Synthesis of New Mono- and Bi-bridged Acridine Dimers

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Received 11 January 1999

Abstract : The preparation of new mono- and bi-bridged acridine derivatives by acylation of 4-amino-5-hydroxy-9(10H)-acridinone **6**, 4-amino-5-hydroxyacridine **9** and 4-amino-5-propargyloxy-9(10H)-acridinone **7** is reported.

Key words: acridines, bi-bridged compounds, DNA intercalands

Acridine derivatives are well known therapeutic agents due to their wide range of pharmacological and biological activities, and many bisacridinic compounds have been reported in the literature.[1] We reported previously the preparation of some mono and bi-bridged acridine dimers[2] and crown ethers[3] obtained from amino or hydroxy acridines respectively.

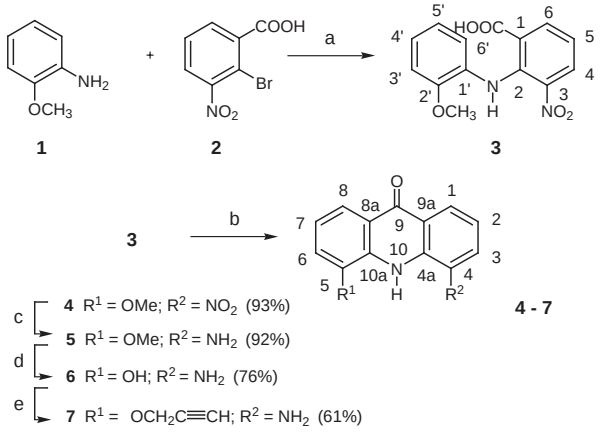
Hence we were interested in the preparation of new bisintercalands bridged at positions 4 and 5 using the corresponding amino hydroxy acridine derivatives. Our approach towards this synthesis was based on the preparation of the 4-amino-5-hydroxy-9(10H)-acridinone **6** and 4-amino-5-hydroxyacridine **9** followed by *N*- or *O*-acylation with different acyl halides to obtain the desired acridin dimers.

The initially applied Ullmann condensation[4] method between *o*-anisidine **1** and 2-bromo-3-nitrobenzoic acid **2**[5] for the synthesis of 2'-methoxy-3-nitrophenylanthranilic acid **3** suffered from tedious purification and poor yields; in contrast, use of ultrasonic irradiation or reflux in ethanol[6] led to more than 60% yield. Cyclisation of anthranilic acid **3** with polyphosphoric acid yielded the corresponding 5-methoxy-4-nitro-9(10H)-acridinone **4**.[7] Reduction of **4** and demethylation gave the corresponding aminohydroxy derivative **6**,[8] which could be propargylated to give the 4-amino-5-propargyloxy-9(10H)-acridinone **7**.[9]

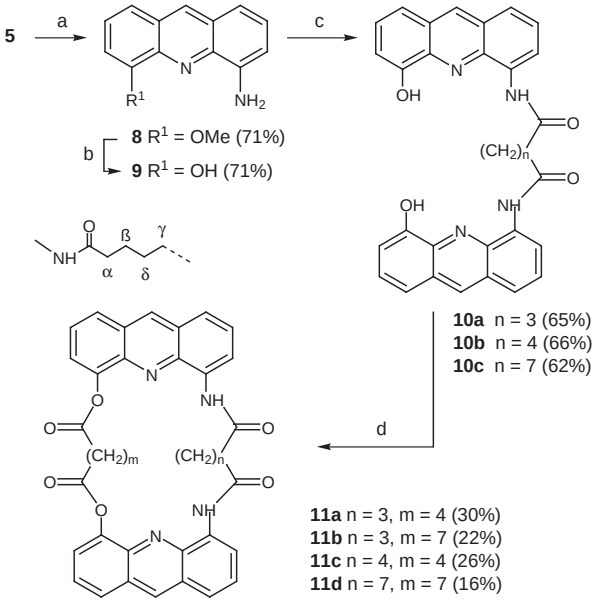
To synthesize the 4-amino-5-hydroxyacridine **9** we used the intermediate methoxy acridinone **5**, whose reduction with sodium amalgam,[10] followed by HBr demethylation, led to **9** in good yield.

We proceeded to the acylation of the 4-amino-5-hydroxyacridine **9**, but in anhydrous acetone and at room temperature, according to a procedure previously described in our laboratory on monoamino-acridine dimerisation.[2] The first time, a series of mono bridged acridinic dimers was obtained using the same acid halides, e.g. the 4.4'-(diamino-α",ω'"-acyl)-bis-(5-hydroxyacridines) **10a-c**.[11]

After acylation of the amino group, we studied the reactivity of the hydroxy group in position 5; the goal was the



Scheme 1. a) Na_2CO_3, Cu, C_2H_5OH, 3 h,))), 80 °C; b) PPA, 3 h, 100 °C or H_2SO_4, 1/2 h, 90 °C; c) $SnCl_2$, HCl, 4 h, reflux; d) HBr 48 %, 48 h, reflux; e) $CH_2CCl \equiv CH$, Cs_2CO_3, DMF, 4 h, 60 °C.



Scheme 2. a) i: Na/Hg, $NaHCO_3$, C_2H_5OH, 3 h, reflux; ii: $FeCl_3$, H_2O, 0.5 h; b) HBr 48 %, 24 h, reflux; c) $ClCO(CH_2)_nCOCl$, CH_3COCH_3, 3 h, r.t.; d) i: CH_3CH_2OTl, C_2H_5OH, 2.5 h, r.t.; ii: $ClCO(CH_2)_mCOCl$, pyridine, 18 h, r.t.

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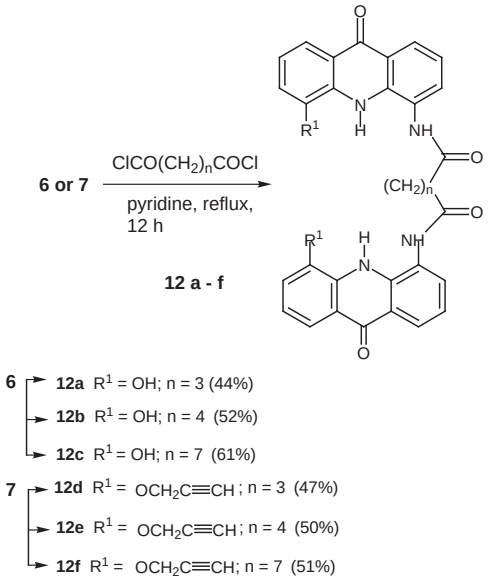
preparation of macrocylic bisintercalands able to have new therapeutic properties. We tried first an *O*-alkylation by phase transfer catalysis but all our attempts at purification of the final products failed.[12] According to good results previously described on mono- and dihydroxy acridinones in our laboratory we tried alternatively to *O*-acylate in pyridine the intermediate thallous salts of **10a-c**.[13] Indeed, reaction of two acyl dihalides with the bis-(5-hydroxyacridines) led to four bi-bridged compounds **11a-d**.[14]

Acylation of compounds **6**, **7** was next carried out by reaction at the amino substituent at position 4. We chose three acid dichlorides with a variable number of CH_2 groups and performed the reaction on the derivatives **6** and **7** in pyridine under reflux,[15] because of the best solubility of these acridinones in this solvent. The acylated mono-bridged bisacridines **12a-f** were obtained in positions 4,4'.[16]



Scheme 3

The last step was the oxidative coupling of the acetylenic groups of the propargyloxy-9(10H)acridinones **12d-f**, with cupric acetate in pyridine according to the Lehn procedure,[9] in order to obtain intramolecular diacetylenic coupling and bi-bridged acridanone macrocycles. Unfortunately all our attempts of purification and characterization of the recovered crude oil failed.

In conclusion, we reported the preparation of a new class of mono- and bi-bridged acridines: the 4,4'-(diamino-α", ω"-acyl)-bis-(5-hydroxy, or propargyloxy-9(10H)-acridinones), and the 4.4'-(diamino-α", ω"-acyl) -5,5'-(dioxa-α"', ω"'-acyl) bisacridines; biological testing is now currently in progress to investigate their therapeutical activity.

References and Notes

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(5) 2-Bromo-3-nitrobenzoic acid was prepared according to the literature: Culhane, P.J. *Organic Synthese* **1927**, *1*, 125.

(6) See: Hanoun, J.P.; Galy, J.P.; Tenaglia, A. *Synth. Commun.* **1995**, *25*, 2443. Compound **3**:^{1}H NMR (DMSO-d_6) δ:3.78 (s, 3H, OCH_3), 6.75 (m, 2H, H-3' and H-6'), 7.01 (t, 1H, J = 8.01 Hz, H-5), 7.03 (m, 2H, J = 1.4 Hz, H-4' and H-5'), 8.06 (dd, 1H, J = 8.1 and 1.5 Hz, H-6), 8.21 (dd, 1H, J = 7.7 and 1.5 Hz, H-4), 10.04 (s, 1H, NH), 11.34 (s, 1H, COOH). ^{13}C NMR (DMSO-d_6) δ:117.67 (C-3'), 116.31 (C-6'), 117.82 (C-5), 119.30 (C-1), 120.23 (C-5'), 123.82 (C-4'), 129.41 (C-1'), 130.67 (C-4), 138.58 (C-6), 139.08* (C-3), 139.17* (C-2), 150.10 (C-2'), 168.61 (COOH).

(7) See: Brockmann, H.; Muxfeldt, H.; Haese, G. *Chem. Ber.* **1957**, *90*, 44.

(8) Compound **5**:^{1}H NMR (DMSO-d_6) δ:4.05 (s, 3H, OCH_3), 6.00 (s, 2 H, NH_2), 7.11 (dd, 1H, J = 8.0 and 7.6 Hz, H-2), 7.21 (t, 1H, J = 8.0 Hz, H-7), 7.24 (dd, 1H, J = 7.5 and 1.4 Hz, H-3), 7.32 (dd, 1H, J = 7.8 and 1.2 Hz, H-6), 7.72 (dd, 1 H, J = 8.1 and 1.4 Hz, H-1), 7.79 (dd, 1H, J = 8.2 and 1.2 Hz, H-8), 9.56 (s, 1H, NH). ^{13}C NMR(DMSO-d_6) δ:56.35 (OCH_3), 112.41 (C- 6), 116.67 (C-1), 117.16 (C-8), 119.64 (C-3), 120.83 (C-8a), 120.99 (C-7), 121.76 (C-9a), 121.78 (C-2), 130.71 (C-4a), 131.32 (C-10a), 133.64 (C-4), 147.80 (C-5), 176.75 (C-9).

(9) See: Claude, S.; Lehn, J.M.; Perez de Vega, M.J.; Vigneron, J.P. *New J. Chem*. **1992**, *16*, 4.
Compound **7**:^{1}H NMR (DMSO-d_6) δ: 3.70 (t, 1H, J = 2.4 Hz CH), 5.12 (d, 2H, J = 2.4 Hz, OCH_2), 5.79 (s, 2H, NH_2), 7.05 (t, 1H, J = 7.5 Hz, H-2), 7.08 (dd, 1H, J = 7.4 and 2.1 Hz, H-3), 7.21 (t, 1H, J = 8.0 Hz, H-7), 7.43 (dd, 1H, J = 7.8 and 2.4 Hz, H-6), 7.57 (dd, 1H, J = 7.2 and 2.2 Hz, H-1), 7.83 (dd, 1H, J = 8.2 and 1.1 Hz, H-8), 9.40 (s, 1H, NH).^{13}C NMR (DMSO-d_6) δ: 56.61 (OCH_2), 78.88 (C), 79.22 (CH), 114.00 (C-6), 114.14 (C- 1), 117.42 (C-3), 118.06 (C-8), 120.43 (C-7), 120.99 (C-8a), 121.61 (C-9a), 121.98 (C-2), 129.82 (C-4a), 131.59 (C-10a), 137.35 (C-4), 145.50 (C-5), 176.86 (C-9).

(10) See reference 4. Compound **8**:^{1}H NMR (DMSO-d_6) δ: 4.04 (s, 3H, OCH_3), 6.11 (s, 2H, NH_2), 6.88 (dd, 1H, J = 7.2 and 1.3 Hz, H-3), 7.13 (dd, 1H, J = 7.5 and 0.9 Hz, H-6), 7.25 (dd, 1H, J = 8.4 and 1.3 Hz, H-1), 7.34 (dd, 1H, J = 8.3 and 1.2 Hz, H-2), 7.46 (dd, 1H, J = 8.5 and 1.0 Hz, H-7), 7.63 (dd, 1H, J = 8.5 and 0.8 Hz, H-8), 8.82 (s, 1H, H-9). ^{13}C NMR(DMSO-d_6) δ: 55.81(OCH_3), 106.66 (C-3), 106.86 (C-6), 113.77 (C-1), 119.77 (C-8), 125.91 (C-7), 127.04 (C-9a), 127.59 (C-8a), 127.65 (C- 2), 134.97 (C-9), 138.62 (C-4a), 139.03 (C-10a), 144.99 (C-4), 155.00 (C-5).
Demethylation with 48% HBr led to the hydroxy derivative **9**:^{1}H NMR (DMSO-d_6) δ: 6.65 (s, 2H, NH_2), 6.80 (dd, 1H, J = 8.1 and 1.5 Hz, H-3), 7.03 (dd, 1H, J = 8.0 and 1.4 Hz, H-6), 7.19 (dd, 1H, J = 7.9 and 1.5 Hz, H-1), 7.31 (t, 1H, J = 8.0 Hz, H- 2), 7.40 (t, 1H, J = 7.9 Hz, H-7), 7.51 (dd, 1H, J = 8.1 and 1.4 Hz, H-8), 8.79 (s, 1H, H-9), 9.97 (s, 1H, OH). ^{13}C NMR δ: 106.09 (C-3), 108.49 (C-6), 113.06 (C-1), 117.57 (C-8), 126.79 (C-7), 127.11 (C-9a), 127.83 (C-2), 134.94 (C-9), 137.83 (C- 10a), 138.18 (C-4a), 145.60 (C-4), 153.08 (C-5).

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(11) General acylation method: to a solution of 4-amino-5-hydroxyacridine **9** (1 g, 4.76 mmol) dissolved in anhydrous acetone (100 ml), was added dropwise at room temperature the acyl dichloride (1.5 mmol). Then, the stirring was continued for 3 hours, and the obtained precipitate was filtered and washed with acetone, followed by hot ethanol. The corresponding bisacridines **10a-c** were obtained.
Spectroscopic data of selected compound: **10b**: ^{1}H NMR (DMSO- d_6) δ:1.85 (m, 4H, CH_2ß), 2.83 (m, 4H, CH_2α), 7.16 (d, 2H, J = 7.9 Hz, H-6), 7.49 (t, 2H, J = 7.9 Hz, H-7), 7.55 (t, 2H, J = 7.8 Hz, H-2), 7.59 (d, 2H, J = 7.9 Hz, H-8), 7.77 (d, 2H, J = 8.1 Hz, H-1), 8.82 (d, 2H, J = 8.0 Hz, H-3), 9.03 (s, 2H, H-9), 10.68 (s, 2H, NH), 10.71 (s, 2H, OH). ^{13}C NMR(DMSO-d_6) δ: 25.28 (CH_2ß), 36.83 (CH_2α), 110.56 (C-6), 116.34 (C-3), 118.20 (C-8), 122.12 (C-1), 126.61 (C-9a), 126.66 (C-7), 127.53 (C-2), 127.34 (C-8a), 134.94 (C-4), 136.86 (C-9), 138.30 (C-10a), 138.73 (C-4a), 153.11 (C-5), 172.61 (CO). Anal. Calcd. for $C_{32}H_{26}N_4O_4$: C, 72.45; H, 4.91; N, 10.57. Found: C, 72.70; H, 5.11; N, 10.83.

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(14) Vidal, R.; Galy, J.P.; Vincent, E.J.; Barbe, J. *Synthesis* **1988**, *2*, 148. General acylation method to prepare **11a-d**: the 4,4'-(diamino-α", ω"-acyl)-bis-(5-hydroxy acridines) **10a-c** (1.94 mmol) were dissolved in hot absolute ethanol (250 ml). After cooling, thallous ethoxide (3.88 mmol) was added with good stirring and the mixture kept at room temperature for 2.5 h more. The red salt obtained was filtered, washed with hot ethanol and dried. After dissolution of this salt in anhydrous pyridine (100 ml), the acyl dichloride, (1.3 eq.), was added dropwise and the mixture kept at room temperature over 18 h. The solution was filtered and evaporated in vacuo. The obtained oil was precipitated in acetone, washed with hot ethanol, filtered and dried. The 4,4'- (diamino-α",ω"-acyl)-5,5'-(dioxa-α"', ω"'-acyl) bis acridines were obtained in 16-30% yields.
Spectroscopic data of selected compound: **11a**:^{1}H NMR (TFA) δ:2.61 (m, 4H, CH_2ß' and CH_2γ'), 2.83 (m, 2H, CH_2ß), 3.39 (m, 4H, CH_2α' and CH_2δ'), 3.63 (m, 4H, CH_2α and CH_2γ), 8.30 (t, 2H, J = 8.1 Hz, H-7), 8.33 (t, 2H, J = 8.1 Hz, H-2), 8.43 (d, 2H, J = 7.6 Hz, H-6), 8.48 (d, 2H, J = 7.5 Hz, H-3), 8.67 (d, 2H, J = 8.0 Hz, H-8), 8.69 (d, 2H, J = 8.0 Hz, H-1), 10.12 (s, 2H, H-9). ^{13}C NMR(TFA) δ:22.42 (CH_2γ), 26.66 (CH_2γ'), 36.84 (CH_2ß'), 38.50 (CH_2ß), 130.34 (C-4), 130.68 (C- 1), 131.68* (C-8), 131.68* (C-8a), 131.98* (C-7), 132.49 (C-6), 133.11 (C-3), 133.28 (C-9a), 135.24 (C-10a), 136.63 (C-4a), 143.17 (C-5), 152.90 (C-9), 178.09 (CH_2α'), 179.47 (CH_2α). Anal. Calcd. for $C_{37}H_{30}N_4O_6$: C, 70.93; H, 4.79; N, 8.95. Found: C, 71.07; H, 4.92; N, 9.21.

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(16) General acylation method: to a solution of **6** or **7** (1 g, 4.42 mmol or 1g, 3.78 mmol) in freshly distilled pyridine (30 ml), was added dropwise at room temperature the acyl dichloride (2.4 mmol / 2.05 mmol). Stirring was continued for 12 hours and the solution was poured on ice. The obtained precipitate was filtered, washed with water, followed by hot ethanol, to yield the corresponding 4,4'- (diamino-α",ω"-acyl)-bis-(5-hydroxy-9(10H)-acridinones) **12a-c** or 4,4'-(diamino-α",ω"-acyl)-bis-(5-propargyloxy-9(10H)acridin- ones) **12d-f**.
Spectroscopic data of selected compounds: **12b**: ^{1}H NMR (DMSO-d_6) δ: 1.92 (m, 4H, CH_2ß), 2.75 (m, 4H, CH_2α), 7.12 (t, 2H, J = 7.8 Hz, H-7), 7.15 (d, 2H, J = 8.0 Hz, H-6), 7.25 (t, 2H, J = 7.9 Hz, H-2), 7.65 (d, 2H, J = 8.0 Hz, H-8), 7.68 (d, 2H, J = 8.1 Hz, H-3), 8.13 (d, 2H, J = 8.0 Hz, H-1), 10.31 (s, 2H, OH). ^{13}C NMR(DMSO-d_6) δ:21.61 (CH_2ß), 35.18 (CH_2α), 116.03 (C-8), 115.87 (C-6), 120.41 (C-7), 121.16 (C-8a), 121.69 (C-9a), 121.58 (C-2), 123.60 (C-1), 126.02 (C-4), 129.53 (C-3), 131.15 (C-10a), 134.78 (C-4a), 146.33 (C-5), 172.55 (CO), 176.77 (C-9). Anal. Calcd. for $C_{32}H_{26}N_4O_6$: C, 68.33; H, 4.63; N, 9.96. Found: C, 68.58; H, 4.86; N, 10.21.
12e:^{1}H NMR (DMSO-d_6) δ: 1.90 (m, 4H, CH_2ß), 2.62 (m, 4H, CH_2α), 3.67 (m, 2H, CH), 5.02 (sbr, 4H, OCH_2), 7.22 (t, 2H, J = 7.9 Hz, H-7), 7.30 (t, 2H, J = 7.8 Hz, H-2), 7.39 (d, 2H, J = 7.9 Hz, H-6), 7.70 (d, 2H, J = 7.5 Hz, H-3), 7.81 (d, 2H, J = 8.1 Hz, H-8), 8.15 (d, 2H, J = 8.0 Hz, H-1), 10.31 (s, 2H, H-10). ^{13}C NMR(DMSO-d_6) δ:25.26 (CH_2ß), 35.85 (CH_2α), 56.89 (OCH_2), 78.66 (C), 79.32 (CH), 114.61 (C-6), 145.39 (C-4), 118.13 (C-8), 121.08 (C-7), 121.24 (C-8a and C-9a), 122.00 (C- 2), 123.82 (C-1), 126.33 (C-3), 130.01 (C-4), 131.39 (C-10a), 134.77 (C-4a), 145.39 (C-5), 172.77 (CO), 176.67 (C-9). Anal. Calcd. for $C_{38}H_{30}N_4O_6$: C, 71.47; H, 4.70; N, 8.78. Found: C, 71.72; H, 4.85; N, 9.04.

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