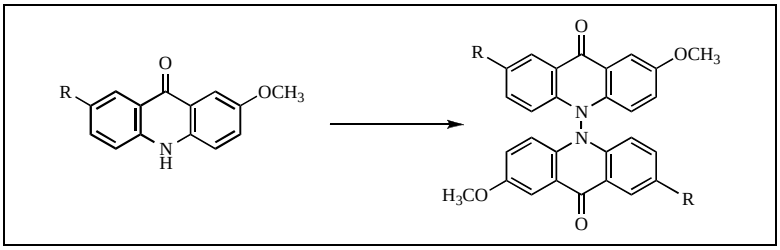
Oxidative Coupling of Acridinones: Synthesis of New C_2-Symmetry Atropisomers

Karine Scarpellini-Charras, Gérard Boyer,* Nathalie Filloux and Jean-Pierre Galy

UMR SYMBIO 6178, Université Paul Cézanne, Case 552, Faculté St-Jérôme,
13397 Marseille Cedex 20, France
E-mail: gerard.boyer@univ-cezanne.fr
Received January 28, 2005



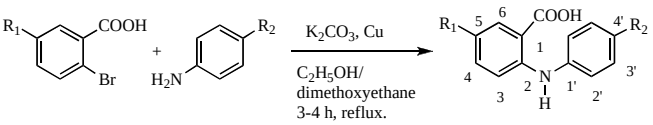
The preparation of symmetric 2,2'-dimethoxy-10,10'-biacridinyl-9,9'-dione atropisomers were obtained by the oxidative coupling of 9(10*H*)-acridinone with 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione

J. Heterocyclic Chem., **45**, 67 (2008).

Acridine derivatives are well known therapeutic agents due to their wide range of pharmacological and biological activities [1], and many C_2-symmetry derivatives have been reported in the literature [2]. We reported previously the prepartion of symmetrical heterocyclic host compounds related to bianthryl [3] using unsubstituted 9,9-biacridinyl [4]; but no inclusion compounds were observed with these derivatives. On the other hand 2,2'-dimethoxy-9,9'-biacridines atropisomers proved useful in molecular recognition showing a 'scissor-like' host conformation and guest inclusion of chloroform in their crystalline structure [5]. Recently we obtained the first chiral (*aR*)-(-)-9,9'-biacridinyl-2,2'-diol atropisomer enantiomerically pure by derivatization and recrystallisation [6]. Hence we were interested in the preparation of new C_2 symmetry derivatives bridged at positions 10,10' and report now the synthesis of 2,2'-dimethoxy-10,10'-biacridinyl-9,9'-diones using the corresponding methoxy-9(10*H*)-acridinones **4a** and **4b**.

Our approach towards this synthesis was based on the preparation of the 2-methoxy- and 2-methoxy-7-methyl-9(10*H*)-acridinones (**4a**) and (**4b**) followed by oxidative coupling to yield the desired acridinone dimers.

First, 4'-methoxyphenyl-*N*-anthranilic acid (**3a**) and 5-methoxy-4'-methyl-*N*-phenylanthranilic acid (**3b**) were prepared by Ullmann's reaction between 2-bromo-benzoic acid and 4-alkylanilines (**2a**) and (**2b**). Compound **3a** was obtained by a modified procedure of Krishnegowda using EtOH as solvant and 2-bromobenzoïc acid [7]; while use of dimethoxyethane instead of 1-pentanol under reflux yielded **3b** [8] (Scheme 1).

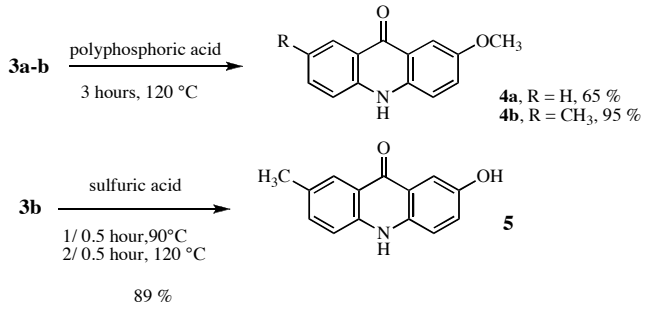


1a, R = H
1b, R = OCH_3

2a, $R_2 = OCH_3$
2b, $R_2 = CH_3$

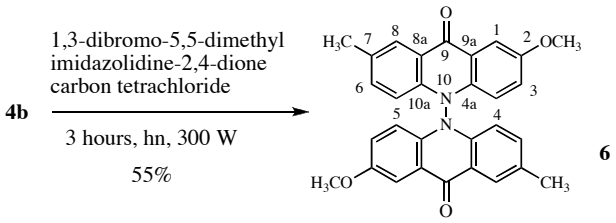
3a, R_1 = H, $R_2 = OCH_3$, 83 %
3b, $R_1 = OCH_3$, $R_2 = CH_3$, 69 %

The cyclization of **3a**,**b** could be performed by Friedel-Crafts acylation in polyphosphoric acid or in sulfuric acid but the best yields were obtained in polyphosphoric acid after purification leading to 2-methoxy-9(10*H*)-acridinone (**4a**) and 2-methoxy-7-methyl -9(10*H*)-acridinone (**4b**) in 65 % and 95 % yield respectively. Demethylation was also observed performing the cyclization of anthranilic acid (**3b**) in sulfuric acid; leading to the hydroxy derivative 2-hydroxy-7-methyl-acridin-9(10*H*)-one (**5**) in 89 % yield (Scheme 2).

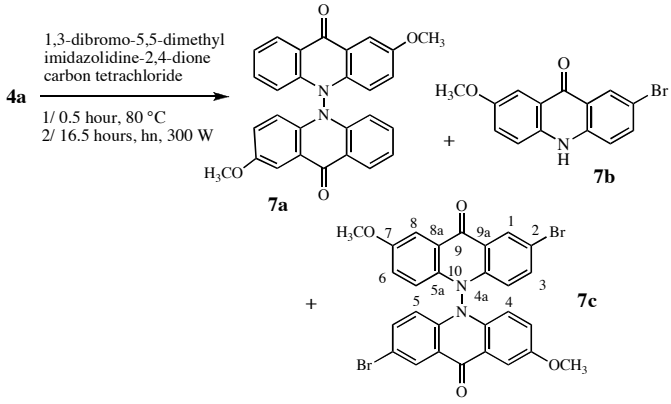


Then, we tried the oxidative homocoupling of 2-methoxy-9(10*H*)-acridinone (**4a**) and 2-methoxy-7-methyl-9(10*H*)-acridinone (**4b**), according to Graebe's procedure with sodium bichromate in acetic acid [9] successfully used in the laboratory for the preparation of 10,10'-biacridinyl-9,9'-dione derivatives, [4] and also with tris(acetyl-acetonato)cobalt(III), in deuteriodimethyl-

sulfoxide [10], but these methods did not lead to satisfactory results. At the same time, benzylic photobromination of 9-chloro-7-methoxy-2-methylacridine with *N*-bromosuccinimide [11] and 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione [12] was studied in the laboratory to prepare polyacridinic ligands [13], and the best yields were obtained using 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione instead of the commonly employed *N*-bromosuccinimide in anhydrous carbon tetrachloride under reflux (Scheme 3).



In the case of **4b**, only one coupling product, the biacridinyl-9,9'-dione (**6**) was obtained using 0.2 equivalent of 1,3-dibromo-5,5'-dimethylimidazolidine-2,4-dione, while coupling and bromination of **4a** gave a mixture of acridinones **7a,c**, (Scheme 4).



However, desired 2,2'-dimethoxy-10,10'-biacri-dinyl-9,9'-dione **7a** was prepared selectively in 50 % yield using 0.05 molar equivalent of 1,3-dibromo-5,5'-dimethyl-imidazolidine-2,4-dione, whereas mono and dibrominated acridinones **7b** and **7c** were obtained, as shown in Table 1

In conclusion, we have reported the oxidative preparation of a new class of C_2-symmetry atropisomers by the reaction of acridinones with 1,3-dibromo-5,5'-dimethylimidazolidine-2,4-dione. Further studies of this reaction are now currently in progress.

EXPERIMENTAL

Thin-layer chromatography (TLC) carried out on aluminium sheets coated with silica gel 60 (Merck 5554). Column chromatography was performed on silica gel 60 (Merck 9385, 230-400 mesh). Melting points were determined with an Electrothermal 9200 melting point apparatus and are uncorrected. The ^{1}H- and ^{13}C-nmr spectra were measured on a BRUKER AC 300 (300.13 MHz) spectrometer. Synchronous excitation-emission fluorescence spectra were recorded with a Perkin Elmer LS-50 spectrometer interfaced to a personal computer. The source was a Xenon flash lamp, power equivalent to 20 kW for 8 µs duration. Samples dissolved in DMF were filled into a 10 mm fused quartz cell. All the spectra were computed at 1 nm resolution between 200 to 600 nm. The fluorescence spectra were collected by synchronous scanning the excitation and emission monochromator in the 200 to 600 nm range with constant wavelength difference $\delta\lambda$= 30 nm between them. The step size and band pass of the monochromator were set to 5 and 4 nm respective1y.

Table 1

Equivalents of 1,3-dibromo-5,5'-dimethylimidazolidine-2,4-dione for the synthesis of **7a-c** from **4a**.

Entry	1,3-dibromo-5,5'-dimethylimidazolidine-2,4-dione equivalent	Yield of **7a-c**
1	0.05	**7a** (50%)
2	0.2	**7b** (4%), **7e** (10%)
3	0.5	**7a** (1%), **7b** (6%), **7c** (34%)
4	0.8	**7a** (1%), **7b** (12%), **7c** (33%
5	1.1	**7a** (1%), **7b** (6%), **7c** (34%)
6 [a]	1.1	mixture **7a**/**7b** (55/45)[b]
7 [c]	2	**7c** (50%), mixture **7a**/**7b** (40/60) [b]

[a] No hν irradiation, [b] isomers were not separated, [c] *N*-bromo-succinimide was used instead 1,3-dibromo-5,5-dimethylimidazolidine-2,4-dione.

4'-Methoxyphenyl-*N*-anthranilic acid (3a). A mixture of 2-bromobenzoic acid (**1a**) (24.31 g, 0.12 mol), 4-methoxyaniline (**2a**) (16 g, 0.13 mol), anhydrous potassium carbonate (41.4 g, 0.17 mol), and copper (0.35 g) in absolute ethanol (200 ml) was heated under reflux with stirring for 4 hours, and the solvent was removed *in vacuo*. The mixture was poured into hot water (400 mL) and filtered. The filtrate was acidified with diluted hydrochloric acid (6 *N*) until pH 6 and filtered to yield 20.2 g (83 %) of a green solid (**3a**), mp 186°C. TLC/R_f: 0.3 (methylenechloride/ethanol, 6/4). ^{1}H-nmr (deuteriodimethyl sulfoxide) δ 3.75 (s, 3H, OCH_3), 6.67 (ddd, J = 8.0, 7.0 and 0.9 Hz, 1H, H-5), 6.91 (dd, J = 0.9 and 8.3 Hz, 1H, H-3), 6.94 (dd, J = 2.2 and 8.9 Hz, 2H, H-3'), 7.17 (dd, J = 2.1 and 8.9 Hz, 2 H, H-2'), 7.31 (ddd, J = 1.6, 7.0 and 8.3 Hz, 1H, H-4), 7.85 (dd, J = 1.6 and 8.0 Hz, 1H, H-6), 9.42 (s, 1H, NH), 12.82 (s, 1H, COOH). ^{13}C-nmr (deuteriodimethyl sulfoxide) δ 55.2 (OCH_3), 111.2 (C-1), 112.8 (C-3), 114.8 (C-3'), 116.2 (C-5), 125.1 (C-2'), 131.7 (C-4), 132.9 (C-4'), 134.2 (C-6), 148.8 (C-2), 156.1 (C-1'), 170.0 (COOH). *Anal.* Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.23, H, 5.69, N, 5.54.

5-Methoxy-4'-methyl-*N*-phenylanthranilic acid (3b). A mixture of 2-bromo-5-methoxybenzoic acid (**1b**) (10 g, 0.043 mol), 4-toluidine (**2b**) (5.78 g, 54 mmol), anhydrous potassium carbonate (7.44 g, 54 mmol), copper (1 g) and dimethoxyethane (100 ml) was heated under reflux with stirring for 3 hours and the solvent was removed *in vacuo*. The mixture was poured into hot water (100 ml) and filtered. The filtrate was acidified with diluted hydrochloric acid (6 *N*) until pH 8 and filtered. Then

more hydrochloric acid (6 *N*) was added to the filtrate until pH 4 to yield the anthranilic acid (**3b**) (7.62 g, 69 %) as a green solid, mp 160°C. TLC/R_f: 0.4 (methylenechloride/ethanol, 7/3). ^{1}H-nmr (deuteriodimethyl sulfoxide) δ 2.32 (s, H, CH_3), 3.78 (s, 3H, OCH_3), 6.99 (dd, J = 3.0 and 9.5 Hz, 1H, H-4), 7.08 (d, J = 6.1 Hz, 2H, H-2'), 7.13 (d, J = 6.1 Hz, 2H, H-3'), 7.14 (d, J = 9.5 Hz, 1H, H-3), 7.49 (d, J = 3.0 Hz, 1H, H-6). ^{13}C-nmr (deuteriodimethyl sulfoxide) δ 20.8 (CH_3), 55.8 (OCH_3), 110.5 (C-1), 113.9 (C-6), 116.2 (C-4), 122.5 (C-2'), 124.3 (C-3), 129.9 (C-3'), 133.1 (C-4'), 138.4 (C-2), 144.0 (C-1'), 150.8 (C-5), 173.5 (COOH). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.29; H, 5.98; N, 5.61.

2-Methoxy-9(10*H*)-acridinone (4a). A mixture of 4'-methoxyphenylanthranilic acid (**3a**) (15.4 g, 63 mmol) and 154 g (1.08 mol) of polyphosphoric acid were heated for 3 h at 120 °C. The mixture was poured into cold water (200 ml) to yield a green precipitate witch was basified until pH = 8 with ammonium hydroxide (10 %), filtered and dried. The recovered powder was then added to hot ethanol (400 mL), and warmed one night under stirring. The solution was filtered hot and water was added (100 mL) to yield a yellow precipitate witch was collected by filtration and dried to yield 9.3 g (65 %) of **4a**, mp 260°C. TLC/R_f: 0.3 (methylenechloride/ethanol, 6/4). ^{1}H-nmr (deuteriodimethyl sulfoxide) δ 3.85 (s, 3 H, OCH_3), 7.21 (ddd, 1H, J = 1.0, 7.0 and 8.0 Hz, H-7), 7.40 (dd, 1H, J = 2.9 and 9.1 Hz, H-3), 7.52 (dd, 1H, J = 1.0 and 8.3 Hz, H-5), 7.53 (dd, 1H, J = 9.1 Hz, H-4), 7.62 (d, 1H, J = 2.9 Hz, H-1), 7.69 (ddd, 1H, J = 1.3, 7.0 and 8.3 Hz, H-6), 8.22 (dd, 1H, J = 1.3 and 8.0 Hz, H-8), 11.73 (s, 1H, NH). ^{13}C-nmr (deuteriodimethyl sulfoxide) δ 55.35 (OCH_3), 104.8 (C-1), 117.3 (C-7), 119.2 (C-4), 119.6 (C-9a), 120.7 (C-7), 121.0 (C-8a), 124.3 (C-3), 125.9 (C-8), 133.0 (C-6), 135.7 (C-4a), 140.4 (C-5a), 153.9 (C-2), 175.1 (C-9). *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.87; H, 4.75; N, 6.40.

2-Methoxy-7-methyl-9(10*H*)-acridone (4b). One g (3.9 mmol) of 5-methoxy-4'-methyl-*N*-phenyl anthranilic acid (**3b**) and 7 g (49 mmol) of polyphosphoric acid were heated for 3 h at 120 °C. The dark mixture was then poored on ice. The obtained solution was basified until pH = 8 with ammonium hydroxide (10 %). The yellow precipitate was collected by filtration, washed with water and dried. The crude solid was washed in hot ethanol (50 ml). The residue was filtered hot, washed with two portions (10 ml) of hot ethanol and dried to give 0.88 g (3.7 mmol, 95 %) of **4b** as a yellow powder, mp 300 °C. TLC/R_f: 0.3 (methylenechloride/ethanol, 7/3). ^{1}H-nmr (deuteriodimethyl sulfoxide) δ 2.40 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 7.37 (dd, 1H, J = 2.9 and 8.9 Hz, H-3), 7.43 (d, 1H, J = 8.6 Hz, H-5), 7.50 (d, 1H, J = 8.6 Hz, H-4), 7.52 (dd, 1H, J = 1.9 and 8.4 Hz, H-6), 7.60 (d, 1H, J = 2.7 Hz, H-1), 8.01 (s, 1H, H-8), 11.64 (s, 1H, NH). ^{13}C-nmr (deuteriodimethyl sulfoxide) δ 20.6 (CH_3), 55.3 (OCH_3), 104.7 (C-1), 117.3 (C-5), 119.1 (C-4), 119.5 (C-9a), 120.8 (C-8a), 124.1 (C-3), 124.9 (C-8), 129.7 (C-7), 134.5 (C-6), 135.7 (C-4a), 138.6 (C-5a), 153.7 (C-2), 176.2 (C-9). *Anal.* Calcd for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.59; H, 5.63; N, 5.60.

2-Hydroxy-7-methylacridin-9(10*H*)-one (5). A mixture of 5-methoxy-4'-methyl-*N*-phenyl-anthranilic acid (**3b**) (3 g, 11.7 mmol) and sulfuric acid (30 mL, 95 %) was heated at 90°C under stirring for 0.5 hour, then at 120°C for 0.5 hour more. The green solution was added to cold water (300 mL) and basified until pH = 8 with ammonium hydroxide (10 %). The green precipitate was collected by filtration, washed with water and dried. The crude residue was washed with hot toluene (60 mL) and filtered to yield 2.34 g (10.4 mmol, 89 %) of **5** as a green powder, mp 225 °C. TLC/R_f: 0.5 (methylenechloride/ethanol, 7/3). ^{1}H-nmr (deuteriodimethyl sulfoxide) δ 2.38 (s, 3H, CH_3), 7.24 (dd, 1H, J = 2.8 and 8.9 Hz, H-3), 7.39 (d, 1H, J = 8.3 Hz, H-5), 7.42 (d, 1H, J = 8.9 Hz, H-4), 7.49 (dd, 1H, J = 1.9 and 8.5 Hz, H-6), 7.52 (d, 1H, J = 2.6 Hz, H-1), 7.96 (s, 1H, H-8), 9.51 (s, 1H, OH), 11.49 (s, 1H, NH). ^{13}C-nmr (deuteriodimethyl sulfoxide) δ 20.7 (CH_3), 108.1 (C-1), 117.2 (C-5), 118.8 (C-4), 119.3 (C-9a), 121.4 (C-8a), 124.0 (C-3), 124.9 (C-8), 129.3 (C-7), 134.4 (C-6), 134.6 (C-4a), 138.7 (C-5a), 151.7 (C-2), 176.0 (C-9). *Anal.* Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.33; H, 4.81; N, 6.48.

2,2'-Dimethoxy-7,7'-methyl-10,10'-biacridinyl-9,9'-dione (6). In a 250 mL pyrex bottle flak, 2-methyl-7-methoxy-9(10*H*)-acridinone (**4b**) (8.37 mmol) was dissolved in freshly distilled carbon tetrachloride (100 mL) at 80 °C under nitrogen atmosphere. 1,3-Dibromo-5,5'-dimethyl-imidazolidine-2,4-dione, (1.92 g, 6.71 mmol, 0.2 equiv.) was added and the mixture was irradiated for 3 h under stirring with a 300 W halogen floodlamp. Then the solvent was removed *in vacuo* and the residue was chromatographied on silica gel (chloroform/ethyl acetate: 3/2) to yield **6**, as a yellow powder (1.10 g, 55 %), mp 205 °C (from ethanol). TLC/R_f: 0.5 (chloroform/ethyl acetate 3/2). ^{1}H-nmr (deuteriodimethyl sulfoxide) δ 2.40 (s, 6H, CH_3), 3.86 (s, 6H, OCH_3), 6.70 (d, 2H, J = 8.5 Hz, H-5), 6.75 (d, 2H, J = 9.1 Hz, H-4), 7.24 (dd, 2H, J = 2.8 and 9.1 Hz, H-3), 7.42 (dd, 2H, J **=** 2.0 and 8.5 Hz, H-6), 7.85 (d, 2H, J = 2.8 Hz, H-1), 8.25 (sbr, 2H, H-8). ^{13}C-nmr (deuteriodimethyl sulfoxide) δ 20.3 (CH_3), 55.6 (OCH_3), 107.4 (C-1), 113.7 (C-5), 115.7 (C-4), 121.2 (C-9a), 122.8 (C-8a), 124.7 (C-3), 126.6 (C-8), 132.6 (C-7), 135.2 (C-4a), 136.4 (C-6), 138.6 (C-5a), 155.4 (C-2), 175.8 (C-9). *Anal.* Calcd for $C_{30}H_{24}N_2O_4$: C, 75.61; H, 5.08; N, 5.88. Found: C, 75.86; H, 5.28; N, 5.63.

General procedure for preparation of (7a-c). A mixture of 2-methoxy-9(10*H*)-acridinone (**4a**) (1 g, 4.44 mmol), 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione, (0.05-2 equiv.), and freshly distilled carbon tetrachloride (50 mL) was heated under stirring at 80°C for 0.5 hour and then was irradiated with a 300 W halogen floodlamp for 16.5 hours. The solvent was removed *in vacuo*. The residue was dissolved in chloroform and filtered. The filtrate was evaporated to yield a crude mixture which was chromatographied on silicagel with chloroform as the eluant to yield the corresponding mono or bisacridinones (**7a-c**) as yellow solids.

2,2'-Dimethoxy-10,10'-biacridinyl-9,9'-dione (7a). With 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione, (0.05 equiv., 0.22 mmol). Mp 381 °C (from ethanol). TLC/R_f: 0.5 (chloroform). ^{1}H-nmr (deuteriochloroform) δ 3.92 (s, 3H, OCH_3), 6.65 (d, 2H, J = 9.2 Hz, H-4), 6.69 (dd, 2H, J = 1.0 and 8.5 Hz, H-5), 7.13 (dd, 2H, J = 3.0 and 9.2 Hz, H-3), 7.36 (ddd, 2H, J = 8.2, 1.0 and 7.9 Hz, H-7), 7.50 (ddd, 2H, J = 1.7, 8.2 and 8.5 Hz, H-6), 8.03 (d, 2H, J = 3.0 Hz, H-1), 8.65 (dd, 2H, J = 1.7 and 7.9 Hz, H-8). ^{13}C-nmr (deuteriochloroform) δ 56.1 (OCH_3), 107.9 (C-1), 113.6 (C-5), 115.6 (C-4), 122.0 (C-8a), 123.4 (C-9a), 123.4 (C-7), 128.5 (C-8), 135.0 (C-6), 135.7 (C-4a), 156.3 (C-2), 177.1 (C-9). *Anal.* Calcd for $C_{28}H_{20}N_2O_4$: C, 74.99; H, 4.50; N, 6.25. Found: C, 75.23; H, 4.31; N, 6.10.

2-Bromo-7-methoxyacridin-9(10*H*)-one (7b). With 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione, (0.5 equiv., 2.22 mmol). Mp 337 °C (from ethanol), litt. 337-339°C (from acetic acid) [14]. TLC/R_f: 0.4 (chloroform). ^{1}H-nmr (deuteriodimethyl sulfoxide) δ 3.84 (s, 3H, OCH_3), 7.42 (dd, 1H, J = 8.7 et 2.8 Hz,

H-6), 7.50 (d, 1H, J = 8.9 Hz, H-4), 7.53 (d, 1H, J = 8.7 Hz, H-5), 7.60 (d, 1H, J = 2.8 Hz, H-8), 7.81 (dd, 1H, J = 2.3 and 8.9 Hz, H-3), 8.28 (d, 1H, J = 2.3 Hz, H-1), 11.90 (s, 1H, NH). ^{13}C-nmr ($CDCl_3$) δ 55.6 (OCH_3), 105.0 (C-8), 113.0 (C-2), 119.6 (C-5), 120.2 (C-4), 121.0 (C-9a), 121.1 (C-8a), 125.0 (C-6), 128.0 (C-1), 135.8 (C-3), 135.8 (C-5a), 139.4 (C-4a), 154.5 (C-7), 175.2 (C-9). *Anal.* Calcd for $C_{14}H_{10}BrNO_2$: C, 55.48; H, 3.31; N, 4.61. Found: C, 55.25; H, 3.59; N, 4.80.

2,2'-Dibromo-7,7'-dimethoxy-10,10'-biacridinyl-9,9'-dione (7c). With 1,3-dibromo-5,5-dimethyl-imidazolidine-2,4-dione, (2 equiv., 8.88 mmol). Mp 264 °C (from ethanol). TLC/R_f: 0.6 (chloroform). ^{1}H-nmr ($CDCl_3$) δ 3.92 (s, 6H, OCH_3), 6.57 (d, 2H, J = 9.2 Hz, H-4), 6.62 (d, 2H, J = 8.9 Hz, H-5), 7.15 (dd, 2H, J = 2.9 and 9.2 Hz, H-3), 7.56 (dd, 2H, J = 2.2 and 8.9 Hz, H-6), 8.00 (d, 2H, J = 2.9 Hz, H-1), 8.75 (d, 2H, J = 2.2 Hz, H-8). ^{13}C-nmr ($CDCl_3$) δ 56.1 (OCH_3), 108.0 (C-1), 115.4 (C-4), 115.4 (C-5), 117.0 (C-7), 123.1 (C-9a), 123.4 (C-8a), 126.0 (C-3), 131.0 (C-8), 135.2 (C-4a), 137.9 (C-6), 139.4 (C-5a), 156.62 (C-2), 175.7 (C-9). *Anal.* Calcd for $C_{28}H_{18}Br_2N_2O_4$: C, 55.47; H, 2.99; N, 4.62. Found: C 55.66, H 3.18, N 4.83.

REFERENCES

[1a] Korth, C.; May, B. C. H.; Cohen, F. E.; Prusiner, S. B. *PNAS* **2001**, *98*, 17, 9836; [b] Wainwright, M. *J. Antimicrob. Chem.* **2001**, *47*, 1.

[2a] Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis*, **1992**, *6*, 503; [b] Whitesell, J.-K. *Chem. Rev.* **1989**, *89*, 7, 1581; [c] Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *102*, 9, 1006.

[3] Weber, E.; Ahrendt, J.; Czugler, M.; Csoeregh, I. *Angew. Chem., Int. Ed. Engl.* **1986**, *98*, 8, 719.

[4] Boyer, G.; Claramunt, R.-M.; Elguero, J.; Fathalla, M.; Foces-Foces, C.; Jaime, C.; Llamas-Saiz, A. L. *J. Chem. Soc., Perkin. Trans. II* **1993**, 757.

[5] Boyer, G.; Lormier, A.-T.; Galy, J.-P.; Llamas-Saiz, A. L.; Foces-Foces, C.; Fierros, M.; Elguero, J.; Virgili, A. *Molecules* **1999**, *4*, 104.

[6] Lormier, A.-T.; Boyer, G.; Faure, R.; Galy, J.-P. *Heterocycles* **2002**, *57*, 3, 449.

[7] Krishnegowda, G.; Thimmaiah, P.; Hegde, R.; Dass, C.; Houghton, P. J.; Thimmaiah, K. N. *Bioorg. Med. Chem.* **2002**, *10*, 7, 2367.

[8] Hannig, E.; Becke, E. *Pharmazie* **1975**, *30*, 5, 289.

[9] Graebe, C.; Lagozinski, K. *Justus Liebig Ann. Chem.* **1893**, 35.

[10] Simandi, L. I., Catalysis by Metal Complexes, in *Advances in Catalytic Activation of Dioxygen by Metal Complexes* **2003**, *26*, 265.

[11a] Acheson, R. M.; Bolton, R. G. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1067; [b] Gruszecki, W. Z.; Ledochowski, Z. *Rocz. Chem.* **1967**, *41*, 2, 393; [c] Takahashi, K. R.; Castle, N. *J. Heterocyclic. Chem.* **1987**, *24*, 977.

[12a] Reed, R. A. *Chem. Prods.* **1960**, *23*, 299; [b] Cagniant, P.; Jecko, G.; Cagniant, D. *Bull. Soc. Chem.* **1964**, *9*, 2217; [c] Stuckwisch, C. G.; Hammer, G.; Blau, N. F. *J. Org. Chem.* **1957**, *22*, 1678.

[13] Filloux, N.; Galy, J.-P. *Synlett* **2001**, *7,* 1137.

[14] Bogucka, M.; Ledochowski, Z. *Roczniki Chemii*, **1966**, *40*, 3, 489.