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SYNTHESIS OF THIOETHER DERIVATIVES OF ETHIDIUM BROMIDE

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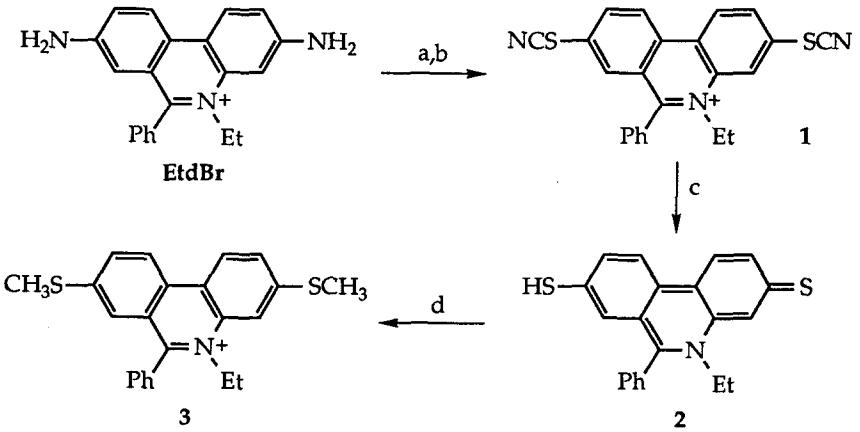
Abstract. 3,8-Dithiocyanato-5-ethyl-6-phenylphenanthridinium iodide was prepared via diazotization of ethidium bromide. Reduction with aqueous Na_2S followed by alkylation gave cationic thioether derivatives.

Complexes which intercalate into DNA have important uses in chemotherapy and molecular biology.[1,2] In conjunction with ongoing studies of metallointercalator complexes,[3] we sought to prepare intercalators with exocyclic thioether substituents for coordination to thiophilic, late transition metals. The resulting compounds and procedure are of potential value to medicinal chemists interested in intercalator based antibiotics.[4]



Conditions. (a) $NaNO_2$, HCl, 0 °C. (b) KSCN. (c) Na_2S, H_2O-acetone. (d) CH_3I.

Diazotization of the DNA intercalator EtdBr[5] was followed by reaction with KSCN to give 3,8-dithiocyanato-5-ethyl-6-phenylphenanthridinium iodide (**1**) in 76% yield after counterion exchange.[6] Reduction of **1** was complicated by the presence of the electrophilic phenanthridinium system which underwent extensive reduction with $NaBH_4$.[7] Aqueous Na_2S,[8] however, cleanly reduced the aryl thiocyanate, **1**, to give air-sensitive dithiol **2** in 63% yield.[9] Alkylation of the intermediate thiol with CH_3I gave thioether **3** in 74% isolated yield.[10]

The procedure described provides a general method for the synthesis of heterocyclic thioethers via diazotization of an aromatic amine. The use of the non-nucleophilic reductant, Na_2S, allows selective reduction of aryl thiocyanates.[11]

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(6) ^{1}H NMR (acetone-d_6) δ 9.48 (d, J=9.6 Hz, 1H, H1); 9.42 (d, J=9.0 Hz, 1H, H10); 9.11 (d, J=1.5 Hz, H4); 8.60 (dd, J=9.0, 1.4 Hz, 1H, H9); 8.44 (dd, J=8.7, 1.2 Hz, 1H, H2); 7.96 (d, J=1.4 Hz, 1H, H7); 7.94 (m, 5H, Ph); 5.17 (q, J=7 Hz, 2H, CH_2); 1.73 (t, J=7 Hz, 3H, CH_3). IR (KBr) 2161 (m) cm-1. HRMS (FAB, *m*-nitrobenzyl alcohol matrix) Calcd for $C_{23}H_{16}N_3S_2^+$: 398.0786, Obsd 398.0783.

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(9) ^{1}H NMR (CD_3OD) δ 8.39 (d, J=8.9 Hz, 1H, H1); 8.34 (d, J=8.9 Hz, 1H, H10); 8.19 (d, J=2 Hz, 1H, H4); 8.05 (dd, J=8.9, 2 Hz, 1H, H9); 7.88 (dd, J=8.9, 2 Hz, 1H, H2); 7.74 - 7.60 (m, 5H, Ph), 7.38 (d, J=2 Hz, 1H, H7); 4.63 (q, J=7 Hz, 2H, CH_2); 1.53 (t, J=7Hz, 3H, CH_3). Mass Spectrum: m/e : 347, $[m]^+$.

(10) ^{1}H NMR (DMF-d_7) δ 9.22 (d, J=8.9 Hz, 1H, H1); 9.18 (d, J=9.0 Hz, 1H, H10); 8.39 (d, J=1.5 Hz, 1H, H4); 8.28 (dd, J=8.7, 2.0 Hz, 1H, H9); 8.09 (dd, J=8.8, 1.5 Hz, 1H, H2); 7.90 (m, 5H, Ph); 7.15 (d, J=2 Hz, 1H, H7); 5.08 (q, J=7 Hz, 2H, CH_2); 2.90 (s, 3H, SCH_3); 2.50 (s, 3H, SCH_3); 1.65 (t, J=7 Hz, 3H, CH_3). HRMS (FAB, *m*-nitrobenzyl alcohol matrix) Calcd for $C_{23}H_{22}NS_2^+$: 376.1194, Obsd 376.1192.

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