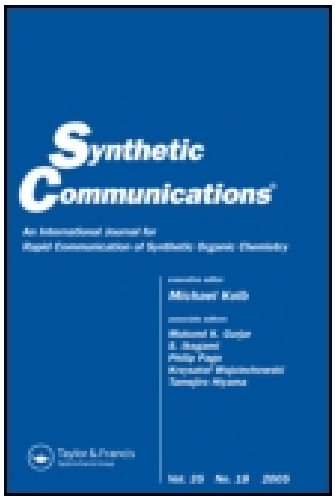

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N-METHYL-3,4-DIHYDRO-[3,1]OXAZINOACRIDINE, A USEFUL INTERMEDIATE IN THE SYNTHESIS OF POLYSUBSTITUTED ACRIDINES

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N-METHYL-3,4-DIHYDRO-[3,1]OXAZINO-ACRIDINE, A USEFUL INTERMEDIATE IN THE SYNTHESIS OF POLYSUBSTITUTED ACRIDINES

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ABSTRACT

3,4-Dihydro-4-methyl-1*H*-[3,1]oxazinoacridine was prepared in four steps from 3-aminoacridine. DDQ induced opening of the dihydrooxazine ring yielded the 3-methylamino-4-formyl derivative. The same strategy was applied to 11-aminobenzo-[b][1,7]phenanthroline.

Polysubstituted acridines constitute a large family of compounds of biological interest (antitumor, antimalarial agents ...). In most cases, the substituents are introduced in an early stage of the synthesis, prior to the formation of the acridine ring. In the course of a program dedicated to the search for new antitumor agents, we applied electrophilic aromatic substitution to introduce various substituents onto the acridine ring.[1–4] The reactions were regioselective. 3-Aminoacridine (**1**) or 3,6-diaminoacridine

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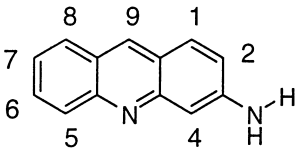
(proflavine) were shown to react at positions 4 or 4 and 5, ortho to the amino groups. No reaction products corresponding to substitution in the 2 (and 7) position could be detected. We took advantage of this reactivity and regioselectivity to prepare a new heterocycle, 10-aminobenzo[b][1,7]-phenanthroline (**2**), from proflavine.[5]



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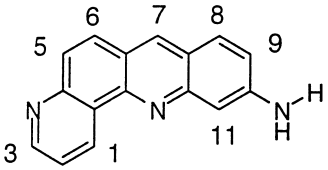

2

Reaction of the amino-heterocycles **1** and **2** with formaldehyde was also studied. Depending on the stoichiometry in formaldehyde and on the nature of the acid used as the solvent, various types of molecules were obtained: Tröger's bases, tetrahydroquinazoline and dihydro-[3,1]oxazine derivatives.[6,7] We report here the synthesis of the N-methyl analogues of dihydro-[3,1]oxazine (**9** and **10**), prepared from 3-methylaminoacridine **7** and 10-methylaminobenzo[b][1,7]phenanthroline **8** and show that DDQ induced ring cleavage yields the corresponding aldehydes in good yields.

RESULTS AND DISCUSSION

The N-methylamino heterocycles were obtained in three steps from the amino derivatives. The reaction with *para*-toluenesulfonyl chloride in pyridine afforded the *para*-toluenesulfonamides **3** and **4**, which were alkylated with methyl iodide in the presence of potassium carbonate to give **5** and **6** in excellent yields. Hydrolysis of the *para*-toluenesulfonamide in sulfuric acid afforded **7** and **8** in quantitative yield. The reaction with formaldehyde was performed in methanesulfonic acid for **8** or 12 N hydrochloric acid for **7**. In both solvents, the reactions proceeded smoothly to give the N-methyl-dihydro-[3,1]oxazines **9** and **10** in good yields (78% and 97% respectively). These compounds were characterized by nmr spectroscopy and mass spectrometry. In the ^{1}H nmr spectra of **9** and **10**, the two methylenes of the dihydrooxazine rings appeared as two singlets at 5.47 and 5.43 ppm respectively for $ArCH_2O$, and 4.72 and 4.73 ppm for NCH_2O.

The N-methyl-dihydro-[3,1]oxazine ring in **9** or **10** was shown to be stable in basic conditions (1 N aqueous sodium hydroxide) and to decompose in strong acidic medium (6 N hydrochloric acid). No reaction occurred with

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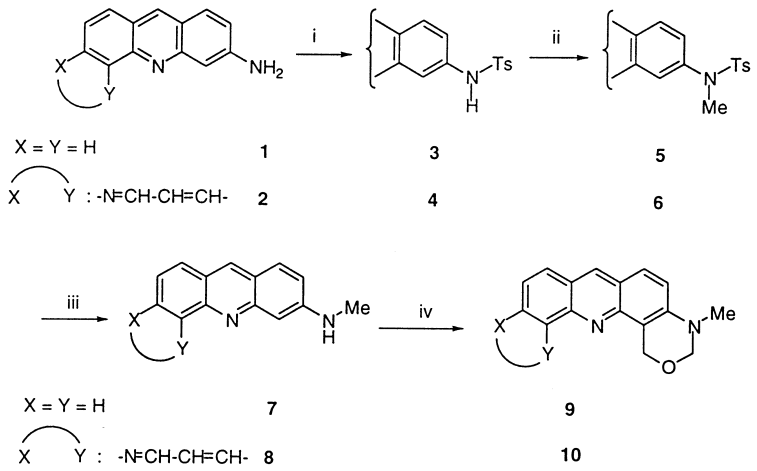

Figure 1.

lithium aluminium hydride, in conditions where the N-unsubstituted analogues were readily cleaved to the corresponding amino-alcohols.[8] Cleavage could be achieved by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), which is known to oxidize benzyl positions.[9–11] To our knowledge, this reagent has never been used to open heterocyclic rings such as dihydrooxazines. Different reaction conditions were tested.

As depicted in Figure 2, compound **9** was reacted at room temperature with DDQ in dioxane. The reaction was followed by hplc. When all the starting dihydrooxazine **9** had reacted, the black solid that was formed in solution was separated and vigorously stirred in hot water to achieve hydrolysis of the hemiacetal intermediate. The aldehyde **11** was thus obtained in good yield (70%). The reaction of **10** with DDQ was performed in methanol. The reaction proceeds smoothly at room temperature. In these conditions, it was possible to isolate the acetal intermediate **12** in 95% yield. Formation of the aldehyde **13** was obtained by acidic hydrolysis of **12** (quantitative yield) or in a one-pot reaction from **10** in 85% yield.

CONCLUSION

We designed an efficient strategy to prepare polycyclic N-methyldihydro-[3,1]oxazine derivatives. The two compounds described in this

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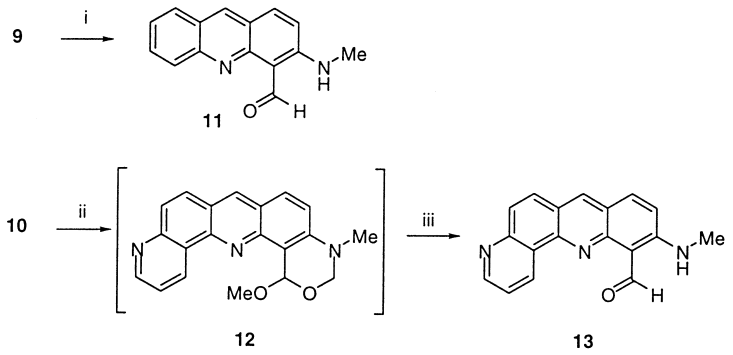

Figure 2.

paper have been tested as anticancer agents. They display significant cytotoxicity on L1210 (IC_{50} 2 μM and 1.3 μM for **9** and **10** repectively). The dihydrooxazine ring was shown to react with DDQ in a regioselective way to afford the corresponding aldehyde. It is to our knowledge the first example of oxidative ring opening achieved by DDQ producing an *ortho*-amino substituted heteroaromatic aldehyde. These type of compounds should be very useful to prepare a large variety of polysubstituted derivatives.

EXPERIMENTAL

Melting points (uncorrected) were determined using the capillary tube. Unless mentioned otherwise ^{1}H NMR spectra were taken at 200 MHz on Bruker AC 200 spectrometer. DMSO-d_6 or $CDCl_3$ were used as solvent and TMS as an internal standard. The chemical shifts are reported in ppm, in δ units. The mass spectra were recorded on a Varian Mat 311 and AET MS 30 instruments. Thin layer chromatography (tlc) was carried out on "Merck Kieselgel 60F_{254}" plates and scanned under ultraviolet light at 254 nm and 365 nm. Column chromatography was carried out with silica gel "Merk Kieselgel 60".

Synthesis of N-Methylamino Heterocycles 7 and 8

3-(*para*-Toluenesulfonylamino)acridine **3**

Para-toluenesulfonyl chloride (6 g, 31 mmol) dissolved in pyridine (30 mL) was added dropwise to a solution of 3-aminoacridine **1** (3 g,

15 mmol) in pyridine (100 mL) cooled at 0°C. After 4 h stirring at room temperature, compound **3** was precipitated by pouring the solution into a large volume of ether-hexane (1–1 mixture). After filtration, **3** was dissolved in the minimum of methanol and crystallized by adding diethylether. Compound **3** was obtained in 85% yield (9.15 g, 26 mmol).

Mp 185–190°C; ^{1}H nmr (DMSO-d_6) δ 11.8 (1H, s, NH), 9.80 (1H, s, H-9), 9.20–8.90 (3H, m, H-1, H-5 and H-8), 8.65 (1H, m, H-6), 8.63 (2H, m, Ts-H), 8.58 (1H, d, H-4), 8.38 (1H, m, H-7), 8.25 (1H, m, H-2), 8.20 (2H, m, Ts-H), 2.40 (3H, s, CH_3); ms (EI) m/z 348 (M^+); Anal. Calcd. for $C_{20}H_{16}N_2O_2S$: C-68.70, H-4.67, N-7.74, Found: C-68.95, H-4.63, N-8.04.

(*para*-Toluenesulfonylamino) Benzo[b][**1,7**]phenanthroline **4**

The same procedure was used starting from **2** (1 g, 4 mmol). Compound **4** (1.5 g, 3.76 mmol) was obtained in 92% yield.

^{1}H nmr (DMSO-d_6, 60 MHz) δ 11.4 (1H, s, NH), 9.5 (1H, dd, J = 8.2 and J = 1.7 Hz, H-1), 9.0 (1H, dd, J = 4.4 and J = 1.7 Hz, H-3), 8.9 (1H, s, H-7), 8.1 (1H, d, J = 9.2 Hz, H-6), 7.9–7.2 (9H, m, H-8, H-5, H-2, H-9, H-11 and TsH), 2.2 (3H, s, $TsCH_3$); ms (EI) m/z 399 (M^+); Anal. Calcd. for $C_{23}H_{17}N_3O_2S$: C-69.15, H-4.29, N-10.52, S-8.03 Found: C-69.35, H-4.41, N-10.71, S-7.86.

3-(N-Methyl-N-*para*-toluenesulfonylamino) Acridine **5**

Compound **3** (0.5 g, 1.4 mmol) was dissolved in DMF (20 mL) in the presence of potassium carbonate (6 mmol). Methyl iodide (4.5 mmol) was added and the solution was stirred at room temperature for 1 h. Salts were removed by filtration and the solvent was evaporated under reduced pressure to dryness. The residue was purified by column chromatography on silica gel. Compound **5** was eluted with ethyl acetate, and was obtained in 85% yield (0.44 g, 1.2 mmol).

Mp 160°C; ^{1}H nmr (DMSO-d_6) δ 8.70 (1H, s, H-9), 8.07 (1H, m, H-5), 7.94 (1H, m, H-8), 7.91 (1H, d, J = 9 Hz, H-1), 7.77 (1H, dd, J = 9 and 2.2 Hz, H-2), 7.71 (1H, m, H-6), 7.52 (1H, d, J = 2.2 Hz, H-4), 7.47 (1H, m, H-7), 7.38 (2H, d, J = 8 Hz, Ts-H), 7.12 (2H, d, J = 8 Hz, Ts-H), 3.26 (3H, s, NCH_3), 2.31 (3H, s, $TsCH_3$); ms (Cl, NH_3, isobutane) m/z 363 $(M+1)^+$; Anal. Calcd. for $C_{21}H_{18}N_2O_2S$, 0.25 H_2O: C-68.74, H-5.08, N-7.63, Found: C-68.60, H-5.07, N-7.47.

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10-(N-Methyl-N-*para*-toluenesulfonylamino) benzo[b][1,7]-phenanthroline **6**

The same method was used to prepare **6** from **4** (0.8 g, 2 mmol) in 90% yield after purification.

Mp 218–219°C; ^{1}H nmr (DMSO-d_6, 60 MHz) δ 9.5 (1H, m, H-1), 9.0 (1H, m, H-3), 8.9 (1H, s, H-7), 8.1 (1H, d, J = 9.2 Hz, H-6), 7.9–7.2 (9H, m, H-2, H-5, H-8, H-9, H-11 and Ts-H), 3.4 (3H, s, NCH_3), 2.3 (3H, s, $TsCH_3$); Anal. Calcd. for $C_{24}H_{19}N_3O_2S$: C-69.71, H-4.63, N-10.16, S-7.75, Found: C-69.41, H-4.68, N-10.26, S-7.64.

3-Methylaminoacridine **7**

Compound **5** (0.2 g, 0.5 mmol) dissolved in sulfuric acid (1 mL) was stirred at room temperature for 90 min. The solution was added dropwise to cold diluted aqueous ammonium hydroxide and compound **7** was extracted with methylene chloride. The solvent was concentrated and compound **7** precipitated by adding diethyl ether, it was obtained in quantitative yield (0.113 g, 0.5 mmol).

Mp 225–227°C; ^{1}H nmr (DMSO-d_6) δ 8.71 (1H, s, H-9), 7.98 (1H, m, H-5), 7.88 (1H, m, H-8), 7.80 (1H, d, J = 9 Hz, H-1), 7.70 (1H, m, H-6), 7.38 (1H, m, H-7), 7.07 (1H, d, J = 9 Hz, H-2), 6.85 (1H, s, NH), 6.68 (1H, s, H-4), 2.84 (3H, s, NCH_3); ms (FAB+, NBA) m/z 209 $(M+1)^+$; Anal. Calcd. for $C_{14}H_{12}N_2$: C-79.71, H-5.88, N-13.28, Found: C-79.93, H-5.72, N-13.40.

10-(Methylamino)benzo[b][1,7]phenanthroline **8**

The same method was used to prepare **8** in quantitative yield starting from **6** (0.2 g, 0.48 mmol).

Mp 286°C: ^{1}H nmr (DMSO-d_6) δ 9.50 (1H, ddd, J = 8.2, 1.8 and 0.6 Hz, H-1), 8.93 (1H, dd, J = 4.5 and 1.8 Hz, H-3), 8.64 (1H, s, H-7), 8.00 (1H, d, J = 9.2 Hz, H-6), 7.81 (1H, d, J = 9 Hz, H-8), 7.68 (1H, d, J = 9.2 Hz, H-5), 7.64 (1H, dd, J = 8.2 and 4.5 Hz, H-2), 7.13 (1H, dd, J = 9 and 2.1Hz, H-9), 6.90 (1H, d, J = 2.1 Hz, H-11), 6.58 (1H, m, NH), 2.90 (3H, d, J = 4.9 Hz, CH_3); ms (EI) m/z 259 (100, M^+); Anal. Calcd. for $C_{17}H_{13}N_3$: C-78.74, H-5.05, N-16.21, Found: C-78.53, H-4.92, N-15.94.

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Obtention of the N-Methyl-dihydro[3,1]oxazine ring

3,4-Dihydro-4-methyl-1*H*-[3,1]oxazinoacridine **9**

Compound **7** (0.64 g, 3.2 mmol) was dissolved in 12 N hydrochloric acid (6 mL) in the presence of paraformaldehyde (0.6 g, 20 mmol). The mixture was stirred at room temperature for 45 min and then basified with diluted aqueous ammonium hydroxide. Compound **9** was extracted with dichloromethane. Concentration of the solvent afforded **9** as a yellow powder in 78% yield (0.62 g, 2.5 mmol).

Mp 154°C; ^{1}H nmr ($CDCl_3$) δ 8.50 (1H, s, H-9), 8.05 (1H, d, J = 8.7 Hz, H-5), 7.84 (1H, d, J = 8.3Hz, H-8), 7.72 (1H, d, J = 9.2 Hz, H-1), 7.63 (1H, m, H-6), 7.38 (1H, m, H-7), 7.18 (1H, d, J = 9.2 Hz, H-2), 5.47 (2H, s, $ArCH_2O$), 4.72 (2H, s, NCH_2O), 3.00 (3H, s, NCH_3); ms (FAB+, NBA) m/z 251 $(M+1)^+$; Anal. Calcd. for $C_{16}H_{14}N_2O$: C-76.23, H-5.68, N-11.11, Found: C-76.27, H-5.64, N-10.70.

3,4-Dihydro-4-methyl-1*H*-[3,1]benzooxazino[5,6-*b*][1,7]-phenanthroline **10**

Compound **8** (1 g, 3.9 mmol) was dissolved in 5 mL of methanesulfonic acid (98%) in the presence of paraformaldehyde (0.3 g, 10 mmol). The mixture was stirred at room temperature for 10 min and then basified with diluted aqueous ammonium hydroxide. Compound **10** was extracted twice with dichloromethane. Concentration of the solvent afforded **10** as a yellow powder in 97% yield (1.12 g, 3.7 mmol).

Mp 183°C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 9.42 (1H, d, J = 8.2 Hz, H-13), 8.96 (1H, dd, J = 4.4 and 1.6 Hz, H-11), 8.73 (1H, s, H-7), 8.0 (1H, d, J = 9.2 Hz, H-8), 7.89 (1H, d, J = 9.1 Hz, H-6), 7.71 (1H, d, J = 9.2 Hz, H-9), 7.65 (1H, dd, J = 8.2 Hz and 4.4 Hz, H-12), 7.36 (1H, d, J = 9.1Hz, H-5), 5.43 (2H, s, $ArCH_2O$), 4.73 (2H, s, NCH_2O), 3.03 (3H, s, NCH_3); ms (EI) m/z 301 (98, M^+); Anal. Calcd. for $C_{19}H_{15}N_3O$: C-75.73, H-5.02, N-13.94, Found: C-75.87, H-5.12, N-13.72.

Oxidative Ring Cleavage

4-Formyl-3-methylaminoacridine **11**

A mixture of **9** (1.5 g, 6 mmol) and DDQ (12 mmol) in dioxane was stirred at room temperature for 3 h. The black solid that deposited was

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filtered, and suspended in water (2 L). The mixture was stirred at 85°C for 7 h. After cooling to room temperature, dichloromethane was added (1 L) and the solution was stirred overnight. The organic layer was then separated, washed with water, dried over sodium sulfate and concentrated under reduced pressure. Compound **11** was precipitated by adding diethyl ether and was obtained in 70% yield (0.991 g, 4.2 mmol).

Mp 233°C; ^{1}H nmr ($CDCl_3$) δ 11.40 (1H, s, CHO), 10.55 (1H, s, NH) , 8.37 (1H, s, H-9), 8.05 (1H, d, J = 8.4 Hz, H-5), 7.85 (1H, d, J = 9.0 Hz, H-1), 7.80 (1H, d, J = 8.0 Hz, H-8), 7.70 (1H, m, H-6), 7.40 (1H, m, H-7) 7.08 (1H, d, J = 9.0 Hz, H-2), 3.10 (3H, s, NCH_3); ms (FAB+, glycerol) m/z 237 $(M+1)^+$; Anal. Calcd. for $C_{15}H_{12}N_2O$: C-76.25, H-5.12, N-11.86, Found: C-76.21, H-5.16, N-11.68.

Ring Cleavage of 3,4-Dihydro-4-methyl-1*H*-[3,1]benzoxazino[5,6-*b*][1,7] Phenanthroline 10 in Methanol: Formation of 3,4-Dihydro-1-methoxy-4-methyl-1*H*-[3,1]benzooxazino[5,6-*b*][1,7]phenanthroline 12 and 4-Formyl-3-methylamino-benzo[b][1,7]phenanthroline 13

DDQ (0.2 g, 0.8 mmol) was added to a solution of **10** (0.1 g, 0.33 mmol) dissolved in 50 mL of dried methanol. The reaction was kept at room temperature for 1 h. The insoluble fraction was filtered off and washed with water and methylene chloride. The organic layer was separated, dried over sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel using ethyl acetate as eluent.

Acetal derivative **12** was thus isolated in 95% yield (0.106 g, 0.32 mmol). One-pot benzylic oxidation and hydrolysis of the acetal was achieved by acidic treatment of the methanolic solution with 2 N HCl (1 mL), for 1 h, under stirring. The insoluble fraction was filtered off and the filtrate basified with aqueous sodium hydrogenocarbonate. The aqueous solution was extracted with methylene chloride, the organic phase was concentrated and subjected to column chromatography using the same conditions as described above. Compound **13** was isolated as pure product (0.081 g, 0.28 mmol) in 85% global yield.

12. Mp 190–192°C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 9.59 (1H, dd, J = 8.2 Hz and 1.8 Hz, H-13), 8.93 (1H, dd, J = 4.5 Hz and J = 1.8 Hz, H-11), 8.41 (1H, s, H-7), 7.87–7.76 (3H, m, H-6, H-8, H-9), 7.57 (1H, dd, J = 8.2 Hz and J = 4.5 Hz, H-12), 7.17 (1H, d, J = 9.2 Hz, H-9), 6.41 (1H, s, H-1), 4.87 (2H, dd, J = 8.8 Hz, H-3), 3.83 (3H, s, OCH_3), 3.11 (3H, s, NCH_3); ms (EI) m/z 331 (56, M^+); Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C-72.49, H-5.17, N-12.68, Found: C-72.22, H-5.01, N-12.59.

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13. Mp 260°C; ^{1}H nmr (DMSO-d_6, 300 MHz) δ 11.47 (1H, s, CHO), 10.23 (1H, q, J = 5.1Hz, NH), 9.52 (1H, dd, J = 8.2 Hz and J = 1.7 Hz, H-1), 8.97 (1H, dd, J = 4.4 Hz and J = 1.7 Hz, H-3), 8.77 (1H, s, H-7), 8.17 (1H, d, J = 9.3 Hz, H-6), 8.05 (1H, d, J = 9.3 Hz, H-8), 7.77 (1H, d, J = 9.3 Hz, H-5), 7.68 (1H, dd, J = 8.2 Hz and J = 1.7 Hz, H-2), 7.36 (1H, d, J = 9.3Hz, H-9), 3.10 (3H, d, J = 5.1Hz, NCH_3); ms (EI) m/z 287 (40, M^+); Anal. Calcd. for $C_{18}H_{13}N_3O$: C-75.25, H-4.56, N-14.62, Found: C-75.03, H-4.67, N-14.49.

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