Novel Synthesis of Potential Bifunctional Nucleic Acid Intercalating Agents: 1,10-Bis-(6-methyl-5*H*-benzo[*b*]carbazol-11-yl)decane

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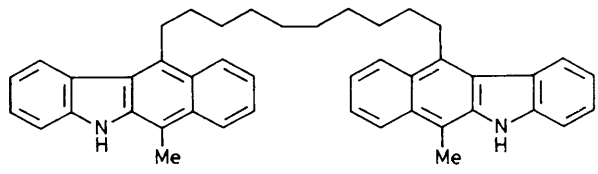
The title compound, a potential DNA bis-intercalating agent, is synthesized from the novel bis-4*H*-furo[3,4-*b*]indole (**7**) by a double Diels–Alder reaction with benzyne followed by deoxygenation and desulphonation.

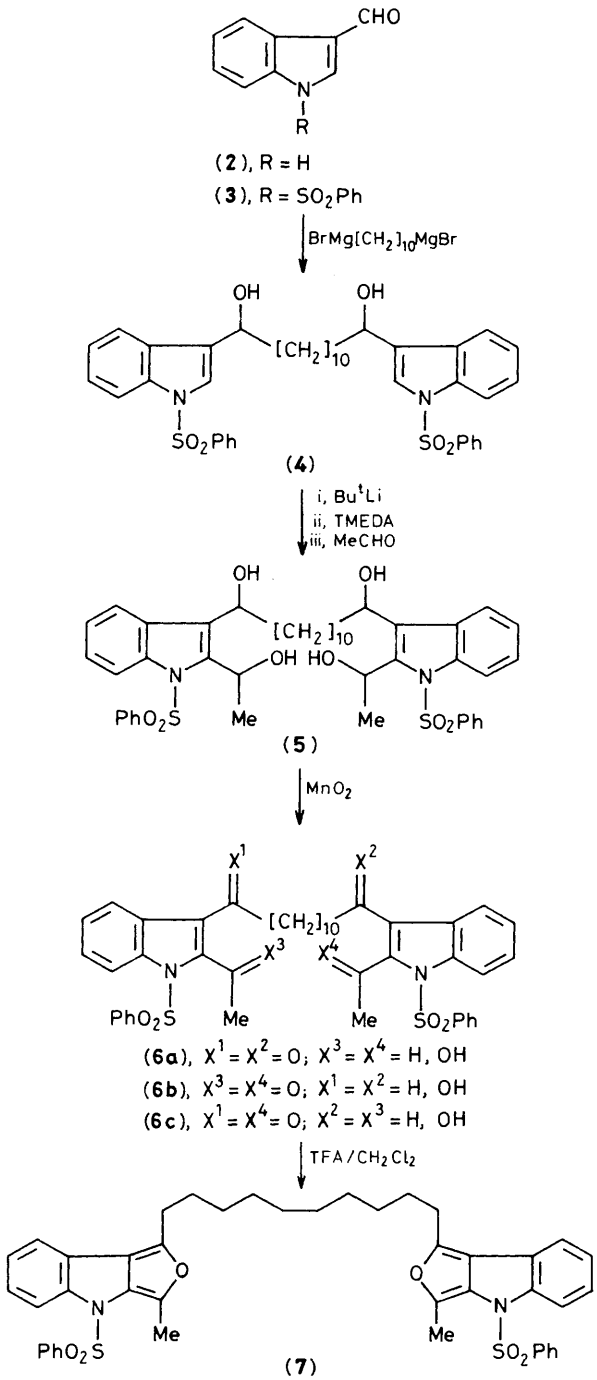
The intercalation of DNA by planar aromatic molecules appears to be an essential event in the action of many anticancer and antibiotic agents.[1] In recent years the important discovery has been made that bifunctional intercalators of a specific design can exhibit extraordinary binding affinities and sequence specificities for DNA.[2–5] For example, Dervan[4] has found that bis(methidium)spermine binds to DNA 10^6 times stronger than the monomeric intercalator ethidium bromide in a 'two-base-pair sandwich.' Kuhlmann[5] has shown that the poor antitumour activity of ethidium salts can be dramatically improved by synthesizing a double intercalating analogue, 1,10-bis(ethidium)decane.

We now describe a novel approach to the synthesis of potential bifunctional intercalating agents, exemplified herein by the preparation of the title compound (**1**). Our methodology is convergent in that the twin intercalating ring systems are constructed late in the synthesis and after the desired linking chain has been introduced. Thus, this strategy allows for the preparation of different bis-intercalators using the same intermediate [*i.e.* (**7**)].



(**1**)

Our synthesis of (**1**) is shown in Scheme 1. Commercially available indole-3-carbaldehyde (**2**) was protected as the *N*-phenylsulphonyl derivative (**3**) (m.p. 157.5—158.5 °C, lit.[6]



Scheme 1

m.p. 158—158.5 °C) in 86% yield [lithium di-isopropylamide (LDA), benzenesulphonyl chloride, tetrahydrofuran (THF), −70 °C]. Treatment of (**3**) with the bis-Grignard reagent derived from 1,10-dibromodecane (0.5 equiv.; Et_2O) gave the diol (**4**) as a mixture of diastereoisomers in 93% yield; *m/z* 712 (M^+). Double regioselective dilithiation of (**4**) (4.2 equiv. of Bu^tLi; THF; −40 → 25 °C, 45 min; then 25 °C, 2 h) followed by the addition of tetramethylethylenediamine (TMEDA) (4.2 equiv.) and then quenching with acetaldehyde (−35 °C) gave a mixture of tetraols (**5**). Without being purified, this mixture was oxidized (activated MnO_2, $CHCl_3$; reflux; 22 h) to afford a nonregioselective mixture of diastereoisomeric hydroxyketones (**6**) [ν_{max}, 3460, 1678 cm^{-1}; δ ($CDCl_3$) 2.71 (s, CH_3CO) and 2.87 (t, $-CH_2CO-$)]. This crude mixture of theoretically six compounds [4 (+), (−) pairs, 2 *meso* forms] was converted into a *single* bis-4*H*-furo[3,4-*b*]indole (**7**)† (glass) [δ ($CDCl_3$) 2.65 (s, 6H); *m/z* 760 (M^+)] after being refluxed for 1.5 h in CH_2Cl_2 containing a catalytic amount of trifluoroacetic acid (TFA). The overall yield of (**7**) from (**3**) is 9% following flash chromatography (CH_2Cl_2). The 4*H*-furo[3,4-*b*]indole ring system is new,[7] although examples of pyrrolo[8]-, thieno[9]- and selenolo-[3,4-*b*]indoles[9] are known.

Reaction of (**7**) with benzyne (2 equiv. of 2-bromofluorobenzene, Mg, THF, reflux; 4.5 h) presumably gave the twin Diels–Alder adduct which, without isolation and in the same flask, was deoxygenated[10] and desulphonated ($NaBH_4$, ethanolic aqueous NaOH, reflux; 46 h) to afford (**1**)† (m.p. 220—221 °C) in 55% yield from (**7**) after flash chromatography (1 : 1 hexane—CH_2Cl_2) [λ_{max} (EtOH) 233, 269, 297.5, 321, 335, 382, and 401 nm (log ε 4.28, 4.52, 4.34, 3.74, 3.61, 3.51, and 3.59); 300 MHz ^1H n.m.r. (C_6D_6) δ 3.70 (t, 4H) and 2.44 (s, 6H); *m/z* 600.3476 (M^+, calc. 600.3505) and 244.1134 ($C_{18}H_{14}N$, calc. 244.1126)]. Although the overall yield of (**1**) from (**3**) thus far is only 5%‡ the entire sequence can be carried out in a week and requires only two simple chromatographic purifications.

We are currently exploring the versatility of (**7**) in the synthesis of other potential bis-intercalators (*e.g.*, bis-ellipticines) and the extension of the methodology to the construction of bis-4*H*-furo[3,4-*b*]indoles linked at C-3.

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† The structure of this new compound is fully supported by spectral and analytical (high-resolution mass spectrometry and/or combustion) data.

‡ We believe that the low-yield step is the cyclodehydration, (**6**)→(**7**), and we are currently trying to improve this conversion.