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New Route to Extended Angular Polyaza-heterocycles

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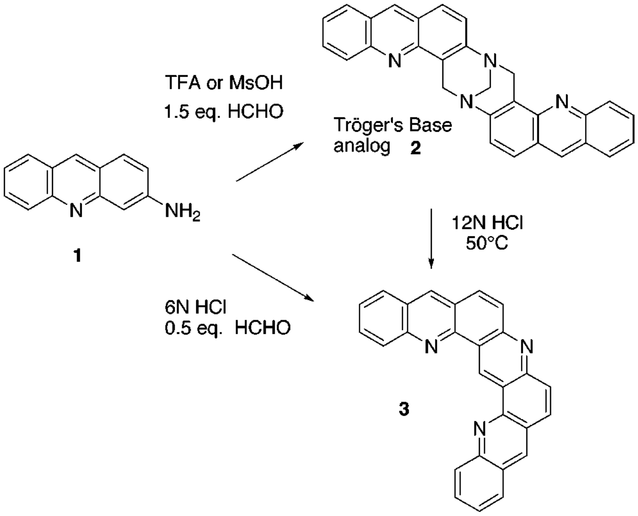
Acridine derivatives have long been known to interact with nucleic acids and show biological properties (antimalaria, anticancer).[1] In the course of a project devoted to the design of new anticancer drugs, we have examined the introduction of functionality on the acridine ring.[1b] In particular, we have studied in detail the Friedel−Crafts reactions of 3-aminoacridine and proflavine (3,6-diaminoacridine) with formaldehyde.[2] These reactions were found to be totally regioselective: substitution occurred only at C-4 in 3-aminoacridine and C-4 and C-5 in proflavine. The reactions were also found to be strongly dependent on the amount of formaldehyde and the nature of the acid (Scheme 1). In trifluoroacetic acid, methanesulfonic acid, or 12 N HCl and in the presence of 1.5 equiv of formaldehyde, the Tröger's base analogue **2** was obtained in almost quantitative yield. In 6 N HCl and in the presence of 0.5 equiv of formaldehyde, however, a very slow reaction led to triaza-heptacycle **3**.[3] The same heptacycle was also obtained by treatment of the Tröger's base **2** with hydrochloric acid (12 N HCl, 50 °C).[4]

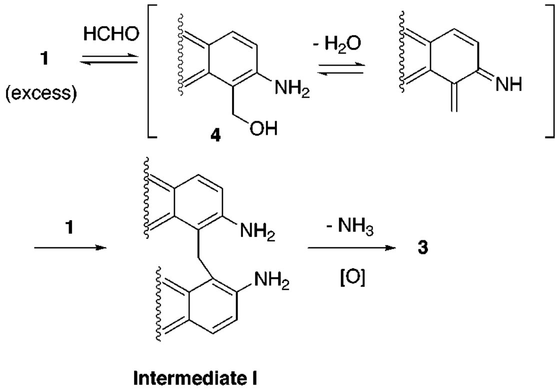
The postulated pathway for these cyclizations, depicted in Scheme 2, is based on that suggested by Wagner in 1954 to explain the products formed from the reaction of aromatic amines with formaldehyde.[5]

In Scheme 2, electrophilic substitution of 3-aminoacridine (**1**) with formaldehyde gives 3-amino-4-hydroxymethylacridine (**4**). In the presence of a large amount of formaldehyde, the reaction yields the Tröger's base **2**. But in the presence of excess aminoacridine, the methylenebis(3-aminoacridine) intermediate **I** is produced. The formation of the aza-heptacycle **3** results from cyclization and oxidation of this intermediate. On the basis of this proposed pathway, we have examined the use of 3-amino-4-hydroxymethylacridine (**4**) as the key intermediate for the preparation through reaction with amino heterocycles of new aza-acridine-fused heterocycles.

Scheme 1. Reactions of 3-Aminoacridine with Formaldehyde



Scheme 2. Formation of Fused Heterocycle via Formation and Reaction of Quinone−Imine−Methide Intermediate



We describe in this paper the synthesis of 3-amino-4-hydroxymethylacridine (**4**) from 3-aminoacridine and its reaction with 5-amino[1,10]phenanthroline to give a new tetraaza heptacycle.[6] This strategy has also been applied to the synthesis of a pentaaza octacycle, starting from a pyrido-fused 3-aminoacridine, i.e., 10-amino-benzo[*b*][1,7]-phenanthroline.

Results and Discussion

Compound **4** was best prepared from the corresponding oxazinone **5**. 1,4-Dihydro[1,3]oxazino[4,5-*c*]acridin-3-one (**5**) is the heterocyclic analogue of well-known 3,1-benzoxazin-2-one derivatives, which are usually prepared from *o*-aminobenzyl alcohols by cyclization with phosgene[7] or by lithiation at the ortho position of *tert*-butoxycarbonylaniline substrates, followed by reaction with ketones or DMF and spontaneous cyclization.[8]

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[1] (1) Albert, A. *The Acridines*, 2nd ed.; Edward Arnold: London, 1966. (b) Demeunynck, M.; Charmantray, F.; Martelli, A. *Curr. Pharm. Des.* **2001**, in press.

[2] (2) (a) Salez, H.; Wardani, A.; Demeunynck, M.; Tatibouët, A.; Lhomme, J. *Tetrahedron Lett.* **1995**, *36*, 1271−1274. (b) Tatibouët, A.; Fixler, N.; Demeunynck, M.; Lhomme, J. *Tetrahedron* **1997**, *53*, 2891−2898.

[3] (3) This method of formation of fused polyheterocycle was used to prepare the first aza-analogue of kekulene in four steps starting from 3,6-diaminoacridine (proflavine), see: Tatibouët, A.; Hancock, R.; Demeunynck, M.; Lhomme, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1190−1191.

[4] (4) Tatibouët, A.; Demeunynck, M.; Salez, H.; Arnaud, R.; Courseille, C.; Lhomme, J. *Bull. Soc. Chim. Fr.* **1997**, *134*, 495−501.

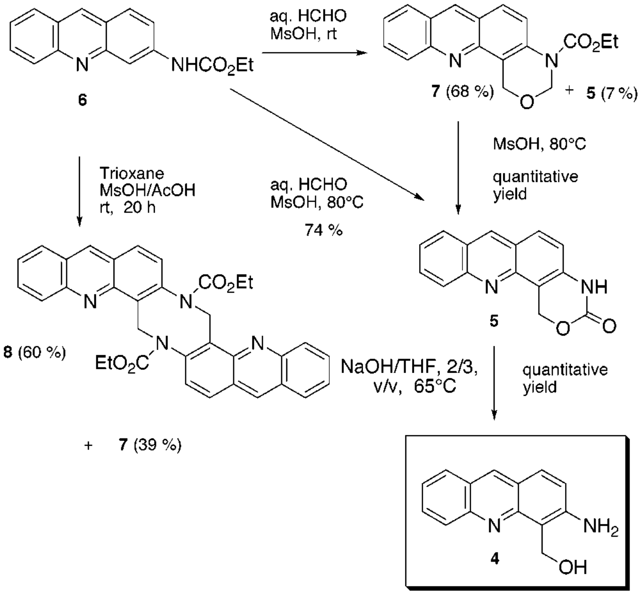
[5] (5) Wagner, E. C. *J. Org. Chem.* **1954**, *19*, 1863−1881.

[6] (6) We chose the phenanthroline ring because of its widespread use as a metal ligand and the biological activity of the resulting complexes.

[7] (7) (a) Consonni, R.; Dalla Croce, P.; Ferraccioli, R.; La Rosa, C. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1809−1814. (b) Nikam, S. S.; Yuen, P.-W.; Kornberg, B. E.; Tobias, B.; Rafferty, M. F. *J. Org. Chem.* **1997**, *62*, 9331−9334.

10.1021/jo015811f CCC: $20.00

Scheme 3. Synthesis of the Key Intermediate 4



Previous studies have shown that 1,4-dihydro[1,3]oxazino-[4,5-*c*]acridin-3-one derivatives are formed in low yields when ethoxycarbonylaminoacridines are treated with formaldehyde in methanesulfonic acid.[9] We have reinvestigated this reaction using 3-ethoxycarbonylaminoacridine (**6**) as the starting material (Scheme 3).

The solvent, the source of formaldehyde, and the temperature of the reaction were varied. Performing the reaction at 20 °C gave the N-protected dihydrooxazine **7** as the main product (68%), along with the oxazinone **5** (7%). Replacing aqueous formaldehyde by trioxane in a mixture of methanesulfonic acid and acetic acid (18/4) dramatically changed the course of the reaction. A new diazocinodiacridine compound **8** was obtained as the main product (60%), dihydrooxazine **7** being isolated in 39% yield. No oxazinone **5** was formed under these conditions. The reaction with aqueous formaldehyde was then performed at different temperatures (40, 65, and 80 °C), with the evolution of the reaction monitored by HPLC. At 65 °C, **7** was formed as an intermediate and on prolonged heating (overnight) was converted into **5** as the main product (60% after purification). In a separate experiment, it was shown that the dihydrooxazine **7**, on stirring at 80 °C in methanesulfonic acid, slowly rearranged to give the oxazinone **5** in high yield. These results indicate that formation of dihydrooxazine **7** is a kinetically controlled process and oxazinone **5** is the thermodynamic product of the reaction. The transformation of **7** into **5** probably involves acid-catalyzed opening of the oxazine ring, followed by intramolecular transcarbamoylation. The *o*-hydroxymethylamine **4** was next quantitatively obtained by treating the oxazinone **5** under basic conditions (THF/1 N NaOH, 3/2, 70 °C), and its reaction with 5-aminophenanthroline **9** was then investigated.

Equimolar amounts of **4** and 5-aminophenanthroline (**9**)[10] were allowed to react in 6 N HCl (65 °C, 24 h), and the reaction was followed by HPLC (Scheme 4). It proceeded slowly to give **10** as major product, which was isolated as a pale yellow powder (80−90% purity, estimated by HPLC). NMR analysis confirmed the structure of the expected product **10**. The ^{1}H NMR spectrum was characterized by the strong deshielding of the H-18 proton (singlet at $\delta = 10.80$ ppm in $CDCl_3$). Moreover, signals corresponding to the two heterocyclic components, acridine and phenanthroline, could be unambiguously attributed. The mass spectrum was also confirmatory ($m/z = 383$ $[M + H]^+$). Compound **10**, however, was difficult to purify due to its low solubility in most organic solvents.

A two-step procedure allowed isolation of the postulated intermediate **11**. Equimolar amounts of compounds **4** and **9** and *p*-toluenesulfonic acid were heated at 50 °C in DMF. The reaction was carefully monitored by HPLC, and the reaction was stopped as soon as the starting materials **4** and **9** disappeared. After treatment, a new product, identified as methylene-bis(aminoacryl) **11**, was isolated. It was characterized by mass spectrometry ($m/z = 402$ $[M + H]^+$) and NMR. Compound **11** appeared unstable, partially decomposing upon crystallization. On stirring in 6 N HCl (90 °C), it slowly underwent transformation to give **10**, which could be isolated as pure product in 54% overall yield (two steps).

This new strategy for the construction of polyazaheterocycles was next applied to 10-aminobenzo[*b*][1,7]phenanthroline (**12**),[11] which contains an additional pyridine ring. The *o*-hydroxymethylamine **16** was prepared following the strategy designed above to prepare **4** in four steps from **12** and in 49% overall yield (Scheme 5).

The coupling of **16** with 5-aminophenanthroline **9** was achieved in DMF (20 °C, 24 h) in the presence of 1.5 equiv of *p*-toluenesulfonic acid. The pyrido analogue of intermediate **11** was isolated and immediately cyclized in 6 N HCl (85 °C, 5 d). The new pentaaza octacycle **17** could thus be obtained in 51% overall yield. The ^{1}H NMR spectrum recorded in TFA-*d* was characterized by a highly deshielded singlet at 12.4 ppm, attributed to H-20. HRMS analysis confirmed the structure.

The facile formation of compounds **10** and **17** demonstrates the usefulness of ortho-hydroxymethyl aminoacridines for regioselective synthesis of nonsymmetrical polyaza polyheterocycles. These two new compounds **10** and **17** should be of interest as new ligands for metal complexation and DNA binding.

Experimental Section

Melting points are uncorrected. 1D NMR spectra were recorded at 200 MHz using solvent as the internal reference ($DMSO\text{-}d_6$ at 2.49 ppm, $CDCl_3$ at 7.24 ppm); the chemical shifts are reported in ppm, in δ units. 2D NOESY were registered at 500 MHz at 25 °C with a mixing time of 600 ms. The mass spectra were recorded on Varian Mat 311. High-resolution mass spectra were obtained from “Centre Regional de Mesures Physiques de l’Ouest”, Université de Rennes.

Reaction of 6 with Aqueous Formaldehyde in Methanesulfonic Acid: Formation of 4-Ethoxycarbonyl-3,4-dihydro-1*H*-[1,3]oxazino[4,5-*c*]acridine (7) and 1,4-Dihydro-[1,3]oxazino[4,5-*c*]acridin-3-one (5). Reaction at Room Temperature. Compound **6**[12] (2.72 g, 10.2 mmol) was solubi-

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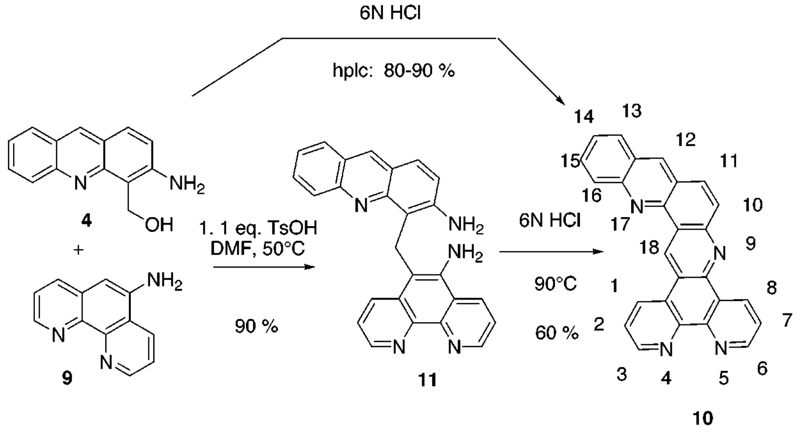
[8] (a) Carretero, J. C.; Ruano, J. L. G.; Vicioso, M. *Tetrahedron* **1992**, *48*, 7373−7382. (b) Tye, H.; Eldred, C.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 770−772.

[9] Fixler, N.; Demeunynck, M.; Duflos, A.; Lhomme, J. *Heterocycles* **1998**, *48*, 755−767.

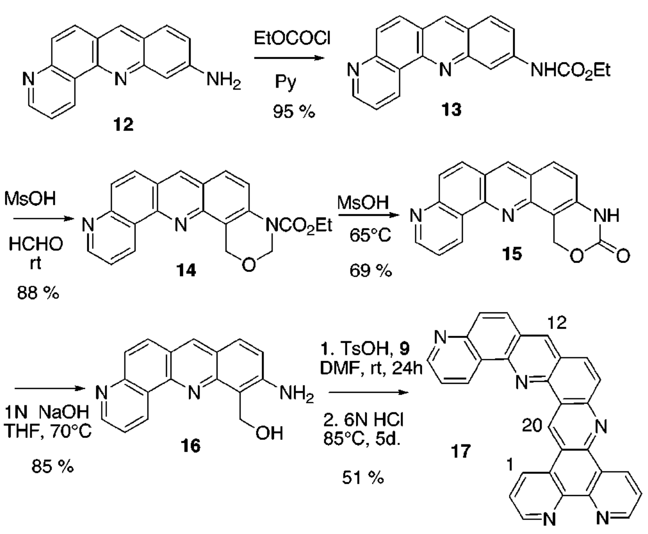
[10] Compound **9** was prepared by reduction of the commercially available 5-nitro[1,10]phenanthroline; see: Lecomte, J.-P.; Kirsch-De Mesmaeker, A.; Demeunynck, M.; Lhomme, J. *J. Chem. Soc., Faraday Trans.* **1993**, *89*, 3261−3269.

[11] Wardani, A.; Lhomme, J. *Tetrahedron Lett.* **1993**, *34*, 6411−6414.

Scheme 4. Formation of Acridine−Phenanthroline Fused Heterocycle 10



Scheme 5. Synthesis of Angular Pentaaza Octacycle 17



lized in methanesulfonic acid (27 mL) in the presence of 37% aqueous formaldehyde (2.7 mL). The solution was stirred at room temperature for 15 h and then slowly poured into a mixture of ice (100 mL), NH$_4$OH (40 mL), and AcOEt (230 mL). The aqueous phase was separated and extracted twice with AcOEt. The organic layers were collected, dried over Na$_2$SO$_4$, and concentrated. The solid that had deposited was filtered, washed with AcOEt, and dried. Compound **5** was thus obtained (0.19 g, 0.75 mmol) in 7% yield. The filtrate was chromatographed on silica gel (elution: CHCl$_3$/CH$_3$CN, 98/2). Compound **7** was obtained in 68% yield (2.2 g, 7.3 mmol).

Reaction at 65 °C. A mixture of **6** (0.18 g, 0.68 mmol) and 37% aqueous formaldehyde (0.45 mL) in methanesulfonic acid (45 mL) was stirred overnight at 65 °C. The solution was then added to a large volume of water and neutralized with diluted NH$_4$OH. The aqueous layer was extracted three times with AcOEt. The organic layers were collected, dried over Na$_2$SO$_4$, and evaporated under reduced pressure to give the crude product **5** in 74% yield (0.125 g, 0.50 mmol). This residue was purified by flash chromatography on silica gel (AcOEt). Crystallization from AcOEt gave an analytically pure sample (60% yield).

7. Mp = 97−98 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 9.06 (1H, s, H-17), 8.18−7.58 (6H, m, H-5, H-6, H-8, H-9, H-10, and H-11), 5.50 (2H, s, ArC*H*$_2$O), 5.29 (2H, s, OCH$_2$N), 4.27 (2H, q, *J* = 7.0 Hz, CO$_2$CH$_2$), 1.31 (3H, t, *J* = 7.0 Hz, CH$_3$). MS (DCI): M = 308, *m/z* = 309 (100, [M + H]$^+$), 279 (13, [M − CH$_2$CH$_3$]$^+$), 235 (12, [M − CO$_2$Et]$^+$). IR (KBr): 3900, 3850, 3005, 3000, 1726, 1471, 1408, 1373, 1298, 1273, 1228, 1194, 1136, 1088, 1037, 925, 756 cm^{-1}. UV (ethanol): λ_{max} (ϵ) 360 (10 200), 263 (85 000) nm.

5. Mp = 210 °C. ^{1}H NMR (200 MHz, DMSO-d_6): δ 10.55 (1H, s, NH), 9.00 (1H, s, H-7), 8.13 (1H, d, *J* = 8.2 Hz, H-11), 8.12 (1H, d, *J* = 9.0 Hz, H-6), 8.10 (1H, d, *J* = 8.2 Hz, H-8), 7.82 (1H, ddd, *J* = 8.2, 6.6, 1.2 Hz, H-9), 7.55 (1H, ddd, *J* = 8.2, 6.6, 1.2 Hz, H-10), 7.25 (1H, d, *J* = 9 Hz, H-5), 5.95 (2H, s, Ar-C*H*$_2$O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 151.0 (C quat), 148.4 (C quat), 144.5 (C quat), 137.5 (C quat), 136.9 (*C*H), 131.0 (*C*H), 130.0 (*C*H), 128.7 (*C*H), 128.4 (*C*H), 125.1 (*C*H), 122.8 (C quat), 116.6 (*C*H), 108.8 (C quat), 66.1 (Ar-*C*H$_2$). MS (DCI): M = 250, *m/z*: 251 (100, [M + H]$^+$). IR (KBr): 3230, 3150, 3050, 2950, 1709, 1647, 1622, 1579, 1533, 1439, 1278, 852, 785 cm^{-1}. UV/vis (ethanol): λ_{max} (ϵ) 387 (5300), 356 (8250), 340 (5000), 265 (77 400), 238 (21 800), 229 (19 300) nm.

Reaction of 6 with Trioxane in Methanesulfonic Acid: Formation of 7 and 10,20-Diethoxycarbonyl-9*H*,19*H*-[1,5]-diazocino[2,3-*c*:6,7-*c*′]diacridine (8). To a solution of **6** (2.55 g, 9.6 mmol) in methanesulfonic acid (18 mL) was added dropwise a solution of trioxane (1.9 g, 21 mmol) in acetic acid (4 mL). The reaction mixture was stirred at room temperature for 20 h. The solution was then poured into ice−water and basified by slow addition of NH$_4$OH. The solid was filtered, washed with water, and dried. It was then chromatographed on silica gel (elution: chloroform). Compound **7** was eluted first and was obtained in 39% yield (1.15 g, 3.7 mmol). Compound **8** was then eluted (1.6 g, 2.87 mmol) and isolated in 60% yield.

8. Mp = 252 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 130 °C): δ 9.00 (2H, s, H-3 and H-13), 8.18 (2H, d, *J* = 8.5 Hz, H-6 and H-16), 8.12 (2H, d, *J* = 8.7 Hz, H-4 and H-14), 7.95 (2H, d, *J* = 8.8 Hz, H-2 and H-12), 7.85 (2H, t, *J* = 7.0 Hz, H-6 and H-16), 7.60 (2H, t, *J* = 7 Hz, H-5 and H-15), 7.52 (2H, d, *J* = 8.8 Hz, H-1 and H-10), 6.60 (2H, m, Ar-CH$_a$), 5.29 (2H, m, Ar-CH$_b$), 5.20 (2H, s, OCH$_2$N), 4.00 (4H, m, CH$_2$), 0.90 (6H, m, CH$_3$). MS (DCI): M = 556, *m/z* = 557 (100, [M + H]$^+$), 279 (13, [M − CH$_2$-CH$_3$]$^+$), 235 (12, [M − CO$_2$Et]$^+$). IR (KBr): 3000, 2950, 2940, 1709, 1692, 1466, 1429, 1398, 1373, 1352, 1217 cm^{-1}. Anal. Calcd for C$_{34}$H$_{28}$N$_4$O$_4$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.61; H, 5.07; N, 10.07.

4-Hydroxymethyl-3-aminoacridine (4). Oxazinone **5** (0.075 g, 0.3 mmol) was dissolved in a mixture of THF (20 mL) and 1 N NaOH (6 mL). The solution was stirred at 65 °C for 6 h. After complete disappearance of oxazinone **5**, the mixture was diluted with water and extracted twice with AcOEt. The organic layers were collected, dried over Na$_2$SO$_4$, and evaporated under reduced pressure. Compound **4** (0.067 g, 0.3 mmol) was obtained as an orange solid in quantitative yield. The compound was used without further purification, as it appeared to slowly decompose upon crystallization.

4. Mp = 90 °C. ^{1}H NMR (200 MHz, CDCl$_3$): δ 8.53 (1H, s, H-9), 8.06 (1H, d, *J* = 8.4 Hz, H-5), 7.88 (1H, d, *J* = 8.2 Hz, H-8), 7.72 (1H, d, *J* = 8.9 Hz, H-1), 7.74−7.65 (1H, m, H-6), 7.45−7.37 (1H, m, H-7), 6.98 (1H, d, *J* = 8.9 Hz, H-2), 5.29 (2H, s, Ar−C*H*$_2$−O), 4.43 (2H, s. wide, NH$_2$). ^{13}C NMR (75 MHz, CDCl$_3$): δ 150.2 (C quat), 148.7 (C quat), 145.9 (C quat), 136.8 (*C*H), 130.8 (*C*H), 129.4 (*C*H), 129.1 (*C*H), 128.7 (*C*H), 125.1 (C quat), 124.7 (*C*H), 122.7 (C quat), 121.4 (*C*H), 113.7 (C quat), 58.7 (Ar-*C*H$_2$OH). MS (DCI): M = 224, *m/z* = 225 (100, [M + H]$^+$). UV/vis (ethanol 95%): λ_{max} (ϵ) 426 (6460), 353 (7100), 268

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(12) Tatibouët, A.; Fixler, N.; Demeunynck, M.; Lhomme, J. *Tetrahedron* **1997**, *53*, 2891−2898.

(53 880) nm. Anal. Calcd for $C_{14}H_{12}N_2O{\cdot}0.2CH_3CO_2Et$: C, 73.49; H, 5.67; N, 11.58. Found: C, 73.52; H, 5.66; N, 11.47. The presence of traces of CH_3CO_2Et was evidenced by the existence on the ^1H NMR spectrum of three signals at 4.10 (q, $J = 7.2$ Hz, CH_2), 2.02 (s, CH_3), and 1.23 (t, $J = 7.2$ Hz, CH_3) ppm.

Benzo[*b*]phenanthrolino[1,10][5,6:j]phenanthroline-[1,7] (10). Method A. Condensation of 4-hydroxymethyl-3-aminoacridine (**4**) with 5-aminophenanthroline (**9**) in acidic medium. Equimolar amounts of 4-hydroxymethyl-3-aminoacridine (**4**) (0.125 g, 0.056 mmol) and aminophenanthroline **9** (0.11 g, 0.056 mmol) in 6 N HCl (2 mL) were stirred at 65 °C for 24 h. As shown by HPLC analysis, heptacycle **10** was obtained as major product (80−90% purity, estimated by HPLC).

Method B. Two-Step Synthesis with Isolation of the Asymmetric Intermediate 11. Equimolar amounts of 4-hydroxymethyl-3-aminoacridine (**4**) (0.090 g, 0.39 mmol), aminophenanthroline **9** (0.078 g, 0.39 mmol), and *p*-toluenesulfonic acid (0.071 g, 0.39 mmol) were dissolved in DMF (25 mL). The mixture was stirred at 50 °C for 6 h. The reaction was monitored by HPLC and was quenched as soon as the starting compounds had reacted. After neutralization of the crude mixture with diluted NH_4OH, the aqueous phase was extracted twice with AcOEt. The organic layers were washed three times with water, dried over Na_2SO_4, and filtered. The resulting organic phase was concentrated under vacuum. After the addition of a large volume of pentane, the crude product **11** deposited and was filtered off. It was isolated as an orange powder (0.140 g, 0.35 mmol) in 90% yield. Any attempt to obtain analytically pure sample failed due to rapid degradation of compound **11**. The purity was estimated to be over 95% by HPLC; therefore, compound **11** was used without purification.

Cyclization into 10. A suspension of compound **11** (0.140 g, 0.35 mmol) in 6 N HCl (10 mL) was stirred at 90 °C until complete transformation of the starting material into product **10**. Compound **10** precipitated during neutralization of the solution with diluted NH_4OH and was collected after centrifugation (4500 revolutions/min), washed three times with water, and finally purified by crystallization from EtOH to give a pale pink product in 54% yield (0.072 g, 0.19 mmol).

11. Mp = 273 °C. ^1H NMR (200 MHz, DMSO-d_6): δ 8.98 (1H, dd, $J = 4.3$, 1.4 Hz, Ar-*H*), 8.88 (1H, dd, $J = 9.0$, 1.4 Hz, Ar-*H*), 8.80−8.73 (2H, m, Ar-*H*), 8.61 (1H, dd, $J = 4.3$, 1.4 Hz, Ar-*H*), 8.08−7.96 (2H, m, Ar-*H*), 7.81−7.67 (3H, m, Ar-*H*), 7.48−7.37 (1H, m, Ar-*H*), 7.36−7.27 (1H, m, Ar-*H*), 7.07 (1H, d, $J = 8.9$ Hz, Ar-*H*), 6.45 (2H, s, NH_2), 5.93 (2H, s, NH_2), 4.95 (2H, s, Ar-C*H*$_2$O). ^{13}C NMR (75 MHz, DMSO-d_6): δ 149.0, 148.7, 147.9, 147.8, 145.2, 144.5, 141.1, 139.1, 136.0, 131.1, 130.5, 130.2, 129.9, 128.3, 127.9, 127.6, 123.7, 123.4, 122.5, 122.3, 121.7, 121.6, 121.4, 121.3, 111.2, 110.6. MS (FAB (+), glycerol): M = 401, *m*/*z* 402 $[M + H]^+$. UV/vis (ethanol 95%): λ_{max} (ϵ) 353 (11 270), 336 (10 820), 271 (56 500) nm. HRMS (LSIMS with Cs^+, mNBA): found 402.1718, calcd for $C_{26}H_{19}N_5 + H$ *m*/*z* = 402.1719.

10. Mp > 350 °C. ^1H NMR (500 MHz, DMSO-d_6/TFA-*d*): δ 10.92 (1H, s, H-18), 10.60 (1H, d, $J = 7.5$ Hz, H-6), 10.48 (1H, d, $J = 8.0$ Hz, H-1), 10.24−10.27 (2H, m, H-3 and H-8), 9.52 (1H, s, H-12), 9.38 (1H, m, H-2), 9.31 (1H, m, H-7), 8.91−8.97 (4H, m, H-15, H-16, H-11 and H-13), 8.69−8.75 (2H, m, H-10 and H-14). ^{13}C NMR (75 MHz, DMSO-d_6/TFA-*d*): δ 149.8 (Cquat), 147.8 (*C*H), 147.0 (*C*H), 145.8 (Cquat), 144.0 (Cquat), 142.6 (Cquat), 138.6 (Cquat), 138.2 (*C*H), 136.8 (*C*H), 136.4 (Cquat), 136.2 (*C*H), 132.2 (*C*H), 131.0 (*C*H), 128.2 (Cquat), 128.1 (*C*H), 127.4 (*C*H), 127.3 (*C*H), 127.2 (Cquat), 126.9 (*C*H), 126.6 (*C*H), 126.4 (*C*H), 126.3 (Cquat), 124.9 (Cquat), 123.5 (Cquat), 119.6 (Cquat). MS (FAB (+), glycerol): M = 382, *m*/*z* 383 $[M + H]^+$. MS (FAB (+), glycerol): M = 382, *m*/*z* 383 $[M + H]^+$. UV/vis (ethanol 95%): λ_{max} (ϵ) 331 (37 550), 324 (37 260), 265 (27 100) nm. HRMS (LSIMS with Cs^+, mNBA): found 383.1300, calcd for $C_{26}H_{14}N_4 + H$ *m*/*z* = 383.1297.

10-Ethoxycarbonylaminobenzo[*b*][1,7]phenanthroline (13). A solution of 10-aminobenzo[*b*][1,7]phenanthroline (**12**) (0.3 g, 1.22 mmol) in pyridine (20 mL) was cooled at −5 °C. Ethylchloroformate (0.16 mL, 1.71 mmol) was added to the solution and the mixture was stirred at 0 °C for 2 h. The solution was then diluted with water (100 mL), and stirred at room temperature for 1 h to allow precipitation of the desired compound. Compound **13** was filtered off, washed with water, and solubilized in a 1/1 mixture of $CHCl_3$ and MeOH. The solution was washed with water and brine, and then dried over $MgSO_4$. Evaporation of the solvent gave a residue that was triturated in diisopropyl ether, filtered off and dried to afford **13** (0.369 g, 1.16 mmol) in 95% yield. Mp = 203−204 °C. ^1H NMR (200 MHz, DMSO-d_6): δ 10.27 (1H, s, NH), 9.62 (1H, dd, $J = 7.9$ Hz, H-1), 9.07 (1H, dd, $J = 3.2$ Hz, H-3), 9.02 (1H, s, H-7), 8.56 (1H, d, H-11), 8.18 (1H, d, $J = 9.3$ Hz, H-6), 8.16 (1H, d, $J = 9.0$ Hz, H-8), 7.86 (1H, d, $J = 9.2$ Hz, H-5), 7.77 (1H, dd, $J = 8.3$, 4.0 Hz, H-2), 7.66 (1H, dd, $J = 8.9$, 1.9 Hz, H-9), 4.25 (2H, q, $J = 7.1$ Hz, CH_2), 1.34 (3H, t, $J = 7.1$ Hz, CH_3). MS (FAB (+) glycerol): *m*/*z* 318 $[M + H]^+$. UV/vis (ethanol 95%): λ_{max} (ϵ) 396 (5060), 376 (5220), 353 (6110), 336 (8020), 311 (31 470), 299 (25 800), 364 (49 180) nm. Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.48; H, 4.60; N, 12.94.

4-Ethoxycarbonyl-3,4-dihydro-4*H*-[3,1]benzoxazino[5,6-*b*][1,7]phenanthroline (14). Compound **13** (0.250 g, 0.79 mmol) was dissolved at room temperature in methanesulfonic acid (70 mL). A large excess of paraformaldehyde (4.5 g, 0.16 mmol) was introduced, and the resulting suspension was allowed to react overnight. The mixture was then poured into cold water (150 mL), and the solution was neutralized by slow addition of 10 N NaOH. The aqueous phase was extracted 3 times with AcOEt (3 × 50 mL). The organic phases were collected and washed four times with distilled water (4 × 50 mL) and finally with brine (50 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure until a precipitate appeared. Product **14** was thus isolated after filtration in 88% yield as a pale yellow powder (0.250 g, 0.70 mmol). Mp = 194−196 °C. ^1H NMR (200 MHz, DMSO-d_6): δ 9.62 (1H, dd, $J = 8.1$, 1.7 Hz, H-13), 9.13 (1H, s, H-7), 9.10 (1H, dd, $J = 4.5$, 1.5 Hz, H-11), 8.26−7.86 (4H, m, H-5, H-6, H-8 et H-9), 7.83 (1H, m, H-12), 5.72 (2H, s, ArC*H*$_2$O), 5.35 (2H, s N−CH_2−O), 4.31 (2H, q, $J = 7.0$ Hz, CCH_2O), 1.33 (3H, t, $J = 7.0$ Hz, CH_3). MS (FAB (+) glycerol): M = 359, *m*/*z* 360 $[M + H]^+$. UV/vis (ethanol 95%): λ_{max} (ϵ) 386 (4660), 366 (5700), 310 (39 090), 298 (38 770), 263 (47 220) nm. Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69. Found: C, 69.82; H, 4.70; N, 11.52.

1,4-Dihydro[3,1]benzoxazino[5,6-*b*][1,7]phenanthrolin-3-one (15). A solution of **14** (0.4 g, 1.11 mmol) dissolved in methanesulfonic acid was stirred at 65 °C for 12 h. After being cooled to room temperature, the solution was diluted with ice−water and neutralized by slow addition of 10 N NaOH. The precipitate that deposited was filtered off and successively washed with water, Et_2O, and AcOEt. Compound **15** was obtained in 69% yield (0.23 g, 0.76 mmol). Mp = 300 °C. ^1H NMR (200 MHz, DMSO-d_6): δ 10.61 (1H, s, NH), 9.61 (1H, q, $J = 1.7$, 8.2 Hz, H-Ar), 9.06 (2H, m, H-7 and Ar-H), 8.18 (2H, d, $J = 8.9$ Hz, Ar-H), 7.88 (1H, d, $J = 9.2$ Hz, Ar-H), 7.80 (1H, m, Ar-H), 7.35 (1H, d, $J = 8.9$ Hz, Ar-H), 6.13 (2H, s, ArCH_2O). ^{13}C NMR (75 MHz, DMSO-d_6/TFA-*d*): δ 151.1 (CO_2), 144.8 (CH), 144.1 (Cquat), 143.6 (Cquat), 141.9 (CH), 139.2 (Cquat), 138.3 (CH), 136.6 (CH), 130.2 (CH), 127.9 (Cquat), 123.8 (Cquat), 123.6 (CH), 122.8 (Cquat), 118.1 (CH), 117.8 (CH), 110.0 (Cquat), 66.1 (Ar-CH_2). UV/vis (ethanol 95%): λ_{max} (ϵ) 401 (3960), 381 (4220), 353 (4420), 337 (6600), 313 (21 940), 300 (21 800), 265 (30 920) nm. HRMS (LSIMS, mNBA): Found 302.0927, calcd for $C_{18}H_{11}N_3O_2 + H$ *m*/*z* = 302.0930.

11-Hydroxymethyl-10-aminobenzo[*b*][1,7]phenanthroline (16). Compound **15** (0.1 g, 0.33 mmol) was dissolved in a mixture of THF and 1 N NaOH (35 mL, 2/3, v/v). The biphasic solution was stirred at 70 °C for 5 h. The organic solvent was eliminated by evaporation under reduced pressure, and the resulting aqueous phase was diluted with water (50 mL) and extracted with AcOEt (5 × 30 mL). The organic phases were separated and washed with water and finally with brine. After evaporation to dryness, the residue was precipitated from a mixture of CH_2Cl_2 and pentane to provide compound **16** as an orange powder (0.05 g, 0.28 mmol). The aqueous phase was kept at room temperature until a precipitate has deposited. A second crop of **16** was thus isolated (0.028 g, 0.10 mmol). Compound **16** was obtained with 85% global yield. Mp = 300 °C. ^1H NMR (300 MHz, DMSO-d_6): δ 9.57 (1H, q, $J = 1.7$, 8.2 Hz, H-1), 9.00 (1H, q, $J = 1.7$, 4.4 Hz, H-3), 8.76 (1H, s, H-7), 8.08 (1H, d, $J = 9.2$ Hz, H-6), 7.88 (1H, d, $J = 9.0$ Hz, H-8), 7.75 (1H, q, $J = 4.4$, 8.2 Hz, H-2), 7.74 (1H, d, $J = 9.2$ Hz, H-5), 7.25 (1H, d, $J = 9.0$ Hz, H-9), 6.13 (1H, s. wide, NH), 5.39 (2H, d, $J = 5.5$ Hz, ArC*H*$_2$-OH), 4.97 (1H, t, $J = 5.5$ Hz, OH). ^{13}C NMR (75 MHz, DMSO-

d_6): δ 151.0 (Cquat), 150.1 (*C*H), 149.5 (Cquat), 147.5 (Cquat), 145.2 (Cquat), 135.6 (*C*H), 132.3 (*C*H), 130.1 (*C*H), 128.3 (*C*H), 126.2 (*C*H), 125.3 (Cquat), 121.7 (Cquat), 121.3 (Cquat), 120.8 (*C*H), 120.7 (*C*H), 113.1 (Cquat), 54.9 (Ar-CH_2OH). UV/vis (ethanol 95%): $\lambda_{\max}$ (ϵ) 363 (5740), 417 (4890), 317 (22 010), 270 (33 480), 242 (21 031) nm. HRMS (LSIMS, mNBA): found 276.1132, calcd for $C_{17}H_{13}N_3O + H$ $m/z = 276.1137$.

Quinolino[5,6-*b*]phenanthrolino[1,10][5′,6′:*j*]phenanthroline[1,7] (17). A mixture of aminophenanthroline **9** (0.140 g, 0.72 mmol) and *p*-toluenesulfonic acid (0.205 g, 1.08 mmol) was dissolved in DMF (7.5 mL) at room temperature. An equimolar amount of compound **16** (0.198 g, 0.72 mmol) was added in portions to the solution over a 5 h period. The reaction mixture was stirred for 24 h. The solvent was then eliminated under reduced pressure, carefully maintaining the temperature of the bath below 30 °C. The viscous residue was diluted with saturated $NaHCO_3$ and the resulting suspension was stirred at room temperature for 2 h. The aqueous phase was extracted twice with AcOEt. The organic layers were washed three times with water, dried over Na_2SO_4 and filtered. The organic solvent was evaporated to dryness to give 0.150 g of crude product that was identified as the methylene di-aryl intermediate. Final cyclization was done by dissolving the crude product (0.100 g) in 6N HCl (10 mL) and heating the solution at 85 °C for 5 days. After cooling, the solution was neutralized with 10 N NaOH. The precipitate that deposited, was filtered off, and successively washed with water, Et_2O, and CH_2Cl_2. The crude product thus obtained (0.093 g) was crystallized from ethanol (450 mL) to give compound **17** as beige solid (0.051 g, 0.12 mmol) in 51% yield from **9** (two steps).

17. Mp > 350 °C. ^1H NMR (500 MHz, TFA-*d*): δ 12.85 (1H, s, H-20), 11.73 (1H, d, $J = 7.7$ Hz, H-18), 11.18 (1H, d, $J = 8.4$ Hz, H-1), 10.70 (1H, d, $J = 8.3$ Hz, H-8), 10.23 (2H, m, H-3 and H-6), 10.18 (1H, s, H-12), 10.00 (1H, d, $J = 5.5$ Hz, H-16), 9.72 (1H, d, $J = 8.0$ Hz, H-13), 9.52 (2H, d, $J = 8.0$ Hz, H-11 and H-14), 9.47 (1H, m, H-2), 9.26 (1H, m, H-17), 9.1 (2H, m, H-7 and H-10). ^{13}C NMR (75 MHz, TFA-*d*): δ 155.3 (*C*H), 146.2 (*C*H), 145.5 (*C*H), 145.4 (Cquat), 144.8 (Cquat), 144.3 (*C*H), 143.1 (*C*H), 142.3 (Cquat), 142.2 (*C*H), 141.4 (Cquat), 141.0 (*C*H), 140.8 (*C*H), 140.0 (Cquat), 138.2 (Cquat), 138.0 (*C*H), 135.4 (*C*H), 129.8 (Cquat), 129.1 (*C*H), 128.8 (Cquat), 128.5 (*C*H), 128.1 (Cquat), 127.6 (Cquat), 127.2 (Cquat), 124.6 (*C*H), 122.3 (Cquat), 122.0 (Cquat), 120.5 (*C*H), 120.1 (*C*H). HRMS (LSIMS, mNBA): found 434.1409, calcd for $C_{29}H_{15}N_5 + H$ $m/z = 434.1406$.

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