New Macrocycles derived from 4,5-diamino- and 4,5-dihydroxyacridin-9(10*H*)-ones

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Abstract. The synthesis of new macrocycles by alkylation and acylation of 4,5-diamino- and 4,5-dihydroxyacridin-9(10*H*)-ones has been performed. Several original macrocycles (dilactames, diamides and dilactones) and crown ethers have been obtained.

Acridine derivatives are well known therapeutic agents due to their wide range of pharmacological and biological activities, and many derivatives have been reported in the literature.⁽¹⁾ Therefore one mechanism of action proceeds by DNA intercalation of the acridine moiety⁽²⁾ and we are interested since a few years in the preparation of new polyacridines and macrocycles with increased DNA binding properties. For this reason we have previously described the preparation of mono and bi-bridged acridine dimers.⁽³⁾ Moreover tetrameric polyacridines have also been reported recently in the lab.⁽⁴⁾

Hence we got involved in the *O*-acylation and alkylation of amino and hydroxy acridinones in order to prepare bisacridin-(10*H*)-ones linked on position 3 or 4⁽⁵⁾ and macrocycles linked on position 2,3 and 2,7. In this later case several crown ethers were prepared by alkylation of the corresponding dihydroxy derivatives.⁽⁶⁾

Now we are interested in the preparation of new macrocycles bridged at positions 4 and 5 using suitable precursors like the symmetrically substituted diamino and dihydroxy acridinones 5 and 8.

Our approach towards this synthesis was based on the preparation of the 4,5-diamino-9(10*H*)-acridinone 5 by reduction of the corresponding 4,5-dinitro-9(10*H*)-acridinone, obtained by Ullmann condensation between the benzoic acid 1 and *o*-nitroaniline 2. This synthesis has been reported in the literature but with low yields, especially in the first step of the condensation (20 % yield),⁽⁷⁾ following this procedure we changed systematically the reported conditions and obtained a yield of 54 % performing the condensation without solvent, during two hours, with 2-bromo-3-nitro benzoic acid 1 and aniline 2, and carrying the reaction with 1.3 % of copper powder per mmol. of 1, (entry 9, Table 1).⁽⁸⁾

Table 1: Condensation reactions of **1** with nitro aniline **2**.
(All the reactions were carried out with 4 mmol of **1**).

Entry	2 mmol	K ₂ CO ₃ mmol	Cu %/mmol	Reaction conditions	Solvent	Yield 3 (%)
1	6.3	4.7	10.0	160°/3 h	2-ethoxy ethanol	-
2	5	4.7	3.3	180°/3 h	pentanol	mixture
3	7.2	8	10.7	180°/5 h	DMF	-
4*	7.2	5	10.0	80°/3 h	ethanol	-
5	7.2	3.8	6.7	190°/2 h	-	24
6	7.2	5.2	10.0	180°/2 h	-	18
7	7.2	12	2.5	190°/2 h	-	50
8	7.2	12	2.5	190°/3 h	-	35
9	7.2	12	4.4	190°/2 h	-	54
10	7.2	12	4.6	190°/2 h	-	25

* (((

Then, the recovered anthranilic acid **3** was cyclized in polyphosphoric acid under reflux to yield the dinitro acridinone **4** with 91 % yield.⁽⁹⁾ Finally, reduction of **5** with SnCl₂ led to desired 4,5-diamino-9(10H)-acridinone with 78 % yield (Scheme 1).⁽¹⁰⁾

Scheme 1. a) Cu, K₂CO₃, 2 h, 190°C; b) PPA, 3 h, 100 °C; c) SnCl₂, HCl, 2 h, 100°C.

The acylation of the 4,5-diamino-9(10H)-acridinone **5** was performed with different alkyl halides containing a variable number of (CH₂) groups, in pyridine according to a procedure precedently described in our laboratory upon monoamino acridine dimerisation.⁽⁵⁾

With suberoyl, (n = 6 is the number of methylene units in a macrocycle), azeloyl or sebacoyl chlorides (n = 7 and 8) a mixture of oligomeric mono and diacylated acridinones was obtained with 1:1 and 1:2 acridinone/acyl chain ratios. These oligomers were separable by crystallization without column chromatography leading to macrocycles **6a-c** (18-24 % yield); e.g. the 4,5-(diamido-α",ω"-alkyl)acridin-9(10H)-ones; and to the 4,5-(diamido alcanoic acid)acridin-9(10H)-ones **7a-c** (32-35 % yield). (Scheme 2).⁽¹¹⁾

Dihydroxy acridinones are also suitable intermediaries for the preparation of acridono ligand, for this reason we tried also the acylation and alkylation of 4,5-dihydroxy-9(10*H*)-acridinone **8**. The ^1H - and ^{13}C NMR spectroscopy of this compound has been described by us,¹² but its preparation was tedious and not reported until recently by Hungarian scientists.⁽¹³⁾ In this latter case only one acridono-18-crown-6 ligand **9** was prepared and reported by *O*-alkylation of the 4,5-dihydroxy-9(10*H*)-acridinone using tetraethylene glycol ditosylate, (Scheme 3).

As in the case of diamino ligand **5** we performed first the *O*-acylation of acridinone **8** with different acyl halides in DMF with cesium fluoride to obtained monomeric macrocycles. With adipoyl chloride, ($n = 4$), a mixture of oligomeric mono and diacylated acridinones was obtained with 1:1 and 1:2 acridinone/acyl chain ratios. These oligomers were not separable by chromatography; whereas use of pimeloyl, suberoyl or adipoyl chlorides, ($n = 5$ to 7), led to only the macrocyclic dilactones **10a-c** with 1:1 ratio after purification. (Scheme 4).⁽¹⁴⁾

The differentiation and characterization of these macrocycles from by-products was unambiguously supported by the ^1H and ^{13}C NMR spectra, in particular by the evaluation of the multiplet pattern of the C-protons signals. For example in the

case of macrocycle **10b**, two doublets are observed at δ 8.14 and 7.63 for H-1 and H-3 respectively while a triplet appears at δ 7.34 for H-2 (acridinic moiety). Three signals related to the aliphatic protons also prove the unique cyclised structure with a triplet at 2.84 ppm (H-13 protons), and two multiplets at 1.73 and 1.49 ppm corresponding to H-14 and H-15.

We tried also to prepare crown ethers using **8**; such compounds are very interesting in their ability to bind metal and organic cations strongly and selectively,⁽¹⁵⁾ and Bradshaw has prepared numerous crown ethers ligands containing pyridines as aromatic moiety and has established a tripod-like hydrogen bonding involving the nitrogen atom and two alternate oxygen atoms in the macrocycle with guest molecule;⁽¹⁶⁾ moreover he recently reported the synthesis of a new ligand based on an acridine subunit whose π -system provided stronger π - π interactions with aromatic guests.⁽¹⁷⁾

To obtain the crown ethers **11a** and **11b**, the acridinone **8** was reacted with ethylene glycol di-*p*-tosylate using cesium fluoride in DMF. The best results in the isolation of only one macrocyclic monomer were obtained with tetra and penta ethylene glycol ditosylate.⁽¹⁸⁾ In this latter case the characterization of **11a** and **11b** by ^1H and ^{13}C NMR spectroscopy, in particular the multiplet patterns in ^1H NMR was very similar to those observed for macrocycles **10a-c**. (Scheme 5).

Scheme 5.

In conclusion, we reported the preparation of a new class of monomeric macrocycles and crown ethers: the 4,5-(diamido- α ," ω "-alkyl)acridin-9(10H)-ones and the 4,5-(dihydroxy- α ," ω "-alkyl)acridin-9(10H)-ones; biological testing is now currently in progress to investigate their therapeutical activity.

Notes and References

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- 8 2-Bromo-3-nitrobenzoic acid **1** was prepared according to the literature: Culhane P.J., *Org. Synth.* **1927**, 7, 12.
Preparation of **3**: 2 g of compound **1**, 1 g of 2-nitroaniline **2**, 0.051 g of Cu powder and 1.66 g of K₂CO₃ were heated at 190 °C for 2 h. Then, after addition of 25 ml of water and active coal, the mixture was refluxed under stirring during 1 h more. The solution was warmed under reflux, filtered and acidified with 36% HCl, the obtained precipitate was filtered, washed with water and dried. The brown powder was dissolved in 5 ml of NaOH 1M, the alkaline solution was filtered and the pH was adjusted to 5 with 36% HCl. The obtained precipitate was filtered, washed with boiling water and dried to yield a yellow powder **3** (54 %). Mp 240 °C. Calcd for C₁₃H₉N₃O₆: C: 51.50, H: 2.99, N: 103.56. Found: C: 51.72, H: 3.02, N: 103.48. ¹H NMR (DMSO-d₆): δ 6.95 (1H, dd, J = 1.3, 8.1 Hz, H-6'), 7.07 (1H, ddd, J = 1.3, 7.1, 8.1 Hz, H-4'), 7.40 (1H, t, J = 8.0 Hz, H-5), 7.51 (1H, ddd, J = 1.4, 7.1, 8.2 Hz, H-5'), 8.12 (1H, dd, J = 1.6, 8.0 Hz, H-3'), 8.20 (1H, dd, J = 1.6, 8.0 Hz, H-4), 8.25 (1H, dd, J = 1.5, 8.1 Hz, H-6), 10.70 (1H, s, NH), 14.00 (1H, s, COOH). ¹³C NMR (DMSO-d₆): δ 117.31 (C-6'), 121.31 (C-4'), 123.35 (C-5), 125.46 (C-1), 126.16 (C-3'), 130.10 (C-4), 135.12 (C-2), 135.60 (C-5'), 136.56 (C-6), 137.35 (C-2'), 138.84 (C-1'), 142.70 (C-3), 167.36 (COOH).
- 9 Preparation of **4**: 5 g of 2',3-dinitrophenylantranilic acid **3** were added to 50 g of PPA and heated at 100 °C for 3 h. Then ice was added to the mixture and stirring maintained until all product dissolved. The solution was precipitated with 1M NaOH (pH = 9-10), and the green powder obtained was filtered and dried to yield 4,5-dinitro-9(10H)-acridinone **4** (91 %). Mp 258 °C. Calcd for C₁₃H₇N₃O₅: C: 54.75, H: 2.47, N: 14.73. Found: C: 54.82, H: 2.53, N: 14.84. ¹H NMR (DMSO-d₆): δ 7.58 (2H, t, J = 8.0 Hz, H-2), 8.69 (2H, dd, J = 1.6, 8.0 Hz, H-3), 8.85 (2H, dd, J = 1.5, 7.9 Hz, H-1), 13.44 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 132.62 (C-3), 134.99 (C-1), 122.34 (C-2), 123.08 (C-8a), 135.44 (C-4a), 134.68 (C-4), 175.00 (CO).
- 10 Preparation of **5**: 3 g of 4,5-dinitro-9(10H)-acridinone **4** and 27.4 g of SnCl₂ were added to 40 ml of 36% HCl and heated at 100 °C for 2 h. The mixture was filtered and the precipitate was washed with HCl 6M (100 ml) and dried. This precipitate was dissolved in cold NaOH 1M (100 ml); and the pH adjusted to 7 with 36 % HCl. The obtained precipitate was filtered, washed with water and dried to yield a green powder of 4,5-diamino-9(10H)-acridinone **5** (78 %). Mp 250 °C. Calcd for C₁₃H₁₁N₃O₂: C: 69.33, H: 4.92, N: 18.66. Found: C: 69.45, H: 4.98, N: 18.85. ¹H NMR (DMSO-d₆): δ 5.69 (4H, s, NH₂), 6.99 (2H, dd, J = 1.5, 8.1 Hz, H-3), 6.99 (2H, dd, J = 1.6, 7.9 Hz, H-1), 7.51 (2H, t, J = 7.9 Hz, H-2), 8.72 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 113.92 (C-3), 116.28 (C-1), 121.31 (C-2), 121.72 (C-8a), 129.63 (C-4a), 137.17 (C-4), 177.61 (CO).
- 11 General preparation for macrocycles **6** and **7**: 4,5-aminoacridinone **5** (0.2 g, 0.88 mmol) was added to refluxed dry pyridine (150 ml). A second solution of acyl dichloride (2.64 mmol) dissolved in DMF (50 ml) was added dropwise to the first solution during 3 h. The red solution was warmed under reflux during 0.5 hour more and filtrated. The solution was concentrated and boiling water (10 ml) was added to the obtained oil. The obtained precipitate was filtered, washed with water and dried to yield a crude mixture of macrocycles **6** and **7**. This mixture was dissolved in 50 ml of NaOH 1M, and filtrated to yield an insoluble precipitate and a filtrate. The precipitate was washed with water and dried to yield a beige powder corresponding to the oligomeric 4,5-(diamido-α",ω"-alkyl)acridin-9(10H)-ones **6**. The filtrate was concentrated, dissolved in acetone (5-10 ml) and filtered, then the solution was evaporated yielding a brown powder of diamides **7**.
Spectroscopic data of selected compound **6c**: Mp 325 °C. Calcd for C₂₃H₂₅N₃O₃: C: 70.57, H: 6.44, N: 10.73. Found: C: 70.60, H: 6.48, N: 10.62. ¹H-NMR (DMSO-d₆): δ 1.37 (8H, m, H-15 and H-16), 1.70 (4H, m, H-14), 2.44 (4H, m, H-13), 7.21 (2H, t, J = 7.9 Hz, H-2), 7.67 (2H, dd, J = 1.5, 7.9 Hz, H-3), 8.11 (2H, dd, J = 1.6, 7.8 Hz, H-1), 10.12 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 23.85 (C-16), 26.53 (C-15), 27.74 (C-14), 35.64 (C-13), 121.51 (C-2), 122.17 (C-8a), 124.09 (C-1), 126.24 (C-4), 130.76 (C-3), 135.57 (C-4a), 173.60 (C-12), 174.00 (CO).
Spectroscopic data of selected compound **7c**: Mp 238 °C. Calcd for C₃₃H₄₃N₃O₇: C: 66.76, H: 6.56, N: 7.81. Found: C: 66.80, H: 6.62, N: 7.65. ¹H-NMR (DMSO-d₆): δ 1.28 (16H, m, H-15 and H-18), 1.48 (4H, m, H-19), 1.66 (4H, m, H-14), 2.14 (4H, t, J = 7.1 Hz, H-20), 2.47 (4H, m, H-13), 7.20 (2H, t, J = 8.0 Hz, H-2), 7.60 (2H, dd, J = 1.6, 8.0 Hz, H-3), 8.11 (2H, dd, J = 1.6, 7.9 Hz, H-1), 9.92 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 27.40 (C-19), 25.12 (C-14), 28.60 (C-18), 28.70 (C-17), 28.76 (C-16), 28.86 (C-15), 35.74 (C-13), 121.43 (C-2), 121.49 (C-8a), 123.40

- (C-3), 126.64 (C-1), 129.61 (C-4), 135.26 (C-4a), 172.63 (CO), 174.62 (COOH), 176.70 (C-9).
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- 14 General preparation for macrocycles **10a-c**: 4,5-dihydroxyacridinone **8** (0.15 g, 0.66 mmol) was added to refluxed dry DMF (90 ml); then cesium fluoride (0.3 g, 1.97 mmol) was added to the solution, (a drop every 10 s), and the mixture stirred during 0.5 h. A second solution of alkyl dichloride (2.8 mmol) dissolved in DMF (50 ml) was added dropwise to the first solution during 4 h. The mixture was warmed under reflux during 3 hours and the orange precipitate obtained was filtered and dried. Boiling water (10 ml) was added to the residue and the mixture was filtered and dried. The corresponding macrocycles **10a-c** were obtained.
- Spectroscopic data of selected compound **10b**: mp 225 °C. Calcd for C₂₁H₁₉NO₃: C: 69.03, H: 5.24, N: 3.83. Found: C: 69.12, H: 5.15, N: 3.68. ¹H-NMR (DMSO-d₆): δ 1.49 (4H, m, H-15), 1.73 (4H, m, H-14), 2.84 (4H, t, J = 7.5 Hz, H-13), 7.34 (2H, t, J = 8.1 Hz, H-2), 7.63 (2H, dd, J = 1.4, 8.1 Hz, H-3), 8.14 (2H, dd, J = 1.5, 8.1 Hz, H-1), 9.54 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 23.19 (C-15), 27.17 (C-14), 32.95 (C-13), 121.86 (C-2), 122.20 (C-8a), 123.92 (C-3), 127.56 (C-1), 133.95 (C-4a), 139.21 (C-4), 171.94 (CO), 176.23 (C-9).
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- 18 General preparation for macrocycles **11a-b**: 4,5-dihydroxyacridinone **8** (0.2 g, 0.88 mmol) was added to refluxed dry DMF (90 ml); then cesium fluoride (0.7 g, 4.6 mmol) was added and the mixture stirred during 1 h. A second solution of tetra or penta ethylene glycol ditosylate (1.9 mmol) was prepared in DMF (15 ml) and added slowly to the mixture (a drop every 10s). The mixture was stirred during 15 days. The red solution was filtered and evaporated. Acetonitrile (10 ml) was added to the recovered red oil and the solution was warmed under reflux and filtered. The solution was evaporated and the residue was added to acetone. This solution was filtered and concentrated. A solution of ethanol/diethyl ether (1/3) was added to the residue and the obtained yellow precipitate was collected by filtration and chromatographed on silicagel in CH₂Cl₂ to yield the final product. The corresponding macrocycles **11a** and **11b** were obtained.
- Spectroscopic data of selected compound **11b**: mp 184 °C. Calcd for C₂₃H₂₇NO₇: C: 65.32, H: 6.34, N: 3.26. Found: C: 65.19, H: 6.20, N: 3.45. MS (FAB): m/z 430 (MH⁺). ¹H-NMR (DMSO-d₆): δ 3.55 (4H, s, H-20), 3.66 (4H, m, H-18), 3.68 (4H, m, H-17), 3.92 (4H, m, H-15), 4.39 (4H, m, H-14), 7.22 (2H, t, J = 7.9 Hz, H-2), 7.37 (2H, dd, J = 1.5, 8.2 Hz, H-3), 7.79 (2H, dd, J = 1.6, 8.0 Hz, H-1), 9.03 (1H, s, NH). ¹³C NMR (DMSO-d₆): δ 68.47* (C-14), 68.87* (C-15), 70.13° (C-17), 70.35° (C-18), 70.45° (C-20), 113.33 (C-1), 117.41 (C-3), 121.24 (C-8a), 121.33 (C-2), 130.67 (C-4a), 146.40 (C-4), 176.47 (CO).
- * : may be reversed.

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