New Polyacridine Compounds: Synthesis of Acridine Dimers and Tetramers

Nathalie Filloux,* Jean-Pierre Galy

UMR 6009, Université d'Aix-Marseille III, case 552, Av. Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France
Fax 33 (4) 91288323; E-mail: m9701745@educ-012.u-3mrs.fr
Received 10 April 2001

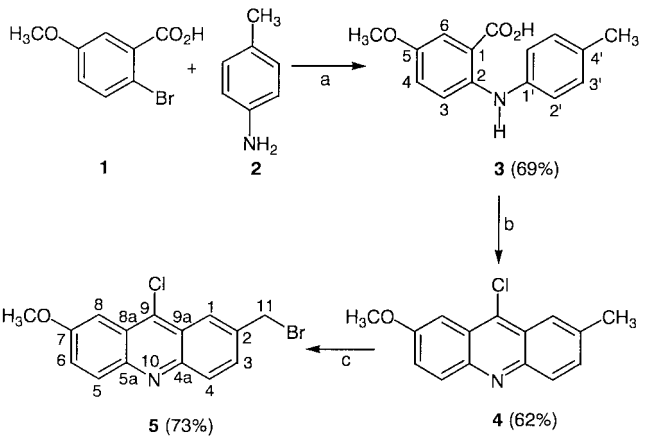
Abstract: A series of 7,9-disubstituted acridine dimers and tetramers have been synthesized from nucleophilic attack of 2-bromomethyl-9-chloro-7-methoxy acridine **5** by different alkyl diamines.

Key words: acridines, DNA polyintercalands, antitumor agents, polycycles, nucleophilic substitution

Acridine derivatives have a wide range of biological applications, especially as antitumor agents.[1] Because of its planar structure, the acridine chromophore has excellent DNA binding properties.[2] Since bis-intercalation would theoretically increase DNA binding, the synthesis of polyacridinic compounds as potential bis-intercalating agents has been extensively studied.[3] Some mono- and bi-bridged acridine dimers have recently been prepared in our laboratory.[4]

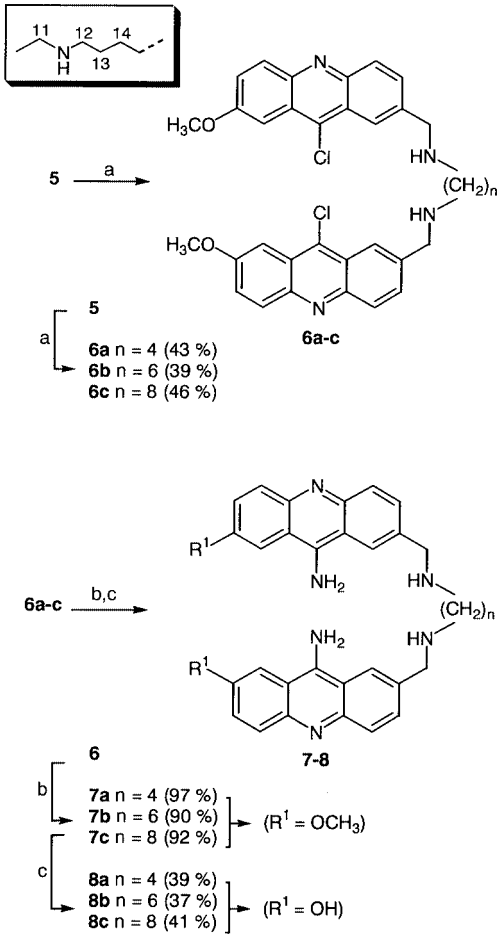
Hence we synthesized new polyintercalands containing two or four acridine moieties linked at position 2. The key intermediate for these preparations was 2-bromomethyl-9-chloro-7-methoxyacridine **5**. Nucleophilic attack of **5** by different alkyl diamines gave two series of new 7,9-disubstituted polyacridinic compounds: dimers **6-8** and tetramers **9-11**.

2-Bromomethyl-9-chloro-7-methoxyacridine **5** was prepared in three steps (Scheme 1): an Ullmann condensation between 2-bromo-5-methoxy benzoic acid **1** and *p*-toluidine **2** yielded 5-methoxy-4'-methyl-N-phenylanthranilic acid **3**,[5] which was then cyclized with phosphorus oxide chloride to give 9-chloro-7-methoxy-2-methylacridine **4**.[6] Finally, benzylic photobromination of **4**, using 1,3-dibromo-5,5'-dimethylimidazolidine-2,4-dione (DBDMI) in cyclohexane and under nitrogen atmosphere, led to **5**.[7] Already used as bromination agent at benzylic position,[8] DBDMI gave higher yield (73%, Scheme 1) than the commonly employed N-bromosuccinimide.[9] Note that DBDMI must be added at two times to avoid the formation of the dibromomethyl compound. Moreover because of its lower toxicity, cyclohexane was chosen rather than the usual carbon tetrachloride.

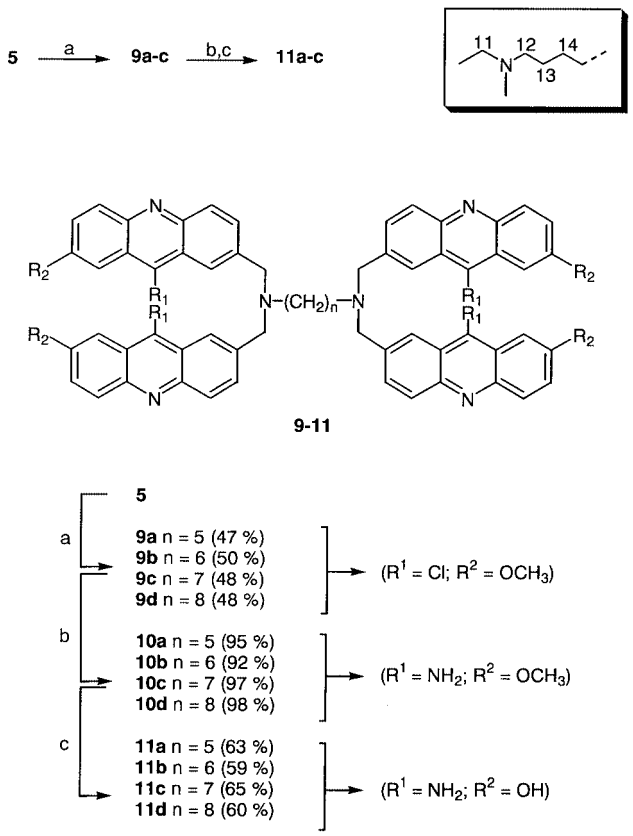


Scheme 1 a) K_2CO_3, Cu, DME, 3 h, reflux; b) $POCl_3$, 15 min, 80 °C and 30 min, 120 °C; c) DBDMI, C_6H_{12}, hν, 12 h.

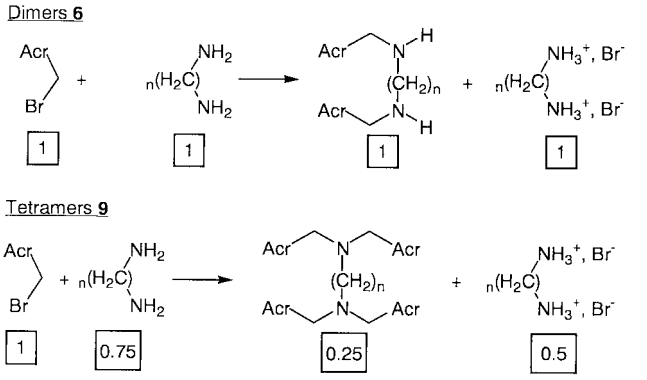
The main step of the synthesis of both dimers **6a-c** and tetramers **9a-d** was the nucleophilic attack of **5** by an alkyl diamine containing a variable number of (CH_2) groups.[10,11] The reaction was performed in CH_2Cl_2 under reflux (Schemes 2 and 3) and yielded compounds **6** and **9**.



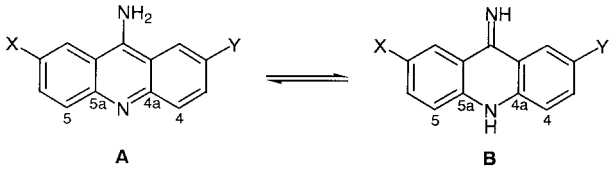
Scheme 2 a) $_2HN\text{-}(CH_2)_n\text{-}NH_2$ (1.2 equiv. mol.), CH_2Cl_2, 5 h, reflux; b) $(NH_4)_2CO_3$, phenol, 5 h, 60 °C; c) HBr 48%, 3 days.



Scheme 3 a) $_2HN\text{-}(CH_2)_n\text{-}NH_2$ (0.5 equiv. mol.), CH_2Cl_2, 12 h, reflux; b) $(NH_4)_2CO_3$, phenol, 5 h, 60 °C; c) HBr 48%, 3 days.



Scheme 4



Scheme 5

To neutralize HBr formed during the reaction, the alkyl diamine was used in excess. As shown in Scheme 4, 1.0 equiv. mol of diamine chain would theoretically be employed for the synthesis of dimers **6** and 0.75 equiv. mol of diamine for tetramers **9**. However, the best yields were obtained with 1.2 equiv. mol of diamine for the preparation of dimers **6** (39-46%) and 0.5 equiv. mol of diamine for tetramers **9** (47-50%). Some attempts with potassium carbonate or pyridine as base were also performed but they did not give better yields.

Next, dimers **6a-c** and tetramers **9a-d** were aminated at position 9 with ammonium carbonate in phenol, with over than 90% yield.[12] In the last step, the demethylation of the OCH_3 groups by HBr under reflux during three days led to the corresponding 9-amino-7-hydroxy dimers **8a-c** and tetramers **11a-d**.[13] Demethylation with aluminium chloride in toluene was also performed but all our attempts at purification failed.

All these compounds were characterized by ^1H and ^{13}C NMR spectroscopy. Moreover unambiguous differentiation between dimer or tetramer compounds was easily obtained from the area of significant protons (e.g. H-12 and H-3).

At least, 9-amino acridine derivatives (compounds **7**, **8**, **10** and **11**) exist in two tautomeric forms A and B, as shown in Scheme 5. For all these compounds the C-4, C-4a, C-5 and C-5a resonances are shielded with respect to the corresponding 9-chloro acridine derivatives. Thus as previously reported,[14] these results suggested that the amino-imino equilibrium is completely shifted towards the imino tautomer B.

In conclusion, a series of new acridine dimers and tetramers linked by different alkyl diamine were synthesized and characterized. All these compounds are undergoing biological tests.

References and Notes

(1) Niedle, S.; Waring, M. *Molecular Aspects of Anticancer Drug-DNA Interactions* Macmillan: Basingstoke **1994**, Vol. *2*; p 270. Baguley, B. C.; Zhuang, L.; Marshall, E. M. *Cancer Chemother. Pharmacol*. **1995**, *36*, 244.
(2) Lerman, L. S. *J. Mol. Biol*. **1961**, *3*, 18.
(3) Le Pecq, J. B.; LeBret, M.; Barbet, J.; Roques, B. *Proc. Natl. Acad. Sci*. **1975**, *72*, 2915. Gamage, S. A.; Spicer, J. A.; Atwell, G. J.; Finlay, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem*. **1999**, *42*, 2383. Wakelin L. P. G. *Medicinal. Res. Rev*. **1986**, *6*, 295.
(4) Issmaili, S.; Boyer, G.; Galy, J. P. *Synlett* **1999**, 641.
(5) Hannig, E.; Becke, E. *Pharmazie* **1975**, 289.
(6) Patent I. G. Farbenind.; DE 632224; **1934**; FTFVA6; Fortschr. Teerfarbenfabr. Verw. Industriezweige; DE; GE; *23*; 539. Patent; Winthrop Chem. Co.; US 2121207; **1935**.
(7) Compound **5**: 9-Chloro-2-methoxy-7-methylacridine **4** (3.11 g, 12.08 mmol) was dissolved in freshly distilled cyclohexane (150 mL) at 80 °C under a nitrogen atmosphere. 1,3-Bibromo-5,5-dimethylimi-dazolidine-2,4-dione (DBDMI, 2.14 g, 7.51 mmol) was added and the mixture was irradiated for 5 h under stirring with a 150 W halogen floodlamp. Next, one more drop of DBDMI (0.93 g, 3.26 mmol) was added to the mixture and the irradiation was performed another 7 h. Then the solvent was removed in vacuo and the residue was washed with CH_3CN (250 mL) to yield **5** as an orange powder (2.96 g,

73%). mp 186 °C.
^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.00 (s, 3H, OCH_3), 4.70 (s, 2H, H-11), 7.43 (d, 1H, *J* = 2.5 Hz, H-8), 7.46 (dd, 1H, *J* = 2.7 and 9.3 Hz, H-6), 7.74 (dd, 1H, *J* = 2.0 and 9.0 Hz, H-3), 8.15 (d, 1H, *J* = 9.3 Hz, H-5), 8.19 (d, 1H, *J* = 8.9 Hz, H-4), 8.30 (d, 1H, *J* = 2.0 Hz, H-1). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 33.45 (C-11), 55.87 (OCH_3), 99.98 (C-8), 123.83 (C-1), 124.06 (C-9a), 125.68 (C-8a), 126.70 (C-6), 130.26 (C-4), 130.88 (C-3), 130.99 (C-5), 136.72 (C-2), 138.95 (C-9), 145.76 (C-5a), 146.07 (C-4a), 158.63 (C-7).

(8) Orazi et al. *Annales Asoc. Quim. Argentina* **1952**, *40*, 91. Pintado, O. A. *Rev. Fac. Cienc. Quim. Univ. La Plata* **1955**, *29*, 53.

(9) Acheson, R. M.; Bolton, R. G. *J. Chem. Soc. Perkin Trans 1* **1975**, 650. Takashi, K.; Castle, N. R. *J. Heterocycl. Chem.* **1987**, *24*, 977.
General procedure for the synthesis of dimers **6a-c**: 2-(Bromomethyl)-9-chloro-7-methoxyacridine **5** (1 g, 2.97 mmol) and 1,4-butanediamine (0.31 g, 3.51 mmol) were refluxed under stirring for 5 h in CH_2Cl_2 (35 mL). The hot mixture was filtered and the resulting precipitate was warmed under stirring in $CHCl_3$ (100 mL) for 1 h. The hot solution was filtered and the organic layer was dried and evaporated to give **6a** (0.38 g, 0.63 mmol, 43%) as a beige powder, mp 206 °C. Dimers **6b-c** were obtained by the same procedure.

(10) Spectroscopy data of selected compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.66 (t, 4H, *J* = 6.0 Hz, H-13), 2.75 (t, 4H, *J* = 6.0 Hz, H-12), 4.00 (s, 6H, OCH_3), 4.02 (s, 4H, H-11), 7.42 (dd, 2H, *J* = 2.7 and 9.2 Hz, H-6), 7.45 (d, 2H, *J* = 2.7 Hz, H-8), 7.70 (dd, 2H, *J* = 1.5 and 8.9 Hz, H-3), 8.04 (d, 2H, *J* = 9.2 Hz, H-5), 8.09 (d, 2H, *J* = 8.9 Hz, H-4), 8.21 (s, 2H, H-1).^{13}C NMR (300 MHz, $CDCl_3$) δ: 27.95 (C-13), 49.42 (C-12), 54.00 (C-11), 55.77 (OCH_3), 99.92 (C-8), 122.04 (C-1), 124.28 (C9a), 125.41 (C-8a), 125.69 (C-6), 130.07 (C-4), 130.36 (C-3), 131.54 (C-5), 137.79 (C-2), 139.15 (C-9), 145.91 (C-5a), 146.85 (C-4a), 158.27 (C-7).

(11) General procedure for the synthesis of tetramers **9a-d**: A mixture of 2-(bromomethyl)-9-chloro-7-methoxyacridine **5** (1.24 g, 3.68 mmol) and 1,5-pentanediamine (0.20 g, 1.93 mmol) in CH_2Cl_2 (80 mL) was refluxed under stirring for 24 h. The hot mixture was filtered. The organic phase was dried and evaporated, and the resulting solid was chromatographed on silica gel ($CHCl_3$/EtOH : 99/1) to yield **9a** (0.49 g, 0.43 mmol, 47%) as a yellow powder, mp 212 °C. Tetramers **9b-d** were obtained by the same procedure.
Spectroscopy data of selected compound **9a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.53 (m, 2H, C-14), 1.81 (m, 4H, H-13), 2.55 (t, 4H, *J* = 6.7 Hz, H-12), 3.67 (s, 8H, H-11), 3.92 (s, 12H, OCH_3), 7.32 (d, 4H, *J* = 1.2 Hz, H-8), 7.32 (dd, 4H, *J* = 2.8 and 10.3 Hz, H-6), 7.72 (dd, 4H, *J* = 1.8 and 8.9 Hz, H-3), 7.97 (d, 4H, *J* = 10.1 Hz, H-5), 8.03 (d, 4H, *J* = 8.8 Hz, H-4), 8.16 (s br, 4H, H-1). ^{13}C NMR (300 MHz, $CDCl_3$) δ: 26.60 (C-14 and C-13), 53.55 (C-12), 55.60 (OCH_3), 58.64 (C-11), 99.92 (C-8), 122.84 (C-1), 123.99 (C-9a), 125.19 (C-8a), 125.50 (C-6), 129.61 (C-4), 130.89 (C-3), 131.21 (C-5), 137.63 (C-2), 139.15 (C-9), 145.59 (C-5a), 146.65 (C-4a), 158.04 (C-7).

(12) General amination method for the preparation of compounds **7a-c** and **10a-d**: **9b** (0.22 g, 0.37 mmol) was dissolved in phenol (3 g) at 60 °C. Ammonium carbonate (0.60 g, 6.25 mmol) was added and the mixture was stirred for 6 h at 60 °C. Then, cold acetone (50 mL) was added to the mixture to obtain a green precipitate. This precipitate was filtered off and stirred 2 h in an alcaline solution (NaOH, 3N, 50 mL). The solution was then filtered and the precipitate was washed with water to obtain **10b** (0.20 g, 0.36 mmol, 92%) as a green powder, mp 227 °C. Dimers **7a-c** and tetramers **10a,c,d** were obtained by the same procedure.
Spectroscopy data of selected compound **10b**: ^{1}H NMR (300 MHz, DMSO-d_6 / TFA) δ: 1.40 (s br, 2H, H-14), 1.99 (s br, 4H, H-13), 3.30 (s br, 4H, H-12), 3.89 (s, 6H, OCH_3), 4.62 (s, 4H, H-11), 7.57 (dd, 2H, *J* = 2.4 and 8.8 Hz, H-6), 7.64 (d, 2H, *J* = 9.0 Hz, H-5), 7.70 (d, 2H, *J* = 8.9 Hz, H-4), 7.77 (d, 2H, *J* = 1.8 Hz, H-8), 7.95 (d br, 2H, *J* = 9.1 Hz, H-3), 8.53 (s br, 2H, H-1), 9.73 (s, 2H, NH). ^{13}C NMR (300 MHz, DMSO-d_6 / TFA) δ: 23.27 (C-14), 23.27 (C-13), 46.59 (C-12), 57.06 (C-11), 56.29 (OCH_3), 102.87 (C-8), 110.63 (C-9a), 112.48 (C-8a), 119.31 (C-4), 120.72 (C-5), 126.08 (C-1), 127.86 (C-2), 128.41 (C-6), 134.75 (C-5a), 136.31 (C-3), 138.30 (C-4a), 156.72 (C-7), 157.08 (C-9).

(13) General demethylation method for the synthesis of compounds **8a-c** and **11a-d**: 0.20 g (0.36 mmol) of **7a** was refluxed 3 days in 10 mL of HBr (48%). Then the mixture was poured into cold water (50 mL). The solution was basified with NH_3 (10%) until pH = 9 and the red precipitate was filtered to give **8a** (0.074 g, 0.14 mmol, 39%) as a red solid, mp 316 °C. Dimers **8b-c** and tetramers **11b-d** were obtained by the same procedure.
Spectroscopy data of selected compound **8a**: ^{1}H NMR (300 MHz, DMSO-d_6 / TFA) δ: 1.77 (s br, 4H, H-13), 3.04 (s br, 4H, H-12), 4.28 (s, 4H, H-11), 7.62 (dd, 2H, *J* = 1.9 and 9.0 Hz, H-6), 7.79 (d, 2H, *J* = 9.1 Hz, H-5), 7.84 (s br, 2H, H-8), 7.86 (d, 2H, *J* = 8.7 Hz, H-4), 8.02 (d br, 2H, *J* = 8.8 Hz, H-3), 8.80 (s br, 2H, H-1). ^{13}C NMR (300 MHz, DMSO-d_6 / TFA) δ: 23.73 (C-13), 46.97 (C-12), 51.00 (C-11), 106.72 (C-8), 111.35 (C-9a), 120.20 (C-8a), 121.02 (C-4), 121.23 (C-5), 127.47 (C-1), 128.73 (C-6), 128.98 (C-2), 134.78 (C-5a), 136.64 (C-3), 139.35 (C-4a), 155.32 (C-7), 157.32 (C-9).

(14) Galy J. P.; Faure R.; Barbe J.; Elguero J. *Spectrosc. Lett.* **1988**, *21*, 809.

Article Identifier:
1437-2096,E;2001,0,07,1137,1139,ftx,en;D04701ST.pdf