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Synthesis of novel fluorescent acridono- and thioacridono-18-crown-6 ligands

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Abstract—Novel fluorescent 18-crown-6 type ligands containing acridono and thioacridono units were synthesised. The acridono ligand was prepared by the oxidation of its acridino analogue, and also by the cyclisation of 4,5-dihydroxyacridine-9(10*H*)-one and tetraethylene glycol di-*p*-tosylate in the presence of K_2CO_3. The acridono macrocycle was converted to the thioacridono ligand using Lawessons's Reagent. The synthesis of several precursors leading to the preparation of an acridono-18-crown-6 fluorophore was also performed. These precursors can also be very useful building blocks for acridine, acridone and thioacridone derivatives of chemotherapeutical importance.

1. Introduction

Incorporation of fluorogenic subunits into the 18-crown-6 type macrocyclic framework can lead to host molecules which are very interesting from a theoretical viewpoint as well as for practical purposes.[1,2] Cationic recognition studies using crown ether type fluorophore macrocycles have increased recently, because these sensors exhibit large changes in their florescence behaviour during interaction with analytes and also, because spectrofluorometry is a very sensitive, selective and fast technique with relatively simple handling and calculation procedures to analyse mixtures of biologically important ions.[1–6] Among a large number of crown ether type fluorophores have been synthesised and studied,[1–6] from the point of view of our research it is noteworthy to mention the work on the synthesis and cation-binding properties of a 4,5-dioxyxanthone unit containing 18-crown-6 type ligand reported by Watt and coworkers.[7] In this case the ethereal oxygens of the highly fluorescent 4,5-dioxyxanthone chromophore are part of the coordination sphere which surrounds the complexed ion, so complexation can give rise to desirable photophysical behaviour.[7]

Recently, we described the synthesis[8] of acridino-18-crown-6 fluorophore **1** (see Fig. 1) and studied its complexation

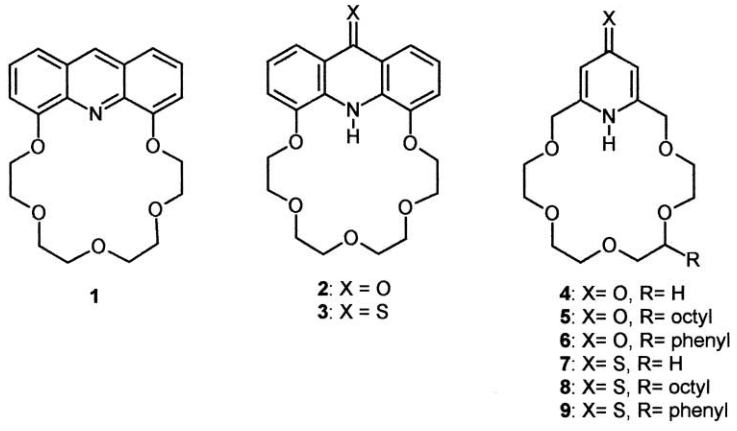

Figure 1. Acridino-, acridono-, thioacridono-, pyridono-, and thiopyridono-18-crown-6 type ligands.

Keywords: acridines; crown ethers; fluorescence; ionophores.
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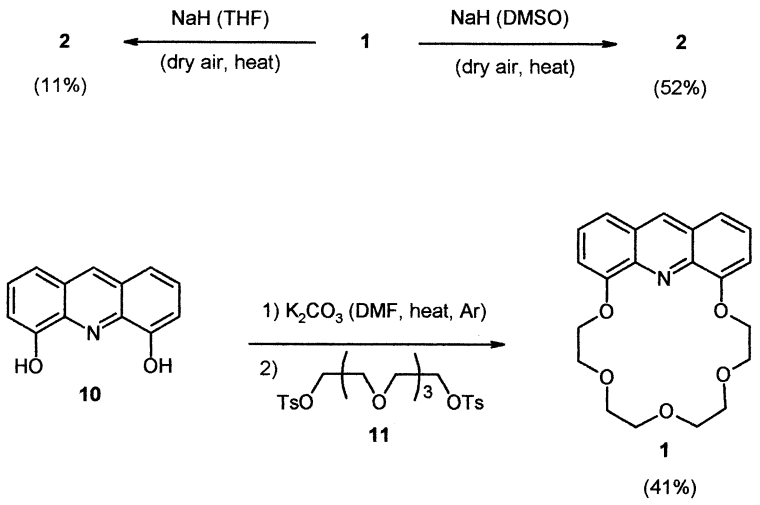
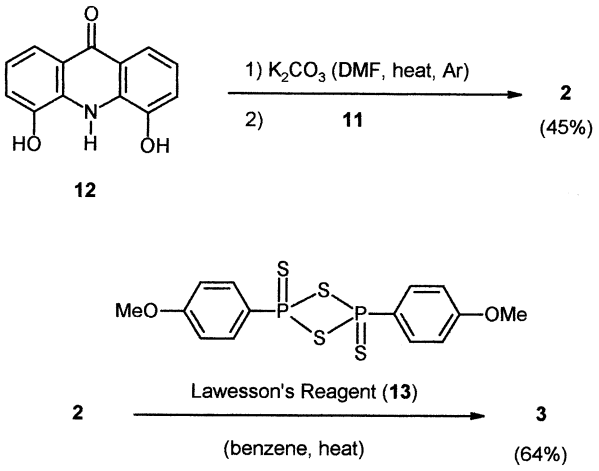


Scheme 1. Formation of new acridono ligand **2** by oxidation of acridino host **1** and improved method for preparation of **1**.

with organic primary ammonium salts by photoluminescence spectroscopy.[9]

In the course of the synthesis of acridino ligand **1** when monitoring the progress of the reaction by thin layer chromatography[8] (TLC) we noticed a very intense blue fluorescent spot on the silica gel TLC plate above the spot of ligand **1**. As the reaction progressed, the size of the blue fluorescent spot compared to the spot of ligand **1** grew slowly, and this tendency continued even when the starting material was consumed. After isolation of the highly fluorescent compound by preparative TLC ^{1}H NMR, ^{13}C NMR, MS and IR spectra were taken, which proved its structure to be the new acridono-18-crown-6 ether **2** (see Fig. 1). Although its yield was only 3% we thought that it had been formed from acridino ligand **1** under strong basic conditions (we used potassium *tert*-butoxide in THF)[8] in the presence of traces of oxygen and that we could transform acridino ligand **1** to acridono ligand **2** in reasonable yield by refluxing the reaction mixture under oxygen for a longer period of time. We note here that Russian scientists obtained a 28% yield of acridine-9(10*H*)-one by fusing acridine and potassium hydroxide.[10] Unfortunately, even prolonged refluxing of ligand **1** with an excess of potassium *tert*-butoxide in THF under an oxygen atmosphere did not give more than 5% yield of ligand **2**, while many other side products formed as well. We substituted potassium *tert*-butoxide by the stronger base NaH getting 11% yield, and when we also replaced the solvent THF by DMSO a yield of 52% was achieved. In this paper we also describe another, more straightforward synthesis of acridono ligand **2** using relatively simple starting materials, and its transformation to thioacridono analogue **3** (see Fig. 1).

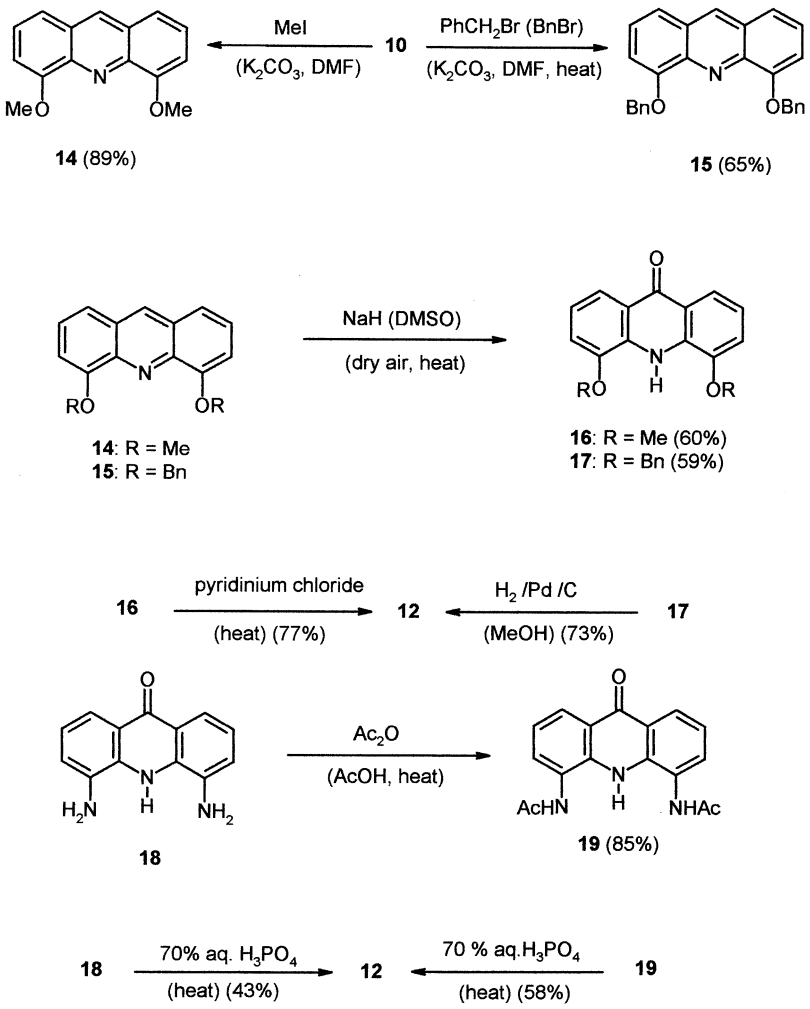


Scheme 2. Preparation of new acridono ligand **2** from 4,5-dihydroxyacridine-9(10*H*)-one (**12**) and its transformation to novel thioacridono-18-crown-6 ether **3**.

In connection with the present research the pyridono- and thiopyridono-18-crown-6 type ligands **4**–**9** (see Fig. 1) should also be mentioned. The latter macrocycles were prepared and studied by Bradshaw and coworkers.[11–16]

Acridono- and thioacridono-18-crown-6 ligands **2** and **3** seem to have several advantageous features compared to their pyridono and thiopyridono analogues **4**–**9**. The acridone and thioacridone tricyclic units make the 18-crown-6 framework more rigid conferring higher selectivity in the molecular recognition process.[17,18] Acridone and thioacridone derivatives have attractive coloration, crystallinity and strong fluorescence.[19–26] The aromatic rings of the acridone unit readily undergo electrophillic substitution[19,20] and by introducing appropriate substituents into them, the tautomerism,[27] the acidity of the NH proton,[19,20] the complexation properties, the chemistry[19,20] and the photophysical behaviour of ligand **2** can favourably be altered. Acridone derivatives can also be converted simply to chloroacridines[19,20,28–31] which readily undergo nucleophilic substitution and other reactions[19,20,28–31] creating scope for the preparation of interesting and useful host molecules. Exploitation of the above-mentioned advantages and also the complexation studies of ligands **2** and **3** with selected cations are in hand, and the results will be reported in future publications.

In this paper the synthesis of novel acridono-, and thioacridono-18-crown-6 ligands **2** and **3**, and also the preparation of their precursors which can also be very useful building

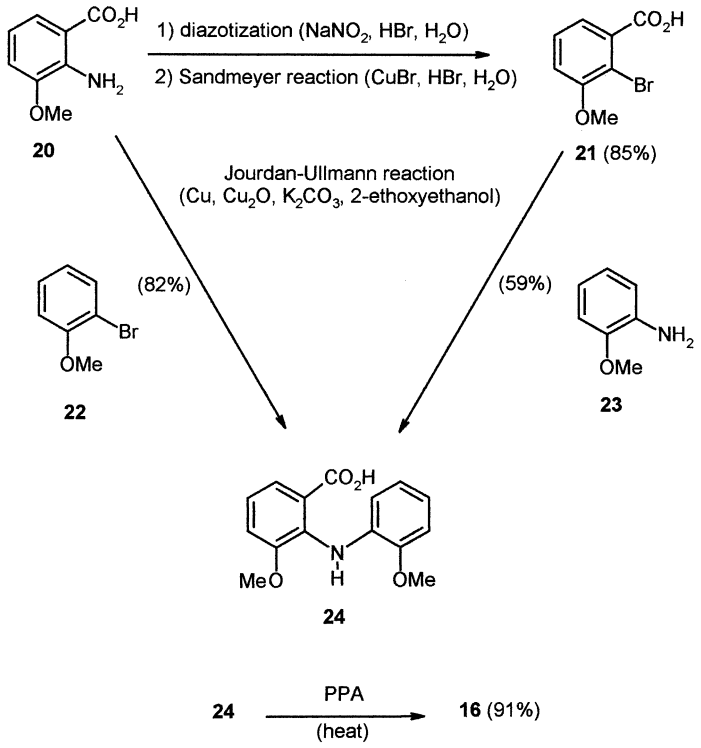


Scheme 3. Preparation of acridonediol **12** from acridinediol **10** and aminoacridone **18**, respectively.

blocks for acridine, acridone and thioacridone derivatives of chemotherapeutical importance[19,20,31–36] are reported.

2. Results and discussion

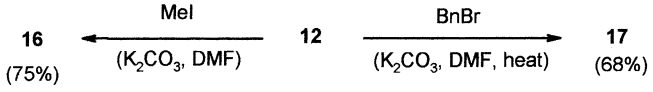
The acridono-18-crown-6 ligand (**2**) was first prepared from its acridino analogue **1** by oxidation with dry air in the presence of NaH using either THF or DMSO as a solvent (see Scheme 1). The yield in the latter case (52%) was much higher than that of in the former case (11%). Carrying out the oxidation in THF the yield did not change when we applied a dry air or dry oxygen atmosphere. Using DMSO as solvent, however, the yield was higher when we carried out the reaction under dry air than we applied a dry oxygen atmosphere, because in the latter conditions a large amount of dimethyl sulfone also formed which made the isolation procedure very difficult with loss of a considerable amount of ligand **2**. As the reported procedure to obtain acridino ligand **1** from acridine-4,5-diol (**10**) and tetraethylene glycol di-*p*-tosylate (**11**) using potassium *tert*-butoxide as base in THF gave only 16% yield[8] we made some changes in the reaction conditions to improve the outcome of this direct route to the acridono crown ether **2**. The best yield for ligand **1** was obtained when we carried out the cyclisation in the presence of K_2CO_3 in DMF at 50°C and when we isolated and purified the potassium tosylate complex of ligand **1** by crystallisation. The free ligand **1** was obtained by decomplexing the product by chromatography on alumina. In the latter case the overall yield of ligand **1** calculated for acridinediol **10** and ditosylate **11** reached 41%. We found that ditosylate **11** also cyclises with 4,5-dihydroxyacridine-9(10*H*)-one (**12**) in similar reaction conditions to those with acridine-4,5-diol (**10**) giving a reasonable yield (45%) of acridone ligand **2** (see Scheme 2). New acridono ligand **2** was transformed to its thioacridono analogue **3** using Lawesson's Reagent (**13**, see Scheme 2) in a similar manner to that reported[14] for the preparation of thiopyridono-18-crown-6 ethers (**7**–**9**, see Fig. 1) starting from their pyridono analogues **4**–**6** (see Fig. 1). Although the ^{1}H- and ^{13}C NMR spectra of 4,5-dihydroxyacridine-9(10*H*)-one (**12**) are reported[37] its preparation is described only in a PhD dissertation[38] which is not readily available. As we were fully convinced that acridonediol **12** is not only the best precursor for acridono ligand **2**, but it can also be a very useful building block for acridine and acridone derivatives of photophysical,[21–26,39] and pharmacological[19,20,32–36,40–44] importance, we devoted a lot of effort to its synthesis and regioselective alkylation. It was shown above that acridino ligand **1** can be oxidised using NaH in DMSO under air.



Scheme 4. Preparation of 4,5-dimethoxyacridine-9(10*H*)-one (**16**) from 2-amino-3-methoxybenzoic acid (**20**).

Keeping this in mind we first prepared 4,5-dimethoxyacridine (**14**) and 4,5-dibenzyloxyacridine (**15**) by alkylation of acridinediol **10** with methyl iodide and benzyl bromide, respectively, then oxidised acridines **14** and **15** to dimethoxyacridone **16** and dibenzyloxyacridone **17** (see Scheme 3) in the same manner as mentioned above for the preparation of acridono ligand **2** from acridino ligand **1**. Dimethoxyacridine[45] **14** and dimethoxyacridone[28,45] **16** are known compounds, but they were previously prepared by different procedures. The synthesis of dibenzyloxyacridine **15** and dibenzyloxyacridone **17**, however, to our knowledge has not been reported. Cleavage of the *O*-methyl group using pyridinium chloride at elevated temperature and the removal of *O*-benzyl group by hydrogenation at room temperature, respectively afforded acridonediol **12**. 4,5-Diaminoacridone (**18**) and its di-*N*-acetyl derivative **19** are also suitable precursors for the preparation of acridonediol **12**. Diaminoacridone **18** was prepared by the reported procedure.[46,47] As the purification of diamine **18** in our hands turned out to be very difficult we identified it through its di-*N*-acetyl derivative **19**. 4,5-Diacetamidoacridine-9(10*H*)-one (**19**) was prepared by heating diaminoacridone **18** with an excess of acetic anhydride in acetic acid (see Scheme 3). We note here that N-acetylation of the primary amino groups took place only at positions 4 and 5 and the NH group at position 10 remained intact. Di-*N*-acetyldiamide **19** can easily be purified by crystallisation, and was fully characterised (see Section 3). Both diaminoacridone **18** and its di-*N*-acetyl derivative **19** were converted to acridonediol **12** by heating them in 70% aqueous phosphoric acid at elevated temperature for a long time. We used this procedure successfully earlier for the transformation of 4-amino-5-methoxyacridine to acridine-4,5-diol (**10**) and 1,9-diaminophenazine to phenazine-1,9-diol, respectively.[8] Using di-*N*-acetyldiamide **19** we obtained better yield (58%, see Scheme 3) for acridonediol **12** than starting form diamine **18** (43%, see Scheme 3).

New Zealand scientists reported a procedure[28] for the preparation of dimethoxyacridone **16** and we applied that method also with some modifications and extensions to obtain acridonediol **12** (see Scheme 4). 2-Amino-3-methoxybenzoic acid (**20**) was converted by diazotisation and Sandmeyer reaction to 2-bromo-3-methoxybenzoic acid (**21**). The bromo acid **21** and *o*-anisidine (**23**) were heated in 2-ethoxyethanol in the presence of K_2CO_3, copper powder and copper(I) oxide to obtain *N*-(2-methoxyphenyl)-3-methoxyanthranilic acid (**24**). Following exactly the reported procedure[28] we obtained a low yield. Changing the reported reaction conditions systematically, we obtained the best yield when we used twice as much solvent 2-ethoxyethanol as reported, and when we carried out the reaction in the presence of copper powder and copper(I) oxide instead of copper(II) oxide.[28] Acid **24** was also prepared in a good yield when 2-amino-3-methoxybenzoic acid (**20**) and *o*-bromoanisole (**22**) were heated in



Scheme 5. Regioselective alkylation of 4,5-dihydroxyacridine-9(10*H*)-one (**12**).

2-ethoxyethanol in the presence of K_2CO_3, copper powder and copper(I) oxide (see Scheme 4). This new procedure has two advantageous features compared to the reported one:[28] the yield is higher by 23% and both starting materials (**20** and **22**) are commercially available. The latter acid (**24**) was then converted to dimethoxyacridone **16** using polyphosphoric acid (PPA) at a higher temperature and for a longer time as reported.[28]

We were interested to find out whether the regioselective alkylation observed in the case of formation of acridono crown ether **2** from ditosylate **11** and acridonediol **12** in weak basic conditions is a general phenomenon. To this end acridonediol **12** was treated with methyl iodide and benzyl bromide, respectively in similar reaction conditions (see Scheme 5) to those applied for the preparation of acridono crown ether **2** (see Scheme 2). We should note here that according to the IR, ^{1}H- and ^{13}C NMR spectra of products **16** and **17** only O-alkylation at positions 4 and 5 took place and all their physical and spectroscopic data were identical to those of acridones **16** and **17** prepared by the other methods described above.

3. Experimental

3.1. General

Infrared spectra were obtained on a Zeiss Specord IR 75 spectrometer. ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were taken on a Bruker DRX-500 Avance spectrometer in $CDCl_3$ unless otherwise indicated. Molecular weights were determined by a VG-ZAB-2 SEQ reverse geometry mass spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were taken on a Boetius micro melting point apparatus and were uncorrected. Starting materials were purchased from Aldrich Chemical Company unless otherwise noted. Silica gel 60 F_{254} (Merck) and aluminium oxide 60 F_{254} neutral type E (Merck) plates were used for TLC. Aluminium oxide (neutral, activated, Brockman I) and silica gel 60 (70–230 mesh, Merck) were used for column chromatography. Solvents were dried and purified according to well established[48] methods. Evaporations were carried out under reduced pressure unless otherwise stated.

3.1.1. 2,5,8,11,14-Pentaoxa-26-azatetracyclo[13.9.3.0.^{19,27}.0^{21,25}]heptacosa-1(25),15,17,19,21,23,26-heptaene 1. (see Fig. 1 and Scheme 1). To a well stirred mixture of finely powdered anhydrous K_2CO_3 (2.20 g, 16 mmol) and acridine-4,5-diol[8] (**10**) (844 mg, 4 mmol) in dry DMF (45 mL) was added at 0°C and under argon a solution of ditosylate[8] **11** (2.10 g, 4 mmol) dissolved in DMF (15 mL). The reaction mixture was stirred at 0°C for 15 min then warmed up to 50°C and it was stirred at this temperature for 5 days. The solvent was removed at 45°C and the residue was taken up in a mixture of ice–water (50 mL) and CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude KOTs complex of **1** was purified by recrystallisation from EtOAc to give yellow crystals (1.3 g, 56%). R_f=0.32 (alumina TLC, 18% EtOH in toluene); mp: 196–198°C; IR (KBr) ν_{max} 3080, 3056, 3000, 2920, 2896, 2872, 1628, 1568, 1460, 1408, 1364, 1320, 1272, 1256, 1232, 1216, 1192, 1120, 1048, 1040, 1024, 1016, 944, 904, 816, 744, 720, 680, 560 cm^{-1}; ^{1}H NMR δ 2.19 (s, 3H), 3.73–3.74 (m, 4H), 3.87–3.88 (m, 4H), 4.15–4.16 (m, 4H), 4.34–4.35 (m, 4H), 6.87 (d, J=7 Hz, 2H), 7.00 (d, J=7 Hz, 2H), 7.41 (t, J=8 Hz, 2H), 7.57 (d, J=8 Hz, 2H), 7.69 (d, J=7 Hz, 2H), 8.71 (s, 1H); ^{13}C NMR δ 21.34, 68.01, 68.22, 69.83, 70.80, 108.18, 121.04, 126.08, 126.17, 128.09, 128.32, 136.85, 138.74, 140.59, 144.11, 154.08. Anal. calcd for $C_{28}H_{30}NO_8SK$: C, 57.99; H, 5.22; N, 2.42. Found: C, 58.00; H, 5.25; N, 2.40. The complex was subjected to chromatography on alumina using 12% EtOH in toluene as an eluent. The free ligand **1** was recrystallised from ether–CH_2Cl_2 mixture to give **1** (610 mg, 73%) as pale yellow crystals. R_f=0.32 (alumina TLC, 18% EtOH in toluene); mp: 104–106°C (ether-CH_2Cl_2), (lit.[8] 104–106°C (ether–CH_2Cl_2)). Other physical properties and spectral data were also identical to those reported[8] for ligand **1**.

3.1.2. 2,5,8,11,14-Pentaoxa-26-azatetracyclo[13.9.3.0.^{19,27}.0^{21,25}]heptacosa-1(24),15,17,19(27),21(25),22-heptaene-20-one 2. (see Fig. 1). *Starting from crown ether* **1** *and using THF as a solvent* (see Scheme 1). To a well stirred suspension of NaH (240 mg, 6 mmol, 60% dispersion in mineral oil) in dry THF (15 mL), was added at room temperature (rt) and under dry air acridino crown ether **1** (739 mg, 2 mmol). The reaction mixture was stirred at rt for 15 min then warmed up to 50°C and it was stirred at this temperature for 5 days. Acetic acid (600 mg, 10 mmol) was slowly added to the ice-cold reaction mixture and it was stirred at 0°C for 15 min then at rt for 30 min. The solvent was removed at rt and the residue was taken up in a mixture of water (30 mL) and CH_2Cl_2 (60 mL). The aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was purified by chromatography on alumina using 12% EtOH in toluene as an eluent. The pale yellow solid was recrystallised from ethanol to give pure crystals of **2** (85 mg, 11%). R_f= 0.35 (silica gel TLC, 5% MeOH in CH_2Cl_2); mp: 184–185°C (EtOH); IR (KBr) ν_{max} 3424, 3008, 2920, 1628, 1616, 1592, 1536, 1488, 1448, 1268, 1244, 1224, 1080, 804, 748, 600 cm^{-1}; ^{1}H NMR δ 2.94 (s, broad, shifted upfield by 0.19 ppm when warming, 0.5 mol H_2O, 1H), 3.71–3.72 (m, 4H), 3.78–3.79 (m, 4H), 3.99–4.00 (m, 4H), 4.32–4.34 (m, 4H), 7.06 (d, J=8 Hz, 2H), 7.14 (t, J=8 Hz, 2H), 8.06 (d, J=8 Hz, 2H), 9.68 (s, broad, shifted upfield by 0.11 ppm when warming, NH, 1H); ^{13}C NMR δ 68.83, 69.49, 70.64, 71.54, 112.39, 118.74, 120.84, 122.25, 131.72, 147.01, 178.03; HRMS calcd for $C_{21}H_{23}NO_6$: 385.1525. Found: 385.1531; Anal. calcd for: $C_{21}H_{23}NO_6$·0.5H_2O: C, 63.95; H, 6.13; N, 3.55. Found: C, 63.86; H, 6.15; N, 3.41.

Starting from crown ether **1** *and using DMSO as a solvent* (see Scheme 1). To a well stirred suspension of NaH (240 mg, 6 mmol, 60% dispersion in mineral oil, previously washed with dry pentane under Ar) in dry DMSO (15 mL) was added at rt and under dry air, acridino crown ether **1** (369 mg, 1 mmol). The reaction mixture was stirred at rt for

15 min then warmed up to 60°C and it was stirred at this temperature for one day. Acetic acid (600 mg, 10 mmol) was slowly added to the reaction mixture at rt and it was stirred at this temperature for 20 min. The solvent was removed at 50°C and the residue was taken up in a mixture of water (20 mL) and CH_2Cl_2 (40 mL). The aqueous phase was extracted with CH_2Cl_2 (3×20 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was purified as above to give **2** (200 mg, 52%) which was identical in every respect to that prepared by the previous procedure.

Starting from acridonediol **12** (see Scheme 2). A mixture of acridonediol **12** (454 mg, 2 mmol), ditosylate[8] **11** (1.11 g, 2.2 mmol), finely powdered anhydrous K_2CO_3 (2.76 g, 20 mmol) and dry DMF (35 mL) was stirred under Ar at rt for 10 min then at 50°C for one day. The solvent was removed at 45°C and the residue was taken up in a mixture of water (60 mL) and CH_2Cl_2 (120 mL). The aqueous phase was extracted with CH_2Cl_2 (3×60 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was purified as above to give **2** (355 mg, 45%) which was identical in every respect to that prepared by the previous procedure.

3.1.3. 2,5,8,11,14-Pentaoxa-26-azatetracyclo[13.9.3.0.^{19,27}.0^{21,25}]heptacosa-1(24),15,17,19(27),21(25),22-heptaene-20-thione 3. (see Scheme 2). A mixture of acridono crown ether **2** (174 mg, 0.44 mmol), Lawesson's Reagent (**13**, 200 mg, 0.49 mmol) and dry benzene (6 mL) was stirred under Ar at rt for 10 min then at reflux temperature for 8 h. Dry CH_2Cl_2 (10 mL) was added to the cold reaction mixture and the clear solution so formed was used for preparative thin layer chromatography (silica gel, eluent for chromatography 5% MeOH in CH_2Cl_2). The product was eluted from the adsorbent using 16% MeOH in CH_2Cl_2, the solvent was removed and the red crystals were recrystallised from dry 1,2-dichloroethane to give 118 mg (64%) of pure **3**. R_f=0.55 (silica gel TLC, 5% MeOH in CH_2Cl_2); mp: 205–207°C (1,2-dichloroethane); IR (KBr) ν_{max} 3400, 3040, 2928, 2896, 2864, 1616, 1577, 1520, 1488, 1452, 1420, 1288, 1280, 1272, 1264, 1228, 1136, 1048, 944, 808, 744, 632, 560, 512 cm^{-1}; ^1H NMR (DMSO-d_6, 70°C) δ 3.27 (s, broad, H_2O, 2H), 3.67 (s, broad, 4H), 3.70 (s, broad, 4H), 3.95 (s, broad, 4H), 4.42 (s, broad, 4H), 7.33 (t, J=8 Hz, 2H), 7.43 (d, J=8 Hz, 2H), 8.41 (d, J=8 Hz, 2H), 9.84 (s, broad, NH, 1H); ^{13}C NMR (DMSO-d_6, 70°C) δ 68.35, 69.11, 69.47, 70.16, 112.57, 120.81, 122.77, 125.75, 129.66, 146.82, 197.72; HRMS. calcd for $C_{21}H_{23}NO_5S$: 401.1297. Found: 401.1297; Anal. calcd for: $C_{21}H_{23}NO_5S{\cdot}H_2O$: C, 60.13; H, 6.01; N, 3.34; S, 7.64. Found: C, 59.97; H, 6.07; N, 3.25; S, 7.82.

3.1.4. 4,5-Dihydroxyacridine-9(10*H*)-one (12). *Starting from 4,5-dimethoxyacridine-9(10H)-one* (**16**, see Scheme 3). Dimethoxyacridone **16** (4.0 g, 15.67 mmol) and pyridinium chloride (56 g) were stirred at 220°C for 2 h. The reaction mixture was mixed with water (900 mL) and stirred at 0°C for 1 h. The precipitate was filtered, washed with water (3×50 mL) and dried. The crude product was recrystallised from DMF to give pure **12** (2.97 g, 77%) as yellow crystals. R_f=0.51 (silica gel TLC, 9% MeOH in CH_2Cl_2); mp: >360°C; IR (KBr) ν_{max} 3392, 1636, 1620, 1568, 1544, 1536, 1432, 1400, 1336, 1280, 1208, 1068, 1008, 732, 540 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.41 (s, broad, H_2O, 2H), 7.09 (t, J=8 Hz, 2H), 7.18 (d, J=8 Hz, 2H), 7.70 (d, J=8 Hz, 2H), 9.07 (s, broad, NH, 1H), 10.87 (s, broad, OH, 2H); ^{13}C NMR (DMSO-d_6) δ 115.56, 115.94, 121.04, 121.33, 130.43, 145.45, 176.77; MS(EI) 227 (M^+); HRMS. calcd for $C_{13}H_9NO_3$: 227.0582. Found: 227.0585; Anal. calcd for: $C_{13}H_9NO_3{\cdot}H_2O$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.55; H, 4.58; N, 5.87.

Starting from 4,5-dibenzyloxyacridine-9(10H)-one (**17**, see Scheme 3). To a stirred mixture of finely powdered dibenzyloxyacridone **17** (1.3 g 3.19 mmol) and 10% palladium on charcoal catalyst (0.26 g) MeOH (390 mL) was added under Ar. Ar was replaced by hydrogen and hydrogenation was carried out in the usual way at rt and atmospheric pressure to give acridonediol **12** (0.77 g, 98%) which was purified as above. Pure **12** (0.57 g, 73%) was identical in every aspect to that prepared by the previous procedure.

Starting from 4,5-diaminoacridine-9(10H)-one (**18**, see Scheme 3). A mixture of finely powdered diamine **18**[46,47] (1.8 g, 8.0 mmol) and 70% (w/w) aqueous H_3PO_4 (40 mL) was stirred in an oil bath at 180°C under Ar for 20 days using a very-long-neck flask equipped with a reflux condenser. The reaction mixture was cooled to rt, poured into ice-cold water (500 mL) and its pH was adjusted to 5.0 with solid NaOAc. The precipitate was filtered, washed with water (3×30 mL) and dried. It was finely powdered and stirred with boiling MeOH (3×150 mL) for 30 min. The hot solutions were filtered and combined. The combined solution was stirred and boiled with charcoal (0.2 g) for 10 min, filtered and the solvent was removed. The crude product was recrystallised from DMF to give acridonediol **12** (0.84 g, 43%) which was identical in every aspect to that prepared by the previous procedure.

Starting from 4,5-diacetamidoacridine-9(10H)-one (**19**, see Scheme 3). Acridonediol **12** was also prepared from diacetamide **19** (2.47 g, 8.0 mmol) as described above starting from diamine **18**. Compound **12** (1.14 g, 58%) obtained this way was identical in every aspect to that prepared by the previous procedure.

3.1.5. 4,5-Dimethoxyacridine 14. (see Scheme 3). A mixture of acridine-4,5-diol[8] (**10**) (910 mg, 4.31 mmol), methyl iodide (2.45 g, 1.07 mL, 17.26 mmol), finely powdered anhydrous K_2CO_3 (5.94 g, 43 mmol) and pure and dry DMF (38 mL) was stirred under Ar at rt for one day. The solvent was removed at 40°C and the residue was taken up in a mixture of water (80 mL) and CH_2Cl_2 (100 mL). The aqueous phase was extracted with CH_2Cl_2 (3×40 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was recrystallised from MeOH to give **14** (3.68 g, 89%) as pale yellow crystals. R_f=0.68 (silica gel TLC, 5% MeOH in CH_2Cl_2); mp: 197–198°C; (lit.[45] mp: 195–196°C (aqueous EtOH)); IR (KBr) ν_{max} 3180, 3130, 3070, 3050, 2960, 2950, 2930, 2880, 2850, 2840, 1715, 1620, 1560, 1460, 1435, 1400, 1360, 1320, 1270, 1125, 1080, 970, 910, 860, 740, 710 cm^{-1}; ^1H NMR δ 4.12 (s, 6H), 7.02 (d, J=7 Hz, 2H), 7.47 (t, J=8 Hz, 2H), 7.57 (d, J=8 Hz,

2H), 8.75 (s, 1H); ^{13}C NMR δ 56.11, 106.58, 119.67, 126.50, 127.98, 136.21, 140.63, 155.35.

3.1.6. 4,5-Dibenzyloxyacridine 15. (see Scheme 3). A mixture of acridine-4,5-diol[8] (**10**) (1.32 g, 6.25 mmol), benzyl bromide (2.67 g, 1.86 mL, 15.63 mmol), finely powdered anhydrous K_2CO_3 (8.64 g, 62.5 mmol) and dry DMF (55 mL) was stirred under Ar at rt for 10 min then at 50°C for 2 days. The solvent was removed at 45°C and the residue was taken up in a mixture of ice–water (100 mL) and CH_2Cl_2 (120 mL). The aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent was removed. The crude product was recrystallised from toluene to give **15** (1.59 g, 65%) as pale yellow crystals. R_f=0.64 (silica gel TLC, 5% MeOH in CH_2Cl_2); mp: 152–153°C (toluene); IR (KBr) ν_{max} 3070, 3030, 3010, 2950, 2920, 2880, 1620, 1595, 1580, 1550, 1470, 1460, 1440, 1400, 1380, 1310, 1270, 1180, 1120, 1080, 1060, 900, 830, 720, 690 cm^{-1}; ^{1}H NMR δ 5.45 (s, 4H), 7.13 (d, J=8 Hz, 2H), 7.36–7.39 (m, 6H), 7.44 (t, J=8 Hz, 2H), 7.59 (d, J=8 Hz, 2H), 7.66–7.67 (m, 4H), 8.70 (s, 1H); ^{13}C NMR δ 71.10, 109.16, 120.32, 126.25, 127.51, 127.75, 128.09, 128.67, 135.46, 137.33, 141.64, 155.10. Anal. calcd for: $C_{27}H_{21}NO_2$: C, 82.84; H, 5.41; N, 3.58. Found: C, 82.68; H, 5.52; N, 3.56.

3.1.7. 4,5-Dimethoxyacridine-9(10*H*)-one (16). *Starting from 4,5-dimethoxyacridine* (**14**, see Scheme 3). Dimethoxyacridone **16** was prepared from dimethoxyacridine **14** (957 mg, 4 mmol), NaH (960 mg, 24 mmol, 60% dispersion in mineral oil) and dry DMSO (25 mL) as described above for obtaining acridono crown ether **2** starting from acridino ligand **1**. The crude product was recrystallised from glacial acetic acid to give **16** (613 mg, 60%) as pale yellow crystals. R_f=0.75 (silica gel TLC, 5% MeOH in CH_2Cl_2); mp: 277–278°C (AcOH); (lit. mp: 268–269°C (DMF–H_2O)[28], 274–275°C (EtOH)[45]); IR (KBr) ν_{max} 3440, 3064, 2984, 2944, 2872, 2840, 1628, 1616, 1596, 1536, 1488, 1472, 1448, 1408, 1376, 1272, 1224, 1076, 968, 824, 744, 576, 536, 528 cm^{-1}; ^{1}H NMR δ 4.05 (s, 6H), 7.08 (d, J=8 Hz, 2H), 7.17 (t, J=8 Hz, 2H), 8.06 (d, J=8 Hz, 2H), 9.11 (s, broad, shifts to a great extent by warming, NH, 1H); ^{13}C NMR δ 56.21, 111.48, 118.48, 120.93, 122.02, 131.29, 147.61, 178.04.

Starting from N-(2-methoxyphenyl)-3-methoxyanthranilic acid (**24**, see Scheme 4). Acid **24** (4.87 g, 17.82 mmol) was stirred in PPA (67 g) under Ar at 125°C for 2 h. Then the warm reaction mixture was slowly poured into vigorously stirred warm water (670 mL) and the resulting slurry was stirred for 30 min. The mixture was kept in an ice-water bath for 2 h, and then filtered. The crude product was washed with water (3×40 mL), dried, and it was purified as above to give **16** (3.68 g, 91%) which was identical in every respect to that prepared by the previous procedure.

Starting from acridonediol **12** (see Scheme 5). Dimethoxyacridone **16** was also prepared from acridonediol **12** (1.06 g, 4.31 mmol) as described above for obtaining 4,5-dimethoxyacridine (**14**) starting from acridinediol **10**. The reaction was completed at rt in 16 h. The crude product was purified as above to give **16** (825 mg, 75%) which was identical in every respect to that prepared by the previous procedure.

3.1.8. 4,5-Dibenzyloxyacridine-9(10*H*)-one (17). *Starting from 4,5-dibenzyloxyacridine* (**15**, see Scheme 3). Dibenzyloxyacridone **17** was prepared from dibenzyloxyacridine **15** (1.57 g, 4 mmol), NaH (960 mg, 24 mmol, 60% dispersion in mineral oil) and dry DMSO (30 mL) as described above for obtaining acridono crown ether **2** starting from acridino ligand **1**. The crude product was purified by column chromatography on silica gel using 1% MeOH in CH_2Cl_2 as an eluent to give **17** (962 mg, 59%) as pale yellow solid. R_f=0.6 (silica gel TLC, 3% MeOH in CH_2Cl_2); mp: 176–178°C; IR (KBr) ν_{max} 3424, 1624, 1616, 1596, 1532, 1488, 1456, 1420, 1384, 1268, 1216, 1072, 1064, 1048, 976, 744, 696, 592 cm^{-1}; ^{1}H NMR δ 5.22 (s, 4H), 7.13–7.17 (m, 4H), 7.30–7.36 (m, 6H), 7.40 (d, J=7 Hz, 4H), 8.05–8.07 (m, 2H), 9.15 (s, broad, shifted by warming, exchangeable with D_2O, NH, 1H); ^{13}C NMR δ 71.22, 113.19, 118.95, 120.94, 122.27, 127.48, 128.46, 128.99, 131.53, 136.19, 146.76, 178.10; Anal. calcd for: $C_{27}H_{21}NO_3$: C, 79.59; H, 5.19; N, 3.44. Found: C, 79.30; H, 5.24; N, 3.70.

Starting from acridonediol (**12**, see Scheme 5). Dibenzyloxyacridone **17** was also prepared from acridonediol **12** (1.53 g, 6.25 mmol) as described above for obtaining 4,5-dibenzyloxyacridine (**15**) starting from acridine-4,5-diol (**10**). The reaction was completed at 50°C in 40 h. The crude product was purified as above to give **17** (1.73 g, 68%) which was identical in every respect to that prepared by the previous procedure.

3.1.9. 4,5-Diacetamidoacridine-9(10*H*)-one 19. (see Scheme 3). To a vigorously stirred mixture of 4,5-diaminoacridine-9(10*H*)-one[46,47] (**18**) (6.76 g, 30 mmol) in acetic acid (120 mL) was added acetic anhydride (9.19 g, 8.76 mL, 90 mmol) at 90°C. After addition, the reaction mixture was stirred for 30 min, the yellow slurry formed was cooled down to rt and the crystals were filtered. The dry crude product was recrystallised from DMF to give **19** (7.89 g, 85%) as yellow crystals. R_f=0.7 (silica gel TLC, 1:1:9:2 HCOOH/AcOH/EtOAc/H_2O); mp: >360°C; IR (KBr) ν_{max} 3419, 3328, 3274, 3127, 3008, 2949, 1711, 1668, 1624, 1565, 1525, 1519, 1461, 1426, 1357, 1328, 1264, 1202, 1027, 811, 712, 537 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 2.22 (s, 6H), 7.27 (t, J=8 Hz, 2H), 7.66 (d, J=7 Hz, 2H), 8.15 (d, J=8 Hz, 2H), 9.88 (s, 3H, broad, exchangeable with D_2O, NH protons, 3H); ^{13}C NMR δ 22.73, 120.49, 121.32, 123.28, 126.25, 129.57, 135.08, 169.34, 176.51; MS(EI) 309 (M^+), 267, 249, 225 (base peak), 169, 43; Anal. calcd for: $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.94; H, 4.97; N, 13.39.

3.1.10. 2-Bromo-3-methoxybenzoic acid 21. (see Scheme 4). To a well stirred mixture of 2-amino-3-methoxybenzoic acid (**20**) and 10% (w/w) aqueous HBr (165 g, 204 mmol) was added at −5°C a solution of $NaNO_2$ (5.0 g, 72.45 mmol) in water (50 mL) dropwise. After addition, the reaction mixture was stirred at −5°C for 10 min, and at this temperature a solution of copper(I) bromide (11.35 g, 79.12 mmol) in 48% (w/w) aqueous HBr (97.0 g, 0.575 mol) was added to it. Stirring was continued at rt for 1 h then in a hot water bath for 3 h. The mixture was cooled to 0°C, kept at this temperature for 2 h and the bromo acid **21** was filtered off. It was washed with ice-cold water (3×40 mL) and recrystallised from water to give pure **21**

(14.05 g, 85%) as white crystals. R_f=0.32 (silica gel TLC, 25% EtOH in toluene); mp: 155–156°C (H_2O); (lit.[28] mp: 154–155°C (H_2O)).

3.1.11. *N*-(2-methoxyphenyl)-3-methoxyanthranilic acid (24). *Starting from bromo acid* **21** *and o-anisidine* (**23**) (see Scheme 4). A mixture of bromo acid **21** (6.16 g, 26.66 mmol), *o*-anisidine (3.48 g, 28.26 mmol), finely powdered anhydrous K_2CO_3 (3.68 g, 26.63 mmol), copper powder (40 mg), copper(I) oxide (40 mg) and dry 2-ethoxyethanol (16 mL) was stirred vigorously under Ar at rt for 10 min, then the temperature was raised to 140°C and it was stirred at this temperature for 1 h. The solvent was removed at 50°C and the residue was taken up in a mixture of ether (200 mL) and 0.5% (w/w) aqueous NaOH (250 g). The aqueous phase was extracted with ether (2×150 mL) and the ethereal phases were discarded. Charcoal (1.0 g) was added to the aqueous solution, boiled for 10 min, filtered, then cooled to 0°C in an ice-water bath. Precipitation with AcOH gave acid **24** which was washed with ice-cold water (3×50 mL) and dried. Crystallisation of the crude product from toluene gave pure **24** (4.3 g, 59%) as yellow crystals. R_f=0.30 (silica gel TLC, 2% MeOH in CH_2Cl_2); mp: 176–177°C (toluene) (lit.[28] mp: 169–170°C (aqueous EtOH)); IR (KBr) ν_{max} 3360, 3050, 3010, 2936, 2840, 1672, 1600, 1524, 1456, 1440, 1432, 1328, 1264, 1172, 1116, 1064, 1024, 920, 744, 536 cm^{-1}; ^1H NMR δ 3.74 (s, 3H), 3.97 (s, 3H), 6.41 (d, J=8 Hz, 1H), 6.75–6.78 (m, 1H), 6.91–6.96 (m, 2H), 7.15 (d, J=8 Hz, 1H), 7.32 (t, J=8 Hz, 1H), 7.90 (d, J=8 Hz, 1H); ^{13}C NMR δ 56.06, 56.27, 110.64, 115.90, 116.42, 120.95, 122.39, 123.77, 126.62, 132.11, 134.23, 149.45, 154.72, 168.04.

Starting from methoxyanthranilic acid **20** *and o-bromoanisole* (**22**, see Scheme 4). A mixture of methoxyanthranilic acid **20** (4.60 g, 27.52 mmol), *o*-bromoanisole (**22**) (5.66 g, 30.27 mmol), finely powdered anhydrous K_2CO_3 (3.68 g, 26.63 mmol), copper powder (40 mg), copper(I) oxide, (40 mg), and pure and dry 2-ethoxyethanol (16 mL) was stirred vigorously under Ar at rt for 10 min, then the temperature was raised to 140°C and it was stirred at this temperature for 2 days. The reaction mixture was worked up, and the crude product was purified as described above to give **24** (6.17 g, 82%) which was identical in every respect to that prepared by the previous procedure.

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