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BICYCLO-BIS-INTERCALANDS : SYNTHESIS OF TRIPLY BRIDGED BIS-INTERCALANDS BASED ON ACRIDINE SUBUNITS

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Macrobicyclic receptor molecules **1-2**, *built on two triply-bridged acridine intercalating subunits, have been synthesized via an efficient procedure involving two intramolecular acetylene coupling reactions; some physico-chemical properties of these compounds are reported.*

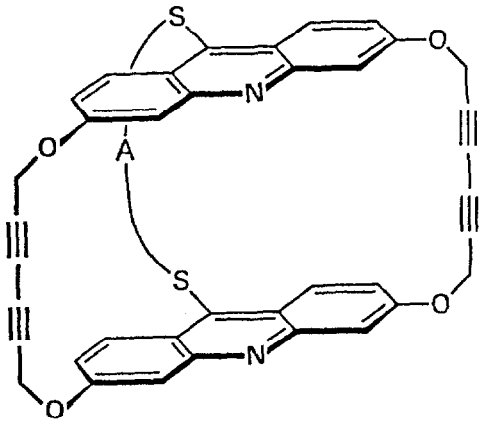
Receptor molecules based on flat subunits incorporated into a macropolycyclic structure may be expected to display molecular recognition of flat substrates. Of special interest as structural groups are the planar heterocyclic molecules that bind to double stranded nucleic acids by intercalation between base pairs[1,2] and may also interact with low molecular-weight planar species by a stacking process.

When two such subunits are incorporated into a macropolycyclic framework, receptors of (poly)*cyclo-bis-intercaland* type are obtained, that may be expected to form intercalative supramolecular structures by face-to-face substrate inclusion. Consequently, they should be able to effect molecular recognition of flat substrate molecules and might present selective binding properties towards nucleic acids. Since the heterocyclic dye molecules also possess a variety of photochemical and electrochemical properties, they may endow the cyclointercaland receptors with the ability to perform electro- or photoinduced reactions on the bound substrate species. We have reported earlier the synthesis and some properties of macrocycles containing one or two intercaland groups derived from porphyrin[3], 2,7-diazapyrene[4] or phenazine[5] units.

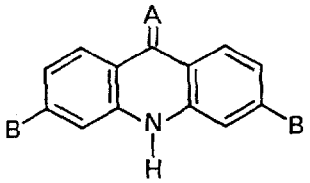
We now describe a general and efficient pathway for the synthesis of several members **1-2** of a novel class of macrobicyclic bis-intercalands resulting from the triple bridging of two acridine type subunits. Receptors containing triply bridged naphthalene groups have been obtained and shown to bind substrates such as phenol[6]. Macropolycycles containing one or two porphyrin units[3] display selective photoinduced cleavage reactions of nucleic acid molecules[7].

Synthesis of the Bicyclo-bis-intercalands 1 Based on 3,6-Dihydroxy-9-mercapto-acridine Subunits

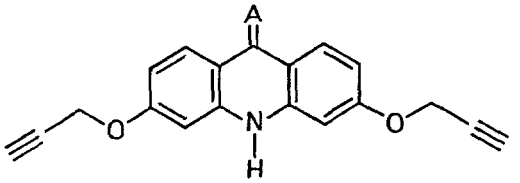
3,6-Dihydroxy-(10H)-acridine-9-one **3** was propargylated by stirring (55°, 24h) in dimethylformamide (DMF) in presence of $ClCH_2CCH$ (2 eq.) and Cs_2CO_3 (2 eq.) giving compound **4** (m.p. > 260°; 94% yield). Treatment of **4** with P_4S_{10} (0.5 eq.) in HMPT (10 ml/g. of **4**; 110°, 4h) yielded the acridine-thione **5** (m.p. > 260°; 95% yield). A biphasic mixture consisting of **5** (2.2 eq.), 1,6-dibromohexane (1 eq.), butanone (50 ml/g. of **5**) and aqueous KOH (25%; 25 ml/g. of **5**)[8] was stirred at room temperature (2.5 h), giving the bis-acridine compound **6a** (m.p.: 205°(d); 95%



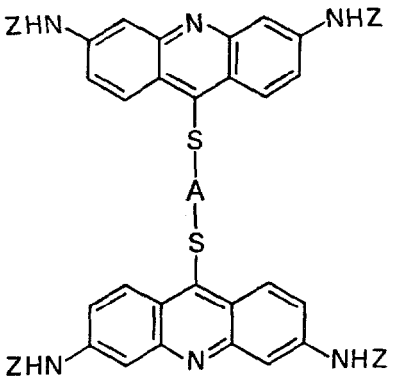
1a A= -$(CH_2)_6$-
1b A= -$CH_2CH_2OCH_2CH_2$-
1c A = -$CH_2CH_2OCH_2CH_2OCH_2CH_2$-
1a-Me_2^{2+} A = -$(CH_2)_6$-; bis-NCH_3^+



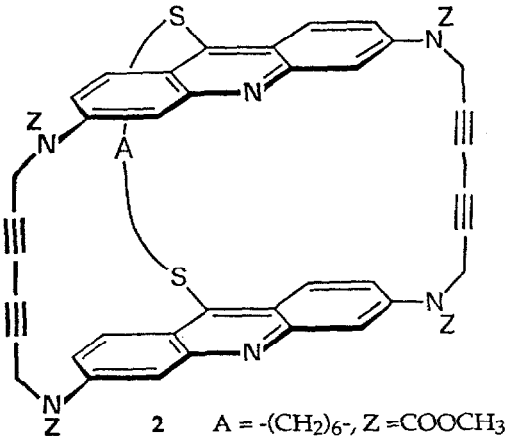
3 A=O, B=OH
7 A=O, B=NH_2
8 A=S, B=NH_2



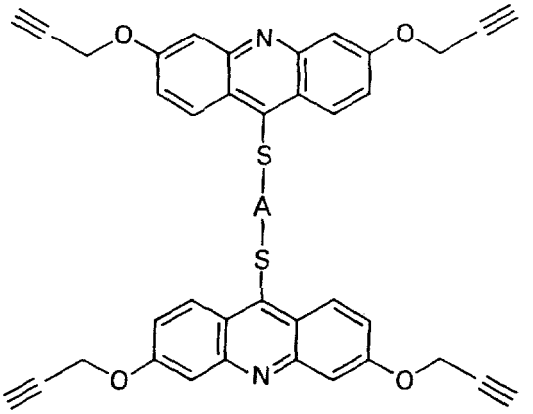
4 A=O
5 A=S



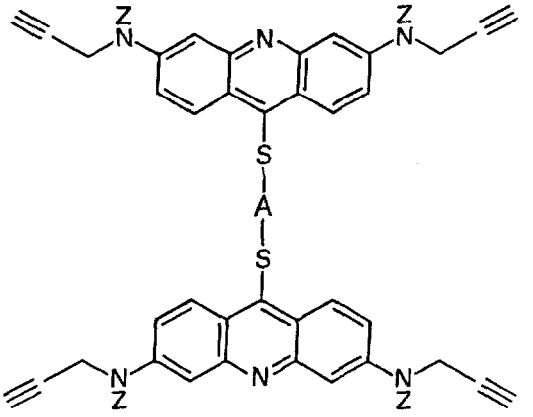
9 A =-$(CH_2)_6$-, Z=H
10 A = -$(CH_2)_6$-, Z=$COOCH_3$



2 A = -$(CH_2)_6$-, Z =$COOCH_3$



6a A = -$(CH_2)_6$-
6b A = -$CH_2CH_2OCH_2CH_2$-
6c A = $CH_2CH_2OCH_2CH_2OCH_2CH_2$-
6d half of **6a** with A = $CH_2CH_2CH_3$
6a-Me_2^{2+} A = -$(CH_2)_6$-; bis-N-CH_3^+



11 A =-$(CH_2)_6$-, Z =$COOCH_3$

yield). Alkylation of **5** (2.2 eq.) with 1,5-diiodo-3-oxapentane[9] (1 eq.) or diethyleneglycol ditosylate[10] (1 eq.) (NaH, THF, RT, 24h) afforded respectively the bis-acridine molecules **6b** (m.p.: 90°; 52% yield) or **6c** (m.p.: 80°; 66%).

Oxidative coupling of compounds **6a, 6b, 6c** with copper(II) acetate[11] produced high yields of the corresponding macrobicyclic compounds **1a, 1b, 1c**, whereas in similar conditions **4** did not give the expected macrocyclic product. Cyclisation was performed as follows. A solution of **6** in pyridine (about 500 ml/g. of **6**) was added dropwise over 45-50h and under nitrogen atmosphere, to a solution of $Cu(OAc)_2.H_2O$ (9 eq.) in pyridine (about 120 ml/g. of $Cu(OAc)_2.H_2O$) heated to 60° and with vigorous stirring. Two further portions of $Cu(OAc)_2.H_2O$ (about 2 eq.) were added in the course of the addition. The mixture was stirred for two additional hours. Work-up (evaporation of the solvent, addition of water, extraction with $CHCl_3$) gave the macrobicyclic compounds **1**, which were recrystallized from hot $CHCl_3$: **1a** (yellow crystals containing one molecule of $CHCl_3$ per molecule of **1a**; m.p. > 260°(d); 58% yield); **1b** (yellow powder, m.p.:> 260°(d) 60% yield); **1c** (yellow powder, m.p. > 260°(d); 60% yield).

N-methylation of **1a** and **6a** was performed by treatment with $CF_3SO_3CH_3$ (3 eq.) in 1,2-dichloroethane (reflux, 3h) giving **1a-Me$_2^{2+}$**, 2 $CF_3SO_3^-$ and **6a-Me$_2^{2+}$**, 2 $CF_3SO_3^-$ in 62 and 69% yield respectively.

Synthesis of the Bicyclo-bis-intercaland 2 Based on 3,6-Diamino-9-mercapto-acridine Subunits

Treatment of the 3,6-diamino-acridinone **7** with P_4S_{10} (0.5 eq.; HMPT, 115°, followed by TLC) gave **8** (m.p. > 190°(d); 39% yield) which on reaction with 1,6-dibromohexane (0.45 eq.) in a biphasic medium (30% aqueous KOH, butanone; at reflux under N_2 for about 5h) gave the bis-acridine **9** as an orange coloured solid (m.p.> 260°(d); 68% yield). Treatment of **9** with $ClCOOCH_3$ (30 eq.) in pyridine (RT, 24h) afforded **10** (m.p.> 200°(d); 72% yield). Reaction of **10** with NaH (4.4 eq., DMF, RT, 1h) followed by addition of $ClCH_2CCH$ (55°, 24h, under N_2) gave the tetra-propargyl compound **11** (m.p.> 110°(d); 62% yield). Double cyclisation of the latter in high dilution conditions (13.5 eq. $Cu(OAC)_2.H_2O$, 60°, 50h, under nitrogen) by the same procedure as above, gave after work-up the macrobicyclic bis-acridine **2** as a yellow-orange powder in about 83% yield (m.p.> 200°(d)).

The structure of all new compounds is in agreement with their spectral (proton and carbon-13 NMR; FAB$^+$ mass) and microanalytical properties.

Structural and Physicochemical Properties of Bicyclo-bis-intercalands 1-2

Compounds **1** and **2** are macrobicyclic molecules of a box-type structure, based on two flat walls of rectangular shape, maintained by two rigid diacetylenic bridges and a more flexible third bridge. The slot-like molecular cavity thus defined is accessible from one side for potential insertion of flat substrates of suitable size. The separation of the side-walls may be estimated to about 4Å (i.e. about 7.4 Å ring-to-ring distance), which is compatible with the van der Waals thickness of aromatic species (3.4 Å). The structural features of molecules **1** and **2** lead to special spectral properties.

The *proton NMR spectra* (200 MHz; $CDCl_3$) of the macrobicycles **1-2** display some special features. Whereas the O-CH2-C≡ protons are equivalent in the acyclic compounds **6a-6c** they become non-equivalent in the cyclized compounds **1** displaying an AB pattern in **1a** (δ_A = 4.95,

δ_B = 5.00 ppm; J = 16.9 Hz) and in **1c** (δ_A = 4.98, δ_B = 5.05 ppm; J = 16.5 Hz). The CH_2 protons of the S-A-S bridge undergo a significant upfield shift on cyclization from 2.83, 1.37 and 1.25 ppm in **6a** to 2.59, 0.83 and 0.54 ppm in **1a** respectively for -S-$(CH_2)_6$-S-. The high field position of the central -$(CH_2)_4$- signals is remarkable and may be attributed to shielding by the heterocyclic units, indicating that the chain is located close to them, reaching to some extent into the molecular cavity. Similarly, the two SCH_2CH_2O triplets of **1b** and the CH_2CH_2O signals of **1c** are shifted upfield by about 0.3-0.4 ppm with respect to **6b** and **6c**. Finally, analogous features are found in the spectrum of **2** with an N-CH_2-C≡ AB pattern (δ_A = 4.63, δ_B = 4.94 ppm; J = 18.1 Hz) and upfield shifted signals for the central -$(CH_2)_4$- protons. The bis-N-methylated derivatives **1a-Me$_2^{2+}$** and **6a-Me$_2^{2+}$** display similar NMR spectroscopic features ($CF_3SO_3^-$ anions; DMSO-d_6 solution) with upfield shifted signals for the central -$(CH_2)_4$- protons of the -$(CH_2)_6$- bridge ($\Delta\delta$ ~ 0.2-0.3 ppm) and an AB pattern for the OCH_2C≡ protons (δ_A = 5.54, δ_B = 5.69 ppm; J_{AB} = 17.1 Hz).

The *electronic absorption spectrum* of **1a** (λ_{max} = 376 nm, ε = 33 900, $CHCl_3$) is unshifted but its absorption coefficient is decreased with respect to **6a** (λ_{max} = 376 nm, ε = 39 300, $CHCl_3$), which itself corresponds to twice the model compound **6d** bearing $SCH_2CH_2CH_3$ in position 9 (obtained from **5** + $CH_3CH_2CH_2Br$; λ_{max} = 376 nm; ε = 19 100, $CHCl_3$). The hypochromic effect observed in **1a** with respect to the non-cyclic compounds is in agreement with stacking interaction between the two heterocyclic subunits.

The *fluorescence spectra* (in $CHCl_3$) show a decrease of emission intensity by a factor of 2 from the model compound **6d** to **6a** (despite the presence of two acridine groups in the latter) and a further large drop in intensity by a factor of about 10 from **6a** to **1a**. The corresponding excitation spectra contain a band at 381 nm for **6d** that splits in **6a** and **1a**, into two bands whose separation increases from **6a** (368.5 and 389.5 nm) to **1a** (353 and 395.5 nm). These spectral effects may again be related to the stacking of the two dye subunits.

Further synthetic work as well as studies on the physico-chemical and substrate binding properties of **1, 2** and their cationic derivatives are in progress[12].

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