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SYNTHESIS OF POLYAMINO AMIDO DERIVATIVES OF ETHIDIUM

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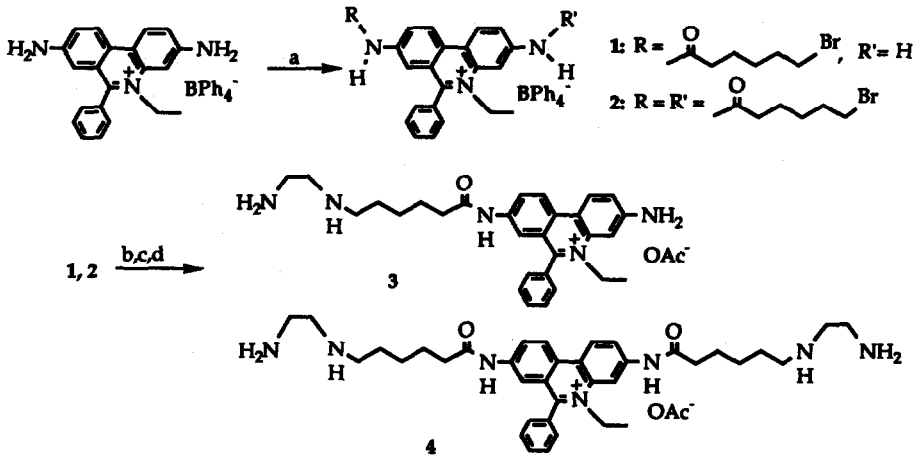
Abstract. The tetraphenylborate salt of ethidium was prepared and allowed to react with acid chlorides, followed by amines, to yield polyamino amido derivatives.

The combination of two or more DNA binding functionalities in a single molecule is currently a subject of considerable interest. Intercalators such as ethidium have been linked to other intercalators,[1] oligonucleotides,[2] and metals[3] to create molecules that cooperatively utilize the features of both DNA binding moieties. In conjunction with studies of intercalators linked to antitumor active platinum complexes,[4] we have devised methods for modifying ethidium and used them to synthesize two novel polyamino derivatives. These compounds combine the intercalative properties of ethidium with the groove binding features of spermine and also have the potential to bind metal ions.

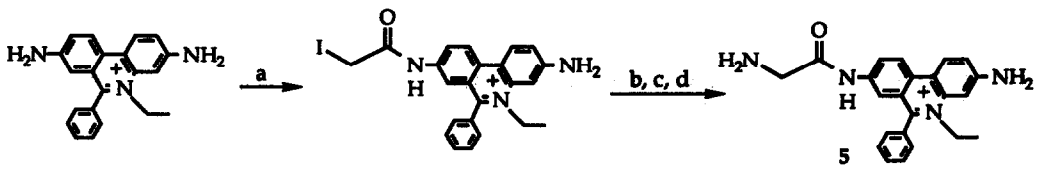


Conditions. (a) 6-Bromohexanoyl chloride, THF, 0 °C. (b) Excess ethylenediamine, methanol, reflux. (c) Tetraethylammonium chloride in methanol, followed by carboxymethylcellulose cation exchange chromatography. (d) HPLC , C18 reverse phase column, eluting with acetonitrile/0.1 M NH_4OAc gradients.

Commercially available ethidium bromide was converted to its tetraphenylborate salt. Addition of sodium tetraphenylborate to an aqueous ethidium bromide solution caused immediate precipitation of ethidium tetraphenylborate, which was collected by filtration and dried. Ethidium tetraphenylborate prepared in this manner could then be modified with reagents incompatible with protic solvents such as water or alcohols.

This strategy was employed to synthesize polyamino derivatized ethidium. Specifically, reaction of ethidium tetraphenylborate with one equivalent of 6-bromohexanoyl chloride produced a mixture of mono- and disubstituted amido compounds **1** and **2**. Subsequent reaction of this mixture with an excess of ethylenediamine quantitatively yielded the corresponding tethered ethylenediamine derivatives. Cation exchange to obtain the chloride salts of the mixture, followed by HPLC purification, afforded pure **3** and **4** as very hygroscopic acetate salts in 65% and 20% yields, respectively.[5] Alternatively, **2** was formed in 82% yield by an identical procedure but employing two equivalents of the acid chloride.

We have also prepared derivatives with shorter tethers by allowing ethidium bromide to react with iodoacetic anhydride in water (30% yield),[6] followed by quantitative conversion of the iodide to the terminal amine by the Gabriel procedure[7] to produce 3-amino-8-(2-aminoacetamido)-5-ethyl-6-phenyl-phenanthridium chloride (**5**).[8] The use of acid chlorides and anhydrous conditions, however, as described above results in better yields.



Conditions. (a) Iodoacetic anhydride, H_2O, 8 hr. (b) Potassium phthalimide, DMF. (c) Hydrazine, MeOH, reflux, 8 hr. (d) HCl, reflux, 2 hr.

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(5) (3) ^{1}H NMR (300 MHz, CD_3OD) δ 8.76 (d, H10, J 9.3 Hz) 8.74 (d, H1, J 9.8 Hz) 8.26 (dd, H9, J 9.0 Hz, ^{4}J 2.0 Hz) 7.86 (d, H7, J 2.0 Hz) 7.44 (d, H4, J 1.8 Hz) 7.42 (dd, H2, J 7.8 Hz, ^{4}J 2.0 Hz) 4.67 (q, 3H) 2.95 (q, 2H) 2.90 (q, 2H) 2.73 (t, 2H) 2.35 (t, 2H) 1.9 (s, 9H) 1.1 - 1.4 (m, 9H). high res. FABMS(+) calcd. 470.2920 obsd. 470.2922. (4) ^{1}H NMR (300 MHz, CD_3OD) δ 9.26 (d,H4, J 1.6 Hz) 9.03 (d, H1, J 9.1 Hz) 8.96 (d, H10, J 9.3 Hz) 8.43 (dd, H9, J 11.3 Hz, ^{4}J 2.3 Hz) 8.05 (dd, H2, J 8.5 Hz, ^{4}J 1.6 Hz) 7.82 (m, 3H phenyl) 7.69 (m, 2H phenyl) 4.85 (q, 3H) 2.93 (m, 8H) 2.76 (m, 4H) 2.57 (t, 2H) 2.39 (t, 2H) 1.90 (s, 3H) 1.3 - 1.9 (m, 15H). high res. FABMS(+) calcd. 626.4182 obsd. 626.4185.

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(8) ^{1}H NMR (300 MHz, CD_3OD) δ 8.80 (d, H10, J 9.1 Hz) 8.76 (d, H1, J 9.1 Hz) 8.25 (dd, H9, ^{3}J 9.3 Hz, ^{4}J 2.3 Hz) 7.88 (d, H7, J 2.0 Hz) 7.78 (m, 3 H ph) 7.65 (m, 2 H ph) 7.46 (d, H4, J 2.0 Hz) 7.6 (dd, H2, ^{3}J 2.0 Hz, ^{4}J 9.7 Hz) 4.8 (q, 2 H) 3.8 (s, 2 H) 1.6 (t, 3 H). FABMS(+) 371 (M^+).

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