For the synthesis of the *p*-trifluoromethylbenzyl oxybispyridine **1c** slightly different conditions had to be developed in comparison to 4-benzyl-4′-nitro-3,3′-oxybispyridine 1′-oxide **(1b)**: The *p*-trifluoromethyl group enhances the acidity of the methylene group, therefore side reactions more readily occur. This is assumed to be the reason for the low yield (12%) of the 3,3′-oxybispyridine **1c** when using the unmodified general procedure. The yield of this reaction was improved to 43% by exactly controlling the oil-bath temperature (130 °C) when preparing the potassium salt **7c**, and using a mixture of DMF/dichloromethane (70:30) instead of DMF as a solvent for the oxybispyridine formation.

The first step of our synthesis of the diquaternary oxybispyridine salts **3a–c** is the deoxygenation of the *N*-oxides. Treatment of 4-methyl-4′-nitro-3,3′-oxybispyridine 1′-oxide **(1a)** with phosphorus trichloride[14] gave two products: the main product **2a** (50%) is formed from **1a** by deoxygenation and substitution of the nitro group for chlorine, the minor product **2d** (10%) is the result of the deoxygenation of **1a** (Scheme 3). By adding a portion of phosphorus oxychloride 1 hour after starting the deoxygenation, only the deoxygenated and chlorinated products **2b, c** were obtained in 70–83% yield.

Then the oxybispyridines **2** were converted into their diquaternary salts **3a** in 60–79% yield by reaction with trimethyloxonium tetrafluoroborate (Meerwein's reagent) (Scheme 3). Barker and Summers obtained a slightly lower yield, using excess iodomethane.[3] The diquaternary salts **3b** and **3c** are excellent direct precursors for new 3,6-diazaxanthylium dyes.[1]

As mentioned previously, 3-bromo-4-nitropyridine 1-oxide **(5d)** displays a remarkable reaction with 3-hydroxypyridine salts **4b**, **4c**, **7a–c** as nucleophiles: only bromine is replaced. This result compares well to findings of LaMattina and Taylor[15] who showed that the chlorine of 3-chloro-4-cyanopyridine can be replaced by different nucleophiles, e.g. alkoxides in DMF as solvent. We were interested to find out if 3-chloro-4-cyanopyridine 1-oxide **(13)** exhibited the same reactivity. Therefore compound **13** was stirred with 3-hydroxypyridine, potassium salt **(4c)**. 4-Cyano-3,3′-oxybispyridine 1-oxide **(1f)** was formed in 67% yield at 50 °C (Scheme 5).



Scheme 5

Nitro and cyano groups show the same behavior in DMF: their orientating effect is supported by the *N*-oxide function, which in addition reduces the π-electron density at the 3-position.[16]

Table 1. ^{13}C NMR Data for the 3,3′-Oxybispyridines **1a–d, 1f, 2a–c**, and **3a–c** in $CDCl_3$, δ in ppm

Product	C-2	C-3	C-4	C-5	C-6	C-2′	C-3′	C-4′	C-5′	C-6′	Others
1a	141.59	149.00	139.14	126.73	147.94	130.65	149.75	134.09	122.46	134.50	15.49
1b	142.25	148.57	136.89	126.20	148.27	130.54	149.63	133.86	122.06	134.16	36.06, 127.04, 128.77, 128.93, 142.42
1c	141.50	148.79	141.37	126.16	147.96	131.00	149.15	134.17	122.30	134.78	36.67, 123.85[a], 125.74[b], 129.42, 129.46[c], 140.99
1d	132.14	149.41	135.00	122.39	135.13	141.64	150.68	126.84	124.82	147.56	
1f	129.90	157.40	99.70	128.80	135.20	142.40	149.95	127.70	124.90	148.10	112.90
2a	139.71	151.50	137.97	126.31	145.87	141.10	149.59	134.29	125.58	145.71	15.61
2b	139.46	150.88	137.73	125.44	145.87	141.44	149.32	134.49	125.44	145.82	35.41, 126.74, 128.68, 129.07, 140.57
2c	139.28	150.92	139.13	125.28	145.95	141.67	148.96	134.67	125.42	146.19	35.36, 124.07[a], 125.62[b], 129.16[c], 129.37, 141.93
3a[d]	135.69	152.81	151.90	131.32	143.16	138.24	146.05	151.41	130.99	144.15	16.80, 48.83, 49.39
3b[e]	137.80	152.86	154.67	131.57	144.74	137.79	152.32	146.13	131.49	144.28	37.48, 49.78, 50.10, 129.05, 130.55, 130.96, 137.10
3c[f]	137.45	149.99	150.68	129.53	143.17	137.76	150.03	142.38	129.36	142.95	34.91, 47.91, 48.10, 124.18[a], 125.68[b], 128.07[c], 130.17, 141.05

[a] $^1J_{CF} = 272$ Hz
[b] $^3J_{CF} = 3.7$ Hz
[c] $^2J_{CF} = 32$ Hz
[d] in D_2O
[e] in CD_3NO_2
[f] in DMSO-d_6

In conclusion, 3-chloro-4-cyanopyridines and 4-alkyl- (or benzyl)-substituted 3-hydroxypyridines are convenient starting materials in a synthesis of 4,4′-dialkyl- or (benzyl)-3,3′-oxybispyridines.

4-Alkyl- and 4-benzyl-substituted 3,3′-oxybispyridines **1**, **2** and **3** are easily accessible in DMF in high yields at room temperature from pyridinol salts **4**, **7** and 3-bromo-4-nitropyridine 1-oxide **(5d)**.

NMR spectra were recorded on a Bruker AM 400 spectrometer (^1H: 400.1 MHz; ^{13}C: 100.6 MHz) using TMS or the solvent signal as internal standards. Chemical shifts are reported in ppm (δ) downfield from TMS. The degree of substitution of the carbon atoms was determined by DEPT 135° experiments. Further assignments were made with the help of homo-decoupling experiments, CH correlation and COLOC spectra. Mass spectra were obtained on a Finnigan MAT 8430 instrument (EI: 70 eV; FAB: 3-nitrobenzyl alcohol was used as liquid matrix). UV/Vis spectra were performed on a Hewlett Packard HP 8452 A spectrometer. IR spectra (KBr) were determined on a Nicolet 320 FTIR instrument. TLC was carried out on silica gel (Polygram Sil G/UV_{254}, Macherey & Nagel, art. 805021) and column chromatography on silica gel 60 (70–230 mesh; Merck, art. 7734). All new compounds with the exception of **2d**, **3c** and **13** gave satisfactory microanalyses (C ± 0.26, H ± 0.15, N ± 0.40) performed with a Carlo Erba elemental analyzer 1106 by the Institut für Pharmazeutische Chemie, Techn. Univ. Braunschweig. All chemicals purchased were reagent grade and used without further purification.

3-Chloro-4-cyanopyridine 1-Oxide (13):
Compound **13** was prepared according to a protocol of Ochiai.[14] 3-Chloro-4-cyanopyridine[15] (1.26 g, 9.3 mmol) was dissolved in AcOH (100%) (30 mL) and 50% aq H_2O_2 (3 mL) was added. The mixture was stirred at 80–85 °C for 9 h, then AcOH was removed under reduced pressure and the resulting solid was recrystallized (toluene) to give **13**; yield: 1.08 g (74%); mp 176–179 °C.

^1H NMR (DMSO-d_6): $\delta = 8.03$ (d, $^3J = 6.9$ Hz, 1 H, 5-H), 8.38 (dd, $^3J = 6.9$ Hz, $^4J = 1.7$ Hz, 1 H, 6-H), 8.82 (d, $^4J = 1.7$ Hz, 1 H, 2-H).

^{13}C NMR (DMSO-d_6): $\delta = 107.66$ (C-4), 114.29 (C-7), 129.81 (C-5), 134.72 (C-3), 139.11 (C-6), 139.71 (C-2).

EIMS: m/z (%) = 156 (32; M^+, ^{37}Cl), 154 (100; M^+, ^{35}Cl), 138 (22), 99 (24), 91 (32), 64 (52).

4-Benzyl-3-benzyloxypyridines 11; General Procedure:
Compounds **11** were prepared according to a modified procedure of Shing:[11]

To a solution of BnBr (12 mmol) in anhydr. THF (20 mL) is added at 0 °C activated Zn (915 mg, 14 mmol). After stirring at 0–5 °C under N_2 for 3 h, this solution is added to anhydr. THF (20 mL) containing anhydr. CuCN (940 mg, 10.8 mmol) and anhydr. LiCl (890 mg, 10.8 mmol; dried at 150 °C in vacuo) at −78 °C. After warming to −20 °C for 5 min, the mixture is cooled again to −78 °C. This solution is added to a preformed solution of pyridinium chloride [from ethyl chloroformate (1.17 g, 10.8 mmol), 3-benzyloxypyridine (**8**; 2.00 g, 10.8 mmol), anhydr. THF (35 mL), at −25 °C for 30 min] at −78 °C. The mixture is allowed to warm up to r.t.

After standing 12–14 h the mixture was quenched with 5% aq NH_3 (30 mL) and the resulting solids were filtered off, washed with H_2O (10 mL) and Et_2O (10 mL). After separation of the organic layer the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed with 10% aq HCl (50 mL) and brine (25 mL), dried (Na_2SO_4) and evaporated to dryness in vacuo. The oily dihydropyridine was dissolved in anhydr. toluene (60 mL) and *p*-chloranil (tetrachloro-1,4-benzoquinone) (2.95 g, 12 mmol) was added in small portions. The mixture was stirred for 2.5 h at 20 °C, then 10% aq NaOH (40 mL) was added and the solution stirred for a further 15 min. The mixture was filtered through Celite and the organic layer was separated. The aqueous layer was extracted with toluene (30 mL) and the combined toluene extracts were washed with 10% aq NaOH (50 mL) and H_2O (40 mL). The organic layer was dried (K_2CO_3), and the solvent removed under reduced pressure. The residue was purified on silica gel by column chromatography (cyclohexane/EtOAc, 1:1).

4-Benzyl-3-benzyloxypyridine **(11a)**:
Compound **11a** was obtained from benzyl bromide (2.06 g, 12 mmol). Column chromatography afforded a viscous oil ($R_f = 0.44$); yield: 2.35 g (79%), bp 180–200 °C/0.3 mbar, Kugelrohr.

UV (CH_2Cl_2): λ_{max} (ε) = 232 nm (7400), 282 (7200).

^{1}H NMR ($CDCl_3$): δ = 4.00 (s, 2H, CH_2), 5.14 (s, 2H, OCH_2), 6.98 (d, ^3J = 4.7 Hz, 1H, 5-H), 7.16–7.38 (m, 10H, phenyl), 8.15 (d, ^3J = 4.7 Hz, 1H, 6-H), 8.28 (s, 1H, 2-H).

^{13}C NMR ($CDCl_3$): δ = 35.46, 70.57, 124.78 (C-5), 126.37, 127.38, 128.13, 128.50, 128.59, 129.12, 134.23 (C-2), 136.40 (C-4), 138.60, 138.85, 142.94 (C-6), 152.96 (C-3).

EIMS: *m/z* (%) = 275 (56, M^+), 184 (33), 91 (100).

3-Benzyloxy-4-(p-trifluoromethylbenzyl)pyridine **(11b)**:

Compound **11b** was obtained from *p*-trifluoromethylbenzyl bromide (2.87 g, 12 mmol). After column chromatography (R_f = 0.60) the residue was recrystallized (pentane) to give colorless crystals; yield: 2.82 g (76%); mp 57–59°C.

UV (CH_2Cl_2): λ_{max} (ε) = 232 nm (8000), 284 (7100).

^{1}H NMR ($CDCl_3$): δ = 4.03 (s, 2H, CH_2), 5.12 (s, 2H, OCH_2), 7.01 (d, ^3J = 4.8 Hz, 1H, 5-H), 7.25–7.27 and 7.30–7.37 (m, 7H, phenyl), 7.51 (d, 2H, phenyl), 8.19 (d, ^3J = 4.8 Hz, 1H, 6-H), 8.30 (s, 1H, 2-H).

^{13}C NMR ($CDCl_3$): δ = 35.53 (CH_2), 70.63 (OCH_2), 124.27 (q, J = 274.6 Hz, C-14), 124.81 (C-5), 125.39 (q, J = 3.8 Hz, C-10, 12), 127.47 (C-17, 21), 128.28 (C-19), 128.61 (C-18, 20), 128.91 (q, J = 29.7 Hz, C-11), 129.32 (C-9, 13), 134.25 (C-2), 136.09 (C-4), 137.40 (C-16), 142.90 (C-6), 143.05 (C-8), 152.94 (C-3).

EIMS: *m/z* (%) = 343 (27, M^+), 91 (100).

Hydrogenation of 3-Benzyloxypyridines 11; General Procedure:

Benzyloxypyridine **11** (3.6 mmol) was dissolved in MeOH (30 mL) and 10% Pd/C (80 mg) was added. The suspension was hydrogenated for 2 h at 20°C and atm pressure. After separation of the catalyst the solvent was removed. The residual white solid was recrystallized (cyclohexane/EtOAc, 1:1).

4-Benzyl-3-hydroxypyridine **(12a)**:

From **11a** (1 g, 3.6 mmol) was obtained **12a** as white crystals; yield: 480 mg (72%), mp 148–149°C.

UV (MeOH): λ_{max} (ε) = 204 nm (19950), 278 (2800).

^{1}H NMR (DMSO-d_6): δ = 3.89 (s, 2H, CH_2), 7.01 (d, ^3J = 4.7 Hz, 1H, 5-H), 7.16–7.30 (m, 5H, phenyl) 7.93 (d, ^3J = 4.7 Hz, 1H, 6-H), 8.12 (s, 1H, 2-H), 9.89 (s, 1H, OH).

^{13}C NMR (DMSO-d_6): δ = 34.35 (C-7), 124.71 (C-5), 126.08 (C-11), 128.37 (C-10, 12), 128.78 (C-9, 13), 135.36 (C-4), 137.15 (C-2), 139.50 (C-8), 140.54 (C-6), 151.77 (C-3).

EIMS: *m/z* (%) = 185 (100, M^+).

4-(p-Trifluoromethylbenzyl)-3-hydroxypyridine **(12b)**:

From **11b** (2.3 g, 6.7 mmol) and 10% Pd/C (150 mg) was obtained **12b** as colorless needles and rectangles; yield: 1.39 g (82%), mp 168°C.

UV (MeOH): λ_{max} (ε) = 204 nm (20600), 214 (15100), 280 (4900), 318 (1800).

^{1}H NMR (DMSO-d_6): δ = 3.99 (s, 2H, CH_2), 7.08 (d, ^3J = 4.8 Hz, 1H, 5-H), 7.45 (d, 2H, 9, 13-H), 7.63 (d, 2H, 10, 12-H), 7.96 (d, ^3J = 4.8 Hz, 1H, 6-H), 8.14 (s, 1H, 2-H), 9.97 (s, 1H, OH).

^{13}C NMR (DMSO-d_6): δ = 34.29 (C-7), 124.39 (J = 271.7 Hz, C-14), 124.86 (C-5), 125.21 (J = 3.8 Hz, C-10, 12), 126.94 (J = 31.5 Hz, C-11), 129.49 (C-9, 13), 134.39 (C-4), 137.31 (C-2), 140.65 (C-6), 144.53 (C-8), 151.85 (C-3).

EIMS: *m/z* (%) = 253 (100, M^+), 252 (23), 184 (23).

3,3-Oxybispyridines 1; General Procedure:

To a stirred and cooled (0°C) solution of 3-bromo-4-nitropyridine 1-oxide **(5d)** (500 mg, 2.3 mmol) in anhydr. DMF (20 mL), hydroxypyridine, potassium salt (2.4 mmol) was added in 3–4 portions. After the addition was complete the mixture was stirred at 20°C for 6 h. The solution was then poured into ice-water (20 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The organic layer was washed with 10% aq KOH (10 mL) and brine (10 mL). The organic layer was dried ($MgSO_4$) and the solvents removed. The resulting yellowish solid was recrystallized from a suitable solvent.

4-Nitro-3,3'-oxybispyridine 1-Oxide **(1d)**:

Compound **1d** was obtained from **5d** (500 mg, 2.3 mmol) and 3-hydroxypyridine potassium salt **(4c)**, (320 mg, 2.4 mmol). The residual solid was recrystallized from cyclohexane/isopropanol (1:2) to give **1d** as yellow needles yield: 345 mg (66%) of mp 104–105°C (Lit[5] 109°C).

UV (CH_2Cl_2): λ_{max} (ε) = 259 nm (8500), 342 (12900).

^{1}H NMR ($CDCl_3$): δ = 7.43 (ddd, ^3J = 8.4, 4.6 Hz, ^4J = 0.4 Hz, 1H, 5'-H), 7.49 (ddd, ^3J = 8.4 Hz, ^4J = 2.7, 1.3 Hz, 1H, 4'-H), 7.84 (d, ^4J = 1.8 Hz, 1H, 2-H), 8.01 (dd, ^3J = 7.2 Hz, ^4J = 1.8 Hz, 1H, 6-H), 8.05 (d, ^3J = 7.2 Hz, 1H, 5-H), 8.52 (d, ^4J = 2.7 Hz, 1H, 2'-H), 8.58 (dd, ^3J = 4.6 Hz, ^4J = 1.3 Hz, 1H, 6'-H).

EIMS: *m/z* (%) = 233 (100, M^+), 186 (31), 149 (24), 140 (21), 110 (20), 95 (31), 94 (36), 81 (35), 78 (70), 66 (80), 51 (78).

4-Methyl-4'-nitro-3,3'-oxybispyridine 1'-Oxide **(1a)**:

Compound **1a** was prepared from **5d** (3.55 g, 16 mmol) and 4-methyl-3-hydroxypyridine potassium salt **(7a)**, (2.65 g, 18 mmol). The yellow solid was recrystallized from cyclohexane/EtOAc (1:3); yield: 2.65 g (67%), mp 141–142°C.

UV (CH_2Cl_2): λ_{max} (ε) = 262 nm (8000), 344 (11900).

^{1}H NMR ($CDCl_3$): δ = 2.32 (s, 3H, CH_3), 7.31 (d, ^3J = 4.8 Hz, 1H, 5-H), 7.70 (d, ^4J = 1.8 Hz, 1H, 2'-H), 7.97 (dd, ^3J = 7.2 Hz, ^4J = 1.8 Hz, 1H, 6'-H), 8.05 (d, ^3J = 7.2 Hz, 1H, 5'-H), 8.34 (s, 1H, 2-H), 8.46 (d, ^3J = 4.8 Hz, 1H, 6-H).

EIMS: *m/z* (%) = 247 (41, M^+), 217 (28), 140 (22), 108 (26), 96 (39), 80 (100), 65 (39), 53 (56).

4-Benzyl-4'-nitro-3,3'oxybispyridine 1'-Oxide **(1b)**:

Compound **1b** was obtained from **5d** (550 mg, 2.5 mmol) and **7b** (558 mg, 2.5 mmol), the reaction time was 5 h. The solid was recrystallized twice from cyclohexane/EtOAc (1:1). The solution was filtered hot to separate insoluble particles. Yield: 460 mg (65%); yellow crystals, mp 125.5–126°C.

UV (CH_2Cl_2): λ_{max} (ε) = 230 nm (11600), 242 (9000), 268 (8850), 344 (8800).

^{1}H NMR ($CDCl_3$): δ = 4.02 (s, 2H, CH_2), 7.10–7.24 (m, 5H, phenyl), 7.29 (d, ^3J = 4.9 Hz, 1H, 5-H), 7.36 (d, ^4J = 1.8 Hz, 1H, 2'-H), 7.81 (dd, ^3J = 7.2 Hz, ^4J = 1.8 Hz, 1H, 6'-H), 7.90 (d, ^3J = 7.2 Hz, 1H, 5'-H), 8.32 (s, 1H, 2-H), 8.50 (d, ^3J = 4.9 Hz, 1H, 6-H).

EIMS: *m/z* (%) = 323 (21, M^+), 276 (81), 199 (100), 183 (56), 182 (39), 167 (25), 139 (22), 128 (21), 105 (25), 91 (29).

4'-Nitro-4-(p-trifluoromethylbenzyl)-3,3'-oxybispyridine 1'-Oxide **(1c)**:

KOH (0.72 g, 12.8 mmol) was dissolved in H_2O (8 mL) and **12b** (3.25 g, 12.8 mmol) was added. The mixture was stirred for 15 min at 20°C, then toluene (60 mL) was added. H_2O was removed with a Dean–Stark trap (temperature of the oil-bath: 130°C). After all H_2O was removed, the solvent was evaporated under reduced pressure to dryness to yield **7c**. To a stirred solution of **5d** (2.85 g, 13 mmol) in anhydr. DMF/CH_2Cl_2 (7:3, 60 mL) the potassium salt **7c** was added in small portions. The mixture was stirred for an additional 6 h at 20°C. The solution was then evaporated under reduced pressure nearly to dryness and the residue was dissolved in H_2O (50 mL). The solution was extracted with CH_2Cl_2 (3–4 × 40 mL). The organic extracts were then washed with 10% aq KOH (50 mL) and brine (40 mL), dried ($MgSO_4$) and evaporated to yield an oily, viscous residue, which was purified on silica gel (250 g) by column chromatography (cyclohexane/isopropanol/MeOH 7:2:1) to give **1c**; yield: 2.19 g (43%). Recrystallization from cyclohexane/EtOAc (3:1) gave analytically pure, pale yellow needles, mp 106–107°C.

UV (CH_2Cl_2): λ_{max}(ε) = 228 nm (8900), 264 (7200), 344 (10500).

^{1}H NMR ($CDCl_3$): δ = 4.11 (s, 2H, CH_2), 7.28 (d, ^3J = 4.7 Hz, 1H, 5-H), 7.29 (d, 2H, 9, 13-H), 7.51 (d, 2H, 10, 12-H), 7.56 (d, ^4J = 1.8 Hz, 1H, 2'-H), 7.91 (dd, ^3J = 7.2 Hz, ^4J = 1.8 Hz, 1H, 6'-H), 7.96 (d, ^3J = 7.2 Hz, 1H, 5'-H), 8.36 (s, 1H, 2-H), 8.52 (d, ^3J = 4.7 Hz, 1H, 6-H).

EIMS: *m/z* (%) = 391 (100, M^+), 372 (29), 361 (44), 344 (45), 328 (20), 352 (62), 240 (27), 224 (40), 199 (82), 182 (64), 159 (57), 128 (17).

4-Cyano-3,3'-oxybispyridine 1-Oxide (**1f**):

To a stirred solution (20 °C) of **13** (510 mg, 3.4 mmol) in anhydr. DMF the 3-hydroxypyridine potassium salt (**4c**), (450 mg, 3.4 mmol) was added in one portion. The mixture was then warmed to 50 °C and stirred for 5 h. The workup was as described in the general procedure. The solid was recrystallized from cyclohexane/isopropanol (1:3) to give colorless needles of **1f**; yield: 460 mg (64%), mp 149–150 °C. The colorless needles turned dark-green in the air after some days.

IR (KBr): ν = 3042, 3103, 2228 (CN), 1612, 1484, 1475, 1441, 1429, 1318, 1279, 1231, 1215, 1113, 705 cm^{-1}.

UV (CH_2Cl_2): λ_{max} (ε) = 232 nm (10400), 252 (11400), 300 (19700).

^1H NMR ($CDCl_3$): δ = 7.45 (dd, ^3J = 4.8, 8.4 Hz, 1 H, 5'-H), 7.54 (ddd, ^3J = 8.4 Hz, ^4J = 1.3, 2.8 Hz, 1 H, 4'-H), 7.57 (d, ^3J = 6.8 Hz, 1 H, 5-H), 7.74 (d, ^4J = 1.5 Hz, 1 H, 2-H), 7.99 (dd, ^3J = 6.8 Hz, ^4J = 1.5 Hz, 1 H, 6-H), 8.55 (d, ^4J = 2.8 Hz, 1 H, 2'-H), 8.61 (dd, ^3J = 4.8 Hz, ^4J = 1.3 Hz, 1 H, 6'-H).

EIMS: *m/z* (%) = 213 (100, M^+), 78 (55).

3'-Bromo-3,4'-oxybispyridine (6):

To a solution of 3-bromo-4-chloropyridine (**5f**)[17] (0.42 g, 2.2 mmol) in anhydr. DMF (10 mL) was added **4c** (0.3 g, 2.2 mmol) in 3–4 portions and the solution was stirred for 3.5 h at 20 °C and for a further 2 h at 95 °C. The workup was performed as described in the general procedure for compounds **1**. The oily residue was distilled in vacuo (Kugelrohr apparatus) to give **6** as white waxy needles; yield: 0.3 g (54%), mp 64 °C, bp 140–150 °C/0.4 mbar.

UV (CH_2Cl_2): λ_{max} (ε) = 230 nm (9500), 260 (4200).

^1H NMR ($CDCl_3$): δ = 6.66 (d, ^3J = 5.5 Hz, 1 H, 5'-H), 7.41 (dd, ^3J = 8.3, 4.5 Hz, 1 H, 5-H), 7.46 (ddd, ^3J = 8.3 Hz, ^4J = 2.6, 1.5 Hz, 1 H, 4-H), 8.34 (d, ^3J = 5.5 Hz, 1 H, 6'-H), 8.50 (d, ^4J = 2.6 Hz, 1 H, 2-H), 8.56 (dd, ^3J = 4.5 Hz, ^4J = 1.5 Hz, 1 H, 6-H), 8.74 (s, 1 H, 2'-H).

^{13}C NMR ($CDCl_3$): δ = 111.16 (C-3'), 111.77 (C-5'), 124.54 (C-5), 127.66 (C-4), 142.72 (C-2), 146.91 (C-6), 150.03 (C-6'), 150.63 (C-3), 153.69 (C-2'), 160.57 (C-4').

EIMS: *m/z* (%) = 252 (52; M^+, ^{81}Br), 250 (52; M^+, ^{79}Br), 171 (100), 78 (46), 51 (46).

4'-Chloro-4-methyl-3,3'-oxybispyridine (2a):

To a stirred and cooled (0 °C) solution of **1a** (0.9 g, 3.64 mmol) in anhydr. $CHCl_3$ (30 mL) PCl_3 (1.14 mL, 12.7 mmol) was added. The mixture was stirred at 20 °C for 2.5 h and made alkaline with 15% aq/NaOH (40 mL) after the reaction was complete. The organic layer was separated and the aqueous layer was washed with $CHCl_3$ (3 × 15 mL). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated. The crude oil was purified on silica gel (40 g) by column chromatography (cyclohexane/isopropanol 4:1) to give **2a** (R_f = 0.37) and 4-methyl-4'-nitro-3,3'-oxybispyridine (**2d**, R_f = 0.27). Compound **2a** was distilled (Kugelrohr apparatus, 90 °C/0.03 mbar) to afford white crystals; yield: (49%), mp 43–44 °C.

UV (CH_2Cl_2): λ_{max} (ε) = 230 nm (500), 270 (4960).

^1H NMR ($CDCl_3$): δ = 2.34 (s, 3 H, CH_3), 7.23 (d, ^3J = 4.8 Hz, 1 H, 5-H), 7.44 (d, ^3J = 5.1 Hz, 1 H, 5'-H), 8.10 (s, 1 H, 2-H), 8.17 (s, 1 H, 2'-H), 8.324 (d, ^3J = 5.1 Hz, 1 H, 6'-H), 8.331 (d, ^3J = 4.7 Hz, 1 H, 6-H).

EIMS: *m/z* (%) = 222 (32; M^+, ^{37}Cl), 220 (100; M^+, ^{35}Cl), 185 (46), 92 (64), 65 (64).

4-Methyl-4'-nitro-3,3'-oxybispyridine (**2d**); yellow oil.

^1H NMR ($CDCl_3$): δ = 2.33 (s, 3 H, CH_3), 7.27 (d, ^3J = 4.8 Hz, 1 H, 5-H), 7.80 (d, ^3J = 5.2 Hz, 1 H, 5'-H), 8.25 (s, 1 H, 2'-H), 8.36 (s, 1 H, 2-H), 8.41 (d, ^3J = 4.8 Hz, 1 H, 6-H), 8.59 (d, ^3J = 5.2 Hz, 1 H, 6'-H).

Chlorination of Benzyl-3,3'-oxybispyridines 1b, c; General Procedure:

To a solution of **1b, c** (0.93 mmol) in anhydr. $CHCl_3$ (10 mL) was added PCl_3 (0.26 mL, 3 mmol) with stirring and this mixture was refluxed for 1 h. Then $POCl_3$ (1 mL) was added and the solution was heated for an additional 30 min at reflux. After cooling to 20 °C the mixture was poured on ice-water (40 mL) and made alkaline with aq KOH (15%) (30 mL). The $CHCl_3$ layer was separated and the aqueous layer was extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were dried (Na_2SO_4) and the solvent removed under reduced pressure.

4-Benzyl-4'-chloro-3,3'-oxybispyridine (**2b**):

Compound **2b** was obtained from **1b** (300 mg, 0.93 mmol). The residue was purified on silica gel (20 g) by column chromatography (cyclohexane/isopropanol 3:1) to give **2b**; yield: 230 mg (83%, R_f = 0.46). An analytically pure sample was obtained by HPLC (RP-8, 7 μm, 250–10, Merck) with MeOH:H_2O (9:1, 2 mL/min) as eluent; white, waxy crystals could be isolated, mp 42–43 °C.

UV (CH_2Cl_2): λ_{max} (ε) = 230 nm (8100), 270 (5300).

^1H NMR ($CDCl_3$): δ = 4.06 (s, 2 H, CH_2), 7.14 (d, ^3J = 4.9 Hz, 1 H, 5-H), 7.19–7.21 (m, 3 H, phenyl), 7.22–7.30 (m, 2 H, phenyl), 7.41 (d, ^3J = 5.1 Hz, 1 H, 5'-H), 8.07 (s, 1 H, 2-H), 8.08 (s, 1 H, 2'-H), 8.30 (d, ^3J = 5.1 Hz, 1 H, 6'-H), 8.33 (d, ^3J = 4.9 Hz, 1 H, 6-H).

EIMS: *m/z* (%) = 298 (17; M^+, ^{37}Cl), 296 (44; M^+, ^{35}Cl), 261 (100), 169 (35), 167 (23), 129 (30), 111 (20).

4'-Chloro-4-(p-trifluoromethylbenzyl)-3,3'-oxybispyridine (**2c**):

Compound **2c** was obtained from **1c** (363 mg, 0.93 mmol). The residue was purified on silica gel (20 g) by column chromatography (cyclohexane/isopropanol 9:4) to give **2c**; yield: 238 mg (70%, R_f = 0.50). An analytically pure sample was obtained by HPLC (RP-8, 7 μm, 250–10, Merck) with MeOH/H_2O (82:18, 1.9 mL/min) as eluent; white waxy crystals were isolated, mp 44–45 °C.

UV (CH_2Cl_2): λ_{max} (ε) = 228 nm (8400), 272 (5600).

^1H NMR ($CDCl_3$): δ = 4.14 (s, 2 H, CH_2), 7.16 (d, ^3J = 4.8 Hz, 1 H, 5-H), 7.34 (d, 2 H, 9, 13-H), 7.43 (d, ^3J = 5.2 Hz, 1 H, 5'-H), 7.45 (d, 2 H, 10, 12-H), 8.08 (s, 1 H, 2-H), 8.16 (s, 1 H, 2'-H), 8.34 (d, ^3J = 5.2 Hz, 1 H, 6'-H), 8.37 (d, ^3J = 4.8 Hz, 1 H, 6-H).

EIMS: *m/z* (%) = 366 (19; M^+, ^{37}Cl), 364 (56; M^+, ^{35}Cl), 329 (100), 167 (27).

Oxybispyridine Diquaternary Salts 3; General Procedure:

Chloro-3,3'-oxybispyridine **2a–c** (2.25 mmol) were dissolved in anhydr. CH_2Cl_2 (20 mL). After addition of trimethyloxonium tetrafluoroborate (Me_3OBF_4) (0.68 g, 4.6 mmol) the mixture was stirred under reflux for 4 h. The workup was different for each compound.

4'-Chloro-1,1',4-trimethyl-3,3'-oxybispyridinium Ditetrafluoroborate (**3a**):

Salt **3a** was prepared from **2a** (500 mg, 2.25 mmol) and Me_3OBF_4 (680 mg, 4.6 mmol). After cooling the mixture, the resulting crystals were filtered off and recrystallized from MeOH/H_2O (3:1) to give **3a**; colorless, quadrangular crystals; yield: 750 mg (79%): mp 247–248 °C.

UV (CH_3CN): λ_{max} (ε) = 192 nm (40400), 206 (30300), 226 (15200), 278 (8000).

^1H NMR (DMSO-d_6): δ = 2.57 (s, 3 H, CH_3), 4.26 (s, 3 H, NCH_3), 4.27 (s, 3 H, NCH_3), 8.22 (d, ^3J = 6.2 Hz, 1 H, 5-H), 8.59 (d, ^3J = 6.6 Hz, 1 H, 5'-H), 8.87 (dd, ^3J = 6.2 Hz, ^4J = 0.8 Hz, 1 H, 6-H), 8.95 (ddd, ^3J = 6.6 Hz, ^4J = 1.3 Hz, 1 H, 6'-H), 8.99 (s, 1 H, 2-H), 9.07 (d, ^4J = 1.3 Hz, 1 H, 2'-H).

MS (+ FAB): *m/z* (%) = 761 (3; 2 cat.$^{2+}$ *3 BF_4^-, ^{35}Cl), 339 (29; cat.$^{2+}$ *BF_4^-, ^{37}Cl), 337 (88; cat.$^{2+}$ *BF_4^-, ^{35}Cl), 249 (40), 213 (27).

MS (-FAB): *m/z* (%) = 511 (7; cat.$^{2+}$ *3 BF_4^-, ^{35}Cl), 87 (100, BF_4^-).

4-Benzyl-4'-chloro-1,1'-dimethyl-3,3'-oxybispyridinium Ditetrafluoroborate (**3b**):

Salt **3b** was obtained from **2b** (460 mg, 1.55 mmol) and Me_3OBF_4 (490 mg, 3.3 mmol). After cooling the mixture, MeOH was added

and then the solvents were evaporated. The resulting solid was recrystallized from acetone to give **3b**; colorless crystals; yield: 465 mg (60%); mp 210–213 °C (Some crystals turn blue on melting).

UV (CH_3CN): λ_{max} (ε) = 194 nm (53900), 204 (36100), 220 (20900), 276 (9300).

^1H NMR (CD_3NO_2): δ = 4.33 (s, 3H, CH_3), 4.42 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 7.27–7.37 (m, 5H, phenyl), 8.12 (d, ^3J = 6.2 Hz, 1H, 5-H), 8.25 (d, ^3J = 6.5 Hz, 1H, 5′-H), 8.32 (d, ^4J = 1.4 Hz, 1H, 2′-H), 8.55 (s, 1H, 2-H), 8.59 (dt, ^3J = 6.5 Hz, ^4J = 1.1, 0.6 Hz, 1H, 6′-H), 8.70 (dd, ^3J = 6.2 Hz, ^4J = 0.7 Hz, 1H, 6-H).

MS (+ FAB): *m/z* (%) = 912 (6; 2cat.$^{2+}$ *3BF_4^-), 415 (34; cat.$^{2+}$ *BF_4^-, ^{37}Cl), 413 (100; cat.$^{2+}$ *BF_4^-, ^{35}Cl), 325 (30), 289 (46).

MS (-FAB): *m/z* (%) = 1086 (2; 2cat.$^{2+}$ *5BF_4^-), 586 (10; cat.$^{2+}$ *3BF_4^-), 240 (44, NBA + BF_4^-), 87 (100, BF_4^-).

4′-Chloro-1,1′-dimethyl-3,3′-oxy-4-(p-trifluoromethylbenzyl)bispyridinium Ditetrafluoroborate (**3c**):

Compound **3c** was prepared from **2c** (90 mg, 0.25 mmol) and Me_3OBF_4 (85 mg, 0.57 mmol). In order to destroy the unreacted Me_3OBF_4, MeOH was added to the cooled mixture, then the solvents were evaporated nearly to dryness. After addition of Et_2O colorless crystals of **3c** were obtained; yield: 100 mg (67%), mp 70 °C.

UV (CH_3CN): λ_{max} (ε) = 192 nm (59200), 206 (33800), 230 (14800), 284 (8500).

^1H NMR (DMSO-d_6): δ = 4.25 (s, 3H, CH_3), 4.26 (s, 3H, CH_3), 4.45 (s, 2H, CH_2), 7.55 (AA′XX′, 2H, 9, 13-H), 7.71 (AA′XX′, 2H, 10, 12-H), 8.26 (d, ^3J = 6.2 Hz, 1H, 5-H), 8.58 (d, ^3J = 6.5 Hz, 1H, 5′-H), 8.95 (t, 2H, 6, 6′-H), 9.08 (s, 1H, 2-H), 9.09 (s, 1H, 2′-H).

MS (+ FAB): *m/z* (%) = 483 (22; cat.$^{2+}$ *BF_4^-, ^{37}Cl), 481 (58; cat.$^{2+}$ *BF_4^-, ^{35}Cl), 393 (42), 357 (100).

MS (− FAB): *m/z* (%) = 655 (14; cat.$^{2+}$ *3BF_4^-), 87 (100, BF_4^-).

(1) Eggers, L.; Grahn, W.; Lüttke, W.; Knieriem, B.; Jones, P.G.; Chrapkowski, A. *Angew. Chem.* **1994** *106*, 903; *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 863.
(2) Butler, D.E.; Poschel, B.P.H.; Marriott, J.G. *J. Med. Chem.* **1981**, *24*, 346.
(3) Barker, D.J.; Summers, L.A. *J. Heterocycl. Chem.* **1983**, *20*, 1411.
(4) For a review see: Summers, L.A. *J. Heterocycl. Chem.* **1987**, *24*, 533.
(5) Talik, T.; Talik, Z. *Pr. Nauk. Akad. Ekon. im. Oskara Langego Wroclawiu* **1984**, *278*, 163; *Chem. Abstr.* **1985**, *103*, 104818.
(6) Johnson, R.M. *J. Chem. Soc. (B)* **1966**, 1058.
(7) Talik, Z.; Talik, T. *Rocz. Chem.* **1962**, *36*, 417.
(8) Boduszek, B.; Wieczorek, J.S. *Rocz. Chem.* **1976**, *50*, 2167.
(9) Katsuta, S. Japanese Patent JP 59152303, 1984; *Chem. Abstr.* **1984**, *102*, 108261.
(10) Miah, M.A.J., Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.
(11) Shing, T.-L.; Chia, W.-L.; Shiao, M.-J.; Chau, T.-Y. *Synthesis* **1991**, 849.
(12) Comins, D.L.; Mantlo, N.B. *J. Heterocycl. Chem.* **1983**, *20*, 1239.
(13) Comins, D.L.; Stroud, E.D. *J. Heterocycl. Chem.* **1985**, *22*, 1419.
(14) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 534.
(15) LaMattina, J.L.; Taylor, R.L. *J. Org. Chem.* **1981**, *46*, 4179.
(16) Sojka, S.A.; Dinan, F.J.; Kolarczyk, R. *J. Org. Chem.* **1979**, *44*, 307.
(17) Compound **5f** was prepared from **5d** according to the general procedure for the chlorination of the oxybispyridines **1b, c**.