Synthesis and calculated properties of some 1,4-bis(amino)anthracene-9,10-diones

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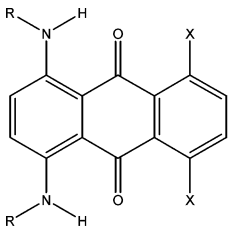
The synthesis of a number of 1,4-bis(amino)anthracene-9,10-diones containing chlorine or sulfur which are related to the anti-cancer drugs Ametantrone and Mitoxantrone are reported. 1,4-Dichloro-2,3-dihydro-5,8-dihydroxyanthracene-9,10-dione reacts readily with a series of alkylamines to yield the corresponding 1,4-bis(alkylamino)-5,8-dichloroanthracene-9,10-dione after oxidation. The subsequent reaction of the products with ethanethiol or thiophenol gives the corresponding 1,4-bis(alkylamino)-5,8-bis(sulfanyl)anthracene-9,10-dione in good yield. Theoretical calculations at the RHF 6-31G** level indicate that the introduction of either chlorine or the phenylsulfanyl group into the 5- and 8-positions of 1,4-bis(alkylamino)anthracene-9,10-diones results in a lowering of the LUMO energies suggesting that related functionalised derivatives might have lower cardiotoxicities than Mitoxantrone.

Introduction

For well over a century substituted anthraquinones or anthracene-9,10-diones such as those based on 1,4-bis(amino)anthracene-9,10-dione (**1a**) and 1,4-bis(amino)-5,8-dihydroxyanthracene-9,10-dione (**1b**) (Fig. 1), have been used as dyes or pigments because of their high chemical, photochemical and thermal stability.[1–5] In the 1970s, however, new applications emerged for these derivatives and Murdock and Child were the first to show that the *N*-alkyl derivatives of (**1b**) were chemotherapeutically active as anti-cancer agents.[6] Subsequently it was shown that functionalised *N*-alkyl derivatives such as Ametantrone (**1c**) and Mitoxantrone (**1d**) were highly effective anti-cancer drugs with an efficacy and therapeutic index exceeding adriamycin, methotrexate, or 5-fluorouracil.[7–13] However, while the additional hydroxyl groups present at the 5- and 8-positions of Mitoxantrone (**1d**) lead to tenfold increase in its antineoplastic activity over Ametantrone (**1c**), this beneficial enhancement is unfortunately countered by a tenfold increase in its cardiotoxicity.[14] As a consequence, the effectiveness of Mitoxantrone and Ametantrone is similar at the optimal dose with the most common dose-limiting factor being myelosuppression though in most cases it is not severe or life threatening. Mitoxantrone (**1c**) is now used for the treatment of adult acute myeloid leukaemia, for symptomatic hormone-refractory prostate cancer, and multiple sclerosis (MS).[15,16] Mitoxantrone (**1d**) appears to be effective in reducing disease progression through a variety of different mechanisms of action. For example, it suppresses the proliferation of T cells, B cells, and macrophages, it impairs antigen presentation, decreases the secretion of proinflammatory cytokines and inhibits macrophage-mediated myelin degradation.[15,16]

The initial antineoplastic mode of action of both Ametantrone (**1c**) and Mitoxantrone (**1d**) almost certainly involves their intercalation into DNA which is facilitated by their planarity.[17–23] This factor alone however does not explain their high activity as other planar derivatives, such as 1,4-diaminoanthracene-9,10-dione (**1a**), are inactive and removal of the terminal hydroxyl groups on the side chain of (**1d**) leads to reduced activity.[9] Furthermore, the distance between the two side chain nitrogen atoms of (**1c**) and (**1d**) is an important factor, with two carbons providing the optimum value. The insertion of additional ethylamino groups into the side



(**1**)

a R = H; X= H
b R = H; X= OH
c R = $CH_2CH_2NHCH_2CH_2OH$; X= H
d R = $CH_2CH_2NHCH_2CH_2OH$; X= OH
e R = $CH_2CH_2CH_3$; X= Cl
f R = $CH_2CH_2CH_3$; X= SCH_2CH_3
g R = $CH_2CH(CH_3)_2$; X= Cl
h R = CH_3; X= Cl
i R = CH_2CH_2OH; X= Cl
j R = $CH_2CH_2N(CH_3)_2$; X= Cl
k R = $CH_2CH_2N(CH_2CH_3)_2$; X= Cl
l R = C_6H_5; X= Cl
m R = $CH_2CH_2CH_3$; X= SC_6H_5
n R = $CH_2CH(CH_3)_2$; X= SC_6H_5
o R = $CH_2CH(CH_3)_2$; X= SCH_2CH_3
p R = CH_2CH_2OH; X= SC_6H_5
q R = CH_2CH_2OH; X= SCH_2CH_3
r R = C_6H_5; X= SC_6H_5
s R = C_6H_5; X= SCH_2CH_3
t R = $CH_2CH_2CH_2CH_3$; X= H
u R = H; X= SCH_2CH_3

Fig. 1 Structures of 1,4-bis(alkylamino)anthracene-9,10-diones.

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chains drastically reduces activity, indicating that additional basic centres and lengthening of the side chain is undesirable. Finally the nitrogen at the centre of the side chain plays an important role in activity as no activity is found when it is replaced by a methylene group or another atom such as sulfur.[9,18]

The structures of the DNA–anthracenedione intercalation complexes[14] have been explored and established using physical techniques such as electron microscopy[24] and high field NMR spectroscopy,[21,25] and modelled using computer graphics[26–28] and *ab initio* calculations.[29] However, a second mode of action always follows the initial binding of the drug to specific base pair sites leading to the death of the cell. Historically, this final process has been attributed to nucleic acid condensations,[22,30] the formation of free radicals,[31–33] a disruption of normal DNA protein interactions during cell replication particularly an interference with the normal mode of action of topoisomerase,[34–36] and possibly reaction with glutathione *via* an enzyme-mediated process.[37] The formation of free radicals in liver microsomes from several cytotoxic alkylaminoanthracenediones, which have been detected by ESR, has suggested that the killing mode may involve radical anion intermediates formed during metabolic activation but other studies have strongly linked this behaviour to the cardiotoxicity of the drug.[38,39] In general, enzymatic reduction of anthracene-9,10-diones can either lead to the formation of a semiquinone by a one-electron reduction process or a hydroquinone by a two-electron reduction. It is well established that the semiquinone radical is capable of transferring its electron to molecular oxygen to form superoxide, a radical anion, which is now widely accepted to be the cause of the cardiotoxicity of most anthracene-9,10-diones.[40,41]

In the present studies we have attempted to synthesise a number of new 1,4-bis(alkylamino)anthracene-9,10-diones related to Ametantrone (**1c**) and Mitoxantrone (**1d**) but containing either chlorine or sulfur on the ring in an attempt to restrict the ability of the molecule to form superoxide from its radical anion and hence reduce the cardiotoxicity of the drug. In this approach we have explored two potential synthetic routes to both 1,4-bis(alkylamino)-5,8-dichloroanthracene-9,10-diones and 1,4-bis(alkylamino)-5,8-bis(sulfanyl) anthracene-9,10-diones such as (**1e**) and (**1f**) respectively starting from the readily accessible 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione using simple alkylamines as reagents and precursors to the more complex side chain present in both (**1c**) and (**1d**) (see later). In tandem we have theoretically calculated the structures and properties of some of these new 1,4-bis(alkylamino)-anthracene-9,10-diones to assess the influence of both chlorine and sulfur on their likely reduction potentials and binding characteristics.

Methods of calculation

Molecular orbital calculations were carried out on empirical structures for the anthracene-9,10-diones at the *ab initio* RHF level using the 6-31G** basis set of the GAMESS program[42] (directives: runtype optxyz, scftype direct rhf). The fully optimised structures and related crystal structures were displayed and analysed using the SYBYL Molecular Modelling package.[43] The following numbering convention was adopted for each structure (Fig. 2)

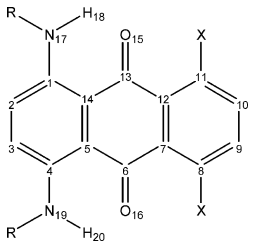


Fig. 2 Numbering convention adopted for calculations on 1,4-bis(alkylamino)anthracene-9,10-diones.

Results and discussion

The introduction of chlorine or sulfur into the aromatic ring of anthracene-9,10-diones would be expected to alter their electronic properties and exert a marked effect on their reduction potentials and hence their ability to reduce oxygen to superoxide. Superoxide can act in both an oxidising and reducing reaction by accepting or donating electrons respectively depending on its environment,[44,45] but it can only be formed if the reduction potential of the anthracene-9,10-dione radical anion is smaller (more negative) than the $O_2/O_2^{\bullet -}$ couple at −325 mV.[45] Mitoxantrone (**1d**, denoted AQ) has a reduction potential of −527 mV[46] for the couple $AQ/AQ^{\bullet -}$ and it is therefore able to reduce oxygen to superoxide [eqn (1)]:

$$AQ^{\bullet -} + O_2 = AQ + O_2^{\bullet -} \quad (1)$$

In contrast, the *O*-acetylated derivative of Ametantrone (**1c**) has a reduction potential of only −348 mV[47] and is therefore a less potent source of superoxide anion. A similar reduction potential has been reported for the related anthracyclines such as Adriamycin at −341 mV[47] but that for Daunomycin is slightly less at −305 mV.[47] Structural and substituent effects therefore play an important role, as expected, in the ability of the anthracene-9,10-diones to facilitate the formation of superoxide, but the effect of chlorine or sulfur is not known, though both 1,4-bis(alkylamino)-5,8-dichloroanthracene-9,10-diones and 1,4-bis(alkylamino)-5,8-bis(sulfanyl)anthracene-9,10-diones such as (**1e**) and (**1f**) would be expected to have different electronic properties to the parent drug which, could be potentially beneficial in terms of a reduced ability to form radical anions while still showing good binding characteristics to DNA.

Synthetic studies

In principle, 1,4-bis(alkylamino)-5,8-bis(sulfanyl)anthracene-9,10-diones such as (**1f**) can be synthesised from 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione by two routes (Fig. 3):

(1) displacement of both chlorine atoms with thiolate ions to give 1,4-dihydroxy-5,8-bis(sulfanyl) anthracene-9,10-diones, followed by subsequent reduction and amination with selected amines;

(2) reduction and subsequent amination with alkylamines to give 1,4-bis(alkylamino)-5,8-dichloroanthracene-9,10-diones followed by displacement of both chlorine atoms with thiolate ions.

The starting material, 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione (**2**), has been synthesised previously from the condensation reaction of 3,6-dichlorophthalic anhydride with benzene-1,4-diol in concentrated sulfuric acid with boric acid[48] but in

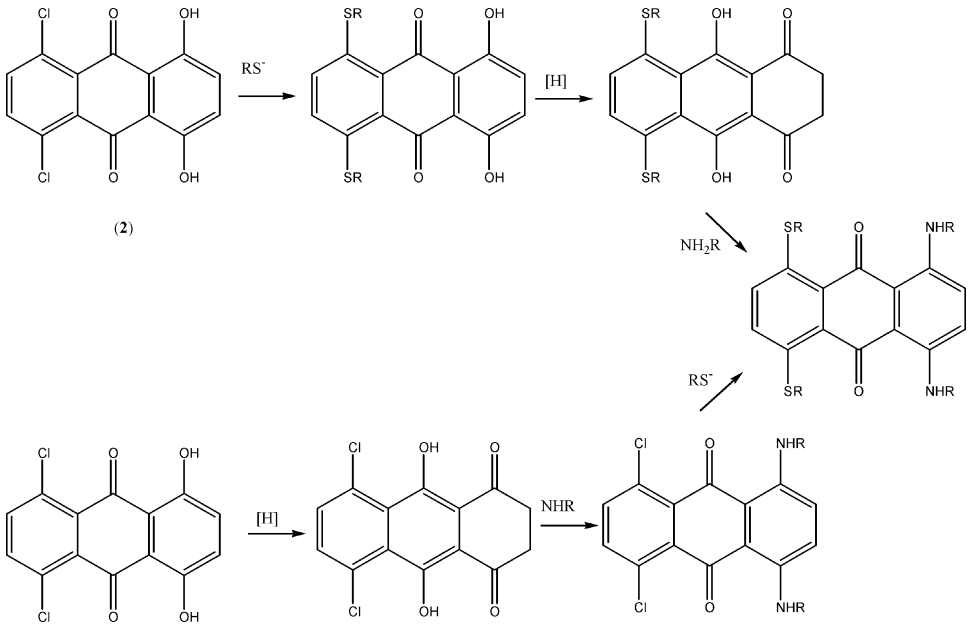
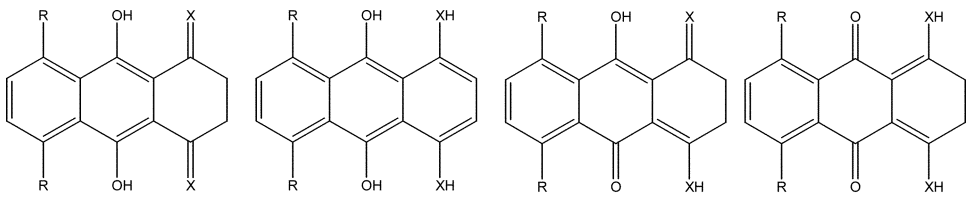


Fig. 3 Potential synthetic routes to 1,4-bis(alkylamino)-5,8-bis(sulfanyl)anthracene-9,10-diones.

these studies it was prepared by the direct chlorination of 1,4-dihydroxyanthracene-9,10-dione in 65% oleum using boric acid and iodine as catalysts.[49–52]

1. Direct reaction of 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione with thiols. Although 1,4-dichloroanthracene-9,10-dione reacts with thiophenol to yield 1,4-bis(phenylsulfanyl)anthracene-9,10-dione,[53] the attempted displacement of the chlorine atoms of 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione (**2**) with various thiols was unsuccessful either in air or under nitrogen. A reaction using sodium hydroxide and thiophenol in ethanol led only to the formation of diphenyl disulfide, and it is clear that the presence of the two electron donating hydroxyl groups or their anions results in the molecule being less reactive towards nucleophilic substitution. The use of either potassium hydroxide, sodium carbonate or potassium carbonate in place of sodium hydroxide as the base was also unsuccessful and only the starting material was recovered. In an attempt to modify the electronic properties of the starting material and facilitate the nucleophilic displacement reaction, the hydroxyl groups were methylated with dimethyl sulfate and a base of potassium carbonate in acetone using a standard procedure[54] to give 1,4-dimethoxy-5,8-dichloroanthracene-9,10-dione. However, the attempted reaction of this product with thiophenol in either ethanol, DMF or DMSO was also unsuccessful and only the starting material was recovered.

2. Reduction and amination of 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione. As the direct thiolation reactions were not successful, another pathway was sought to bypass the suspected deactivation of the molecule by the hydroxyl groups using the reduced or leuco form (**3**) of 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione (**2**). It is well established that the leuco form (**4a**) of 1,4-dihydroxyanthracene-9,10-dione reacts readily with a variety of amines, such as *n*-butylamine to form 1,4-bis(*n*-butylamino)anthracene-9,10-dione *via* the intermediate (**4b**).[55,56] While the leuco derivative (**4a**) can exist in several tautomeric forms (Fig. 4), in practice, only one



3 R = Cl ; X = O

4a R = H ; X = O

4b R = H; X = NC_4H_9

4c R = H; X = NNH_2

Fig. 4 Potential tautomers of the reduced forms of 1,4-disubstituted anthracene-9,10-diones.

tautomer, 2,3-dihydro-9,10-dihydroxyanthracene-1,4-dione (**A**), is found experimentally by NMR studies.[56] In contrast, the preferred tautomeric form of the corresponding intermediate leuco 1,4-bis(butylamino)anthracene-9,10-dione (**4b**) is thought to be 1,4-bis(butylamino)-2,3-dihydroanthracene-9,10-dione (**D**) on the basis of ^{1}H and ^{13}C NMR data in $CDCl_3$[56] (Fig. 4). However, ^{13}C NMR studies on the reduced form of 1,4-bis(hydrazino)anthracene-9,10-dione (**4c**) appears to show only the diimine, 1,4-bis(aminoimino)-2,3-dihydro-9,10-dihydroxyanthracene (**A**).[57]

The reduction of 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione (**2**) using procedures which are known to reduce 1,4-dihydroxyanthracene-9,10-dione, such as tin in acetic acid,[58] or aqueous sodium dithionite under alkaline conditions (our preferred route),[59,60] gives the leuco derivative (**3**) in yields of 64% and 96% respectively with no apparent loss of the chlorine atoms. As before, this product can in principle exist in one of the four tautomeric forms shown (see Fig. 4; R = Cl; X = O), but the ^{1}H NMR spectrum in $CDCl_3$ only shows a sharp singlet consisting of four protons at 3.0 ppm which is only consistent with 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (**3**) and structure type (**A**).

Although the corresponding reactions of 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione with amines might be complicated by side reactions involving the ring chlorine atoms, the reactions proceeded smoothly with a variety of alkylamines and few by-products were detected.

Thus 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (**3**) reacts readily with an excess of *n*-propylamine (used as a solvent) in air to yield 1,4-bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (**1e**) in 32% yield (Fig. 5). The reaction also proceeds readily in ethanol to give the same product 48% yield.

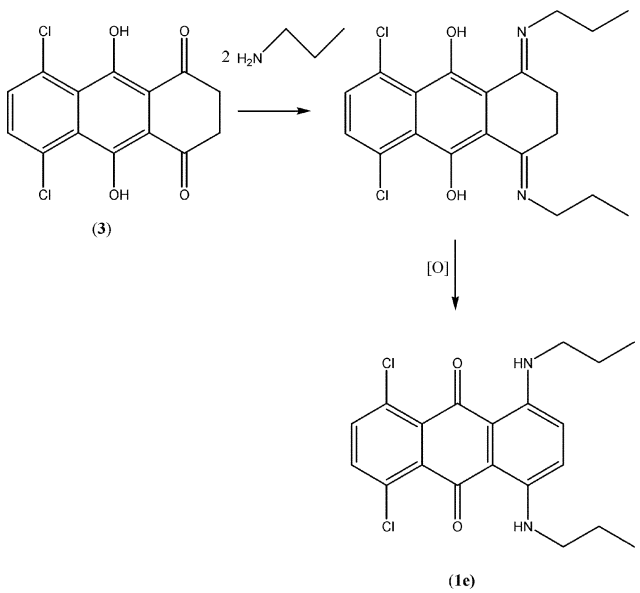


Fig. 5

A similar reaction occurs with isobutylamine in ethanol to give 1,4-bis(isobutylamino)-5,8-dichloroanthracene-9,10-dione (**1g**) in 52% yield. Methylamine (20% in water) also reacts readily with 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione to yield 1,4-bis(methylamino)-5,8-dichloroanthracene-9,10-dione (**1h**) in 43% yield. Likewise, the reaction of 2-aminoethanol with 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione in ethanol gives 1,4-bis(2-hydroxyethylamino)-5,8-dichloroanthracene-9,10-dione (**1i**) in 64% yield.

The corresponding reactions of 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (**3**) with *N*,*N*-dimethylethylenediamine and *N*,*N*-diethylethylenediamine also occur to give 1,4-bis{[2-(dimethylamino)ethyl]amino}-5,8-dichloroanthracene-9,10-dione (**1j**) and 1,4-bis{[2-(diethylamino)ethyl]amino}-5,8-dichloroanthracene-9,10-dione (**1k**) in 29% and 22% yield respectively. These reactions suggest that the side chain could be easily functionalised to contain the same [2-(β-hydroxyethylamino)ethylamino] substituents as those found in Ametantrone (**1c**) and Mitoxantrone (**1d**) though this aspect was not examined in the present studies.

The ^{1}H NMR data for all the 1,4-bis(alkylamino)-5,8-dichloroanthracene-9,10-diones shows that NH proton split into a triplet confirming that the molecules exists as tautomer (**A**) rather than tautomer (**B**) (Fig. 6).

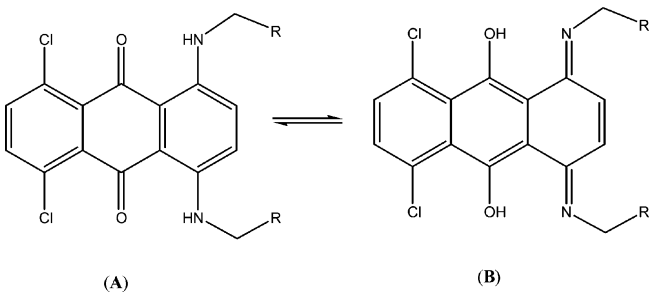


Fig. 6 Potential tautomers of 1,4-bis(alkylamino)-5,8-dichloroanthracene-9,10-diones.

The related amination of 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (**3**) with aniline was unsuccessful under similar conditions to those employed with alkylamines but the reaction did occur in ethanol when boric acid was used as a catalyst to give 1,4-bis(phenylamino)-5,8-dichloroanthracene-9,10-dione (**1l**) in 51% yield.

3. Thiolation of 1,4-bis(alkylamino)-5,8-dichloroanthracene-9,10-diones. Despite the expected deactivating effects of the alkylamino groups, the reaction of 1,4-bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (**1e**) with potassium thiophenoxide proceeded readily in refluxing ethanol during two hours to give 1,4-bis(*n*-propylamino)-5,8-bis(phenylsulfanyl)anthracene-9,10-dione (**1m**) in 41% yield (Fig. 7). The yield improves to 66% when DMF is employed as the solvent.

A similar reaction occurs with 2-ethanethiol during 2 h to yield 1,4-bis(*n*-propylamino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1f**) in 62% yield. 1,4-Bis(isobutylamino)-5,8-dichloroanthracene-9,10-dione (**1g**) also under goes thiolation with both thiophenol and 2-ethanethiol under similar conditions to yield 1,4-bis(isobutylamino)-5,8-bis(phenylsulfanyl)-anthracene-9,10-dione (**1n**) and 1,4-bis(isobutylamino)-5,8-bis(ethylsulfanyl)-anthracene-9,10-dione (**1o**) in 37% and 41% yield respectively.

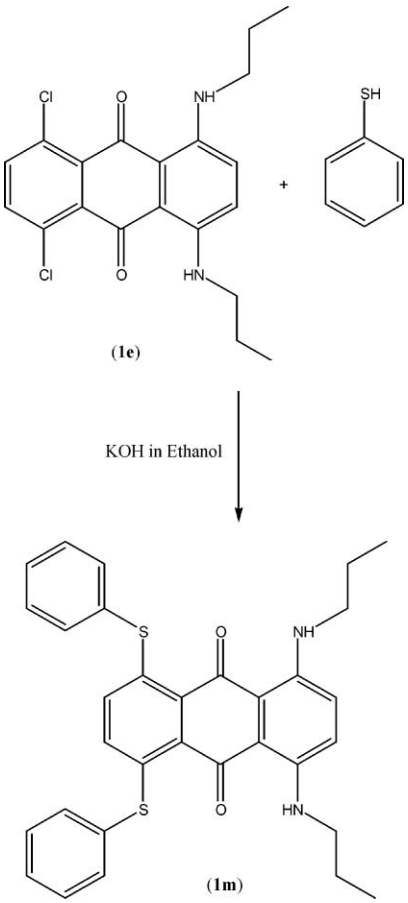


Fig. 7

Similarly, thiolation of 1,4-bis[2-(hydroxyethyl)amino]-5,8-dichloroanthracene-9,10-dione (**1i**) with thiophenol and 2-ethanethiol in DMF gives 1,4-bis[2-(hydroxyethyl)amino]-5,8-bis(phenylsulfanyl)anthracene-9,10-dione (**1p**) and 1,4-bis[2-(hydroxyethyl)amino]-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1q**) in 67% and 51% yield respectively. Likewise 1,4-bis(phenylamino)-5,8-bis(phenylsulfanyl)anthracene-9,10-dione (**1r**) and 1,4-bis(phenylamino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1s**) were synthesised in yields of 60% and 52% respectively from 1,4-bis(phenylamino)-5,8-dichloroanthracene-9,10-dione (**1l**) and the appropriate thiols.

Under prolonged reaction times in DMF, however, dealkylation occurs and both 1,4-bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (**1e**) and 1,4-bis[2-(hydroxyethyl)amino]-5,8-dichloroanthracene-9,10-dione (**1i**) react with ethanethiol and potassium hydroxide during 24 h reflux to give 1,4-bis(amino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1u**) as a major product.

It is not entirely clear why the thiolation of 1,4-bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (**1e**) proceeds readily while the corresponding reaction of either 1,4-dihydroxy-5,8-dichloroanthracene-9,10-dione (**2**) or 1,4-dimethoxy-5,8-dichloroanthracene-9,10-dione does not. Both the *n*-propylamino group, hydroxyl group and methoxyl group are electron donors which would be expected to exert a deactivating effect on nucleophilic substitution at the 5- and 8-positions. However, the electron attracting carbonyl groups provide an opposite activating effect especially when the oxygen atoms O15 and O16 are strongly hydrogen bonded as in the first case to the propylamino hydrogen atoms H18 and H20 respectively (Fig. 2). In the second case, it is possible that the attacking nucleophile, RS^-, initially prefers to remove the acidic proton from the hydroxyl group of (**2**) to generate a much less reactive 1,4-substituted-5,8-dichloroanthracene-9,10-dione oxyanion. In the last case, the oxygen atoms O15 and O16 do not form hydrogen bonds with the methoxyl groups and the carbonyl groups are therefore less effective electron attractors.

Molecular modelling studies

The insertion of either chlorine or sulfur atoms into the 5 and 8-positions of 1,4-bis(alkylamino) anthracene-9,10-diones (**1**) would be expected to change both the electronic properties of the resulting molecule and the energy levels of the frontier orbitals. In these studies we have assessed the likely effect of these changes by theoretical calculations at the *ab initio* level using the 6-31G** basis set. Initially, calculations were carried out on 1,4-bis(*n*-butylamino)anthracene-9,10-dione (**1t**) whose crystal structure is known[61] not only to verify that the method provides a reasonable account of the geometry, but also to provide a simple model for Ametantrone (**1c**). Although the side chain is a critical factor in the antineoplastic activity of Ametantrone (see above) it is not thought to markedly affect the ability of the molecule to form the semiquinone and subsequently generate superoxide (see below).

1. Geometries. The calculated results obtained on (**1t**) using a starting conformation for the *n*-butyl groups which was based on the crystal structure[61] show a reasonably good correlation with the crystallographic data (Table 1) with the anthracene ring system essentially planar and calculated C1–N17/C4–N19 and O15–H18/O16–H20 bond distances of 1.361 and 1.860 Å *versus* average values of 1.353 and 1.840 Å respectively in the crystal structure.[61,62] However, the correlation is less satisfactory for the C6–O16/C13–O15 bond lengths with calculated values of 1.210 Å *versus* the average experimental value of 1.255 Å in the crystal structure (Table 1) possibly because the latter form intermolecular hydrogen bonds with adjacent molecules in the crystalline state. Despite this apparent anomaly, further calculations were carried out on a representative set of molecules all of which had been synthesised, to gauge the effect of both chlorine and sulfur on the molecular properties. Calculations were carried on 1,4-bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (**1e**) and 1,4-bis(*n*-propylamino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1f**) and the results compared with and contrasted to those obtained for the simpler *n*-butylamino derivative (**1t**). The effect of changing the alkylsulfanyl group to a phenylsulfanyl group was examined by calculating 1,4-bis(*n*-propylamino)-5,8-bis(phenylsulfanyl)anthracene-9,10-dione (**1m**) while the effect of the *N*-alkyl group on the molecular properties was examined by calculating the simpler 1,4-bis(amino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1u**). The calculated results show that the anthracene-9,10-dione ring system is essentially planar in all cases with the nitrogen atoms N17 and N18 adopting a mainly planar sp^2 conformation with C1–N17 and C14–N19 bond lengths of 1.36 Å and C1–N17–H18 and C4–N19–H20 angles of 116°. The C–S bond lengths of 1.77 to 1.80 Å for (**1f**), (**1m**) and (**1u**), and C–Cl bond lengths of 1.74 Å for (**1e**) are all consistent with values found in the Cambridge Structural Database for related molecules.[62]

Table 1 Geometries and properties of 1,4-bis(amino)anthracene-9,10-diones calculated at the 6-31G** level *versus* crystallographic data (CSD)[a]

Structure	(**1t**) (CSD)[b]	(**1t**)	(**1e**)	(**1u**)	(**1f**)	(**1m**)
R	*n*-Bu	*n*-Bu	*n*-Pr	H	*n*-Pr	*n*-Pr
X	H	H	Cl	SEt	SEt	SC_6H_5
Distance						
C1N17	1.359	1.361	1.361	1.361	1.363	1.362
C14N19	1.347					
H18N17	0.805	0.991	0.990	0.991	0.991	0.991
H20N19	0.930					
O15H18	1.781	1.860	1.871	1.860	1.880	1.901
O16H20	1.899					
O15C13	1.254	1.210	1.203	1.210	1.207	1.207
O16C6	1.255					
XC8/XC11			1.738	1.770	1.788	1.799
Angles						
C1N17H18	110.2	116.2	116.8	116.3		
C4N19H20	110.4					
C14C13O15	123.1	122.9	121.2	122.9		
C5C6O16	122.4					
SC11C12						
Charges						
O15/O16		−0.630	−0.603	−0.627	−0.629	−0.629
N17/N19		−0.782	−0.825	−0.805	−0.828	−0.825
H18/H20		0.363	0.363	0.362	0.363	0.360
S				0.314	0.314	0.408
Cl			0.065			
Total energy/au			−1946.6307	−1745.8344	−1980.0146	−2282.0211
Dipole moment/D		2.004	3.0504	2.404	1.070	0.996
HOMO/eV		−6.808	−6.867	−6.858	−6.634	−6.729
LUMO/eV		0.971	0.920	1.040	1.046	0.838

[a] Taken from the Cambridge Structural Database (Ref. 62). Bond lengths are in angstroms and angles are in degrees. [b] Ref. 61 (CSD code: CAMJOP).

2. Electronic properties. In the transition from 1,4-bis(*n*-butylamino)anthracene-9,10-dione (**1t**) to either 1,4-bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (**1e**), 1,4-bis(*n*-propylamino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1f**) or 1,4-bis(*n*-propylamino)-5,8-bis(phenylsulfanyl) anthracene-9,10-dione (**1m**), although the substituent at the 5- and 8-positions of the right hand ring of the anthracene-9,10-dione changes from H to either Cl, SC_2H_5 or SC_6H_5, the calculated atomic charges at the hydrogen atoms, H18 and H20, are largely unaffected and all have a similar value of 0.36. However, the charges at the amino nitrogen atoms, N17 and N18, differ and increase from −0.78 in (**1t**) to −0.83 in the other cases (Table 1).

The carbonyl oxygen atoms, O15 and O16, which are intramolecularly hydrogen bonded to H18 and H20, show different trends with a smaller negative charge of −0.60 found in (**1e**) *versus* the value of around −0.63 in (**1t**), (**1f**) and (**1m**) possibly reflecting the electron attracting effect of the chlorine atoms in the former case. The positive charge of 0.31 calculated at the sulfur atoms in both (**1u**) and (**1f**) probably reflects electron donation through the ring to the nitrogen atoms, N17 and N18, as these are more negatively charged than those in (**1t**). However, the larger atomic charge of 0.408 for the sulfur atoms of the phenylsulfanyl derivative (**1m**) (Table 1) possibly arises because of additional electron donation from sulfur into the conjugated phenyl groups. Alternatively, this change may simply reflect the fact that the sulfur is bonded to an sp^3 carbon in (**1f**) but a more electronegative sp^2 carbon in (**1m**). The chlorine atoms in (**1e**) are also positively charged though they exert a much smaller effect than the sulfur atom does. The *N*-alkyl group clearly exerts a significant effect at the nitrogen atoms as the charge increases from −0.81 to −0.83 in moving from (**1u**) to (**1f**). The close similarity between the positive atomic charges at the intramolecularly bound hydrogens, H18 and H20, and negatively charged oxygen and nitrogen and atoms, O15, O16, N17 and N19 respectively, for all these molecules, coupled with their planarity atoms suggest that all would intercalate into DNA.

3. Frontier orbital energies. It is well established that the calculated LUMO energies of many organic systems correlate with the energies of formation of their radicals and radical anions because this property is a reflection of their electron affinity.[63] For example, in a recent relevant theoretical and experimental study on related benzocarbazolediones and anilinenaphthoquinones a good linear relationship was found between the measured first reduction potential and the calculated LUMO energies.[64] Furthermore, very recent work on substituent effects in a number of quinones using density functional theory has shown good correlations between the calculated electron affinities based on the LUMO energies and the experimental redox potentials.[65] Similarly, the LUMO energies of the related 1,4-bis(amino)anthracene-9,10-diones (**1**) discussed here would also be expected to reflect their likely reduction potentials to form the radical anion or semiquinone. These values in turn should also indicate the ability of the semiquinone ($AQ^{\bullet -}$) to

reduce oxygen to superoxide [eqn (1)] and thus mirror the likely trends in their cardiotoxicities. Using the calculated LUMO energy of 1,4-bis(*n*-butylamino)anthracene-9,10-dione (**1t**) as a reference point at 0.971 eV (Table 1), as this is thought to be directly related to the reduction potential of the anti-cancer drug Ametantrone (**1c**), the corresponding values for 1,4-bis(amino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1u**) and 1,4-bis(*n*-propylamino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (**1f**) at 1.040 and to 1.046 eV respectively are significantly larger than (**1t**) and consequently the ethylsulfanyl groups would make the reduction potential of the radical anion more negative. Although it was originally anticipated that the vacant d orbitals on the sulfur atoms would behave as electron attractors[66] and stabilise the radical anion, the overall effect of sulfur in (**1u**) and (**1f**) appears to be similar to the effect of oxygen in Mitoxantrone (**1d**) which has a reduction potential of −527 mV.[46] It follows from the calculations that both (**1f**) and (**1u**) would be expected to display similar reduction potentials to Mitoxantrone (**1d**) and therefore exhibit similar cardiotoxicities.

However, the LUMO energies of the other derivatives considered are more interesting and both 1,4-bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (**1e**) and 1,4-bis(*n*-propylamino)-5,8-bis (phenylsulfanyl)anthracene-9,10-dione (**1m**) possess values of 0.920 or 0.838 eV respectively following substitution at the 5- and 8-positions of the ring (Table 1). This reduction from the value found in the reference molecule (**1t**) probably reflects the effect of the two electron attracting chlorine atoms on the one hand which would be expected to stabilise a derived radical anion, and the increased stabilisation arising from the presence of the two attached phenylsulfanyl rings on the other which would be able to distribute and accommodate the negative charge on a derived radical anion. It follows that the reduction potentials of both these molecules would be expected to be less negative than that of Ametantrone (**1c**) assuming that the complex side chain is not involved in the reduction step. An analysis of the composition of the 6-31G** LUMO wavefunction for all the calculated molecules confirms that it is composed primarily of π atomic orbitals which are located on the anthracene ring only. For example, in 1,4-bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (**1e**) the 204 electrons are accommodated in the first 102 bonding MOs and an analysis of the LUMO (MO 103) shows that it is mainly composed from π atomic orbitals at the ring carbons and oxygen, with smaller contributions from nitrogen and chlorine. There is no contribution from the saturated *n*-butyl side chain and it is highly unlikely that the corresponding side chain of Ametantrone would contribute either, as is not conjugated with the aromatic ring. It follows that the trends in the LUMOs reported here for the simple *n*-alkyl derivatives would probably equally apply to related molecules which contain the optimal side chain necessary for antineoplastic activity.

Conclusions

1,4-Bis(alkylamino)-5,8-dichloroanthracene-9,10-diones are readily synthesised from the reaction of 1,4-dichloro-2,3-dihydro-5,8-dihydroxyanthracene-9,10-dione with alkylamines such as *n*-propylamine, isobutylamine, methylamine, 2-aminoethanol and *N*,*N*-dimethylethylenediamine. A related reaction with aniline in the presence of boric acid gives 1,4-bis(phenylamino)-5,8-dichloroanthracene-9,10-dione. The subsequent reaction of the products with ethanethiol or thiophenol gives the corresponding 1,4-bis(amino)-5,8-bis(sulfanyl)anthracene-9,10-dione in good yield. Theoretical calculations at the RHF 6-31G** level indicate that the presence of either chlorine or the phenylsulfanyl group at the 5- and 8-positions of 1,4-bis(alkylamino)anthracene-9,10-diones results in a lowering of the LUMO energies of (**1e**) and (**1m**) suggesting that their reduction potentials would be significantly different to the unsubstituted derivative (**1t**).

Experimental

All the reagents described including 1,4-dihydroxyanthracene-9,10-dione were supplied by Sigma-Aldrich Chemicals. ^{1}H NMR spectra were recorded on a Bruker AC spectrometer at 400 MHz. Chemical shifts are recorded in parts per million (δ) relative to tetramethylsilane in deuterated dimethyl sulfoxide (DMSO) or chloroform ($CDCl_3$). Mass spectra were recorded using the EPSRC Mass spectrometry centre at Swansea using a VG analytical Quatro II triple quadrupole mass spectrometer. Accurate masses were obtained on a Finngan MAT 900 XL using a perfluorotributylamine as the reference compound for electron ionisation and polyethyleneimine for chemical ionisations. Melting points were recorded on an electrothermal digital melting point apparatus. Most of the known products were synthesised using literature procedures which are described in the text (above). However, where the experimental procedure differed significantly from that published, or the derivatives have not previously been described, full details have been included.

2,3-Dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (3)

This was prepared using modified literature procedures.[58–60] (a) 1,4-Dihydroxy-5,8-dichloroanthracene-9,10-dione (1.00 g, 3.3 mmol) was added to a solution of sodium carbonate (1.4 g, 13.2 mmol) and water (125 ml). The solution was heated until boiling and sodium dithionite (1.7 g, 9.8 mmol) was added. Because of incomplete reduction, it was necessary to add a further quantity of sodium dithionite (0.50 g, 2.9 mmol) after 15 min to complete the reduction. The precipitate was filtered off, washed with dilute acetic acid until alkali free and dried *in vacuo* to yield the title compound (0.90 g, 96%), mp 145 °C, (lit.,[60] 150 °C), δ_H ($CDCl_3$) 3.0 (4H, s), 7.6 (2H, s), 14.5 (2H, *OH*,s). (b) 1,4-Dihydroxy-5,8-dichloroanthracene-9,10-dione (1.00 g, 3.3 mmol) was added to a mixture of tin (3.00 g, 24.4 mmol) and HCl (70 ml) in acetic acid (50 ml). The mixture was heated to 90–95 °C for 24 h. The solution was allowed to cool and the precipitate was filtered off, the solid was washed with water and dried *in vacuo* to yield 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (0.65, 64%), mp 147 °C, δ_H ($CDCl_3$) 3.0 (4H, s), 7.6 (2H, s), 14.5 (2H, *OH*, s).

1,4-Bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (1e)

2,3-Dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (1.00 g, 3.2 mmol) was added to a solution of *n*-propylamine (1.00 g, 17 mmol) in ethanol (25 ml) and the mixture was heated for 1 h at 50–55 °C. The solution was allowed to cool, petroleum ether 40–60 (25 ml) was added and the mixture stirred overnight. The resulting solid was filtered off and purified *via* column chromatography using an eluant of toluene 95% and chloroform

5% to yield the title compound (0.60 g, 48%), mp 150 °C, δ_H ($CDCl_3$) 1.00 (6H, t), 1.50 (4H, m) 3.30 (4H, q), 7.10 (2H, s) 7.40 (2H, s), 10.30 (2H, *NH* t); *m/z* (EI) 390.0901, $C_{20}H_{20}Cl_2N_2O_2$ requires 390.0902.

1,4-Bis(isobutylamino)-5,8-dichloroanthracene-9,10-dione (1g)

A similar procedure using isobutylamine (1.24 g, 17 mmol) in place of *n*-propylamine gave the title compound (0.70 g, 52%), mp 154 °C, δ_H ($CDCl_3$) 1.00 (12H, d), 2.00 (2H, m) 3.10 (4H, t), 7.10 (2H, s), 7.50 (2H, s), 10.40 (2H, *NH*, t), δ_C 180.80, 145.75, 135.69, 133.44, 123.70, 113.30, 110.68, 61.55, 29.09, 20.92.

1,4-Bis(methylamino)-5,8-dichloroanthracene-9,10-dione (1h)

2,3-Dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (1.00 g, 3.2 mmol) was added to a solution of 20% methylamine in water (4.96 g, 32 mmol) and the mixture was heated for 1 h at 50–55 °C. The solution was allowed to cool, the resulting precipitate filtered off, washed with water (50 ml) and purified by column chromatography using an eluant of toluene 95% and chloroform 5% to yield the title compound (0.50 g, 47%), mp 145 °C, δ_H ($CDCl_3$) 3.00 (6H, d), 7.15 (2H, s), 7.45 (2H, s), 10.10 (2H, *NH*).

1,4-Bis[2-(hydroxyethyl)amino]-5,8-dichloroanthracene-9,10-dione (1i)

2,3-Dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (1.00 g, 3.2 mmol) was added to a solution of 2-aminoethanol (1.00 g, 16 mmol) in ethanol (25 ml) and was heated for 1 h at 50–55 °C. The solution was allowed to cool, petroleum ether 40–60 (25 ml) was added and the mixture was stirred for overnight. The resulting solid was filtered off and recrystallised from ethanol to yield the title compound (0.80 g, 64%), mp 197 °C, δ_H ($CDCl_3$) 3.40 (2H, t), 3.60 (2H, q) 4.90 (2H, *OH*, s), 7.35 (4H, s) 7.60 (4H, s), 10.30 (2H, *NH*, t).

1,4-Bis{[2-(dimethylamino)ethyl]amino}-5,8-dichloroanthracene-9,10-dione (1j)[67]

2,3-Dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (1.00 g, 3.2 mmol) was added to a solution of *N*,*N*-dimethylethylenediamine (2.8 g, 32 mmol) in ethanol (25 ml) and the mixture was heated for 2 h at 50–55 °C. The solution was allowed to cool, petroleum ether 40–60 (25 ml) was added and the mixture further cooled with ice. The resulting precipitate was filtered off, added to a solution of diethyl ether (25 ml) and methanol (25 ml) saturated with hydrogen chloride gas and stirred for 15 min. The product was filtered off and purified by column chromatography using an eluant of 10% methanol and 90% chloroform to yield the title compound (0.40 g, 29%), mp 255 °C, δ_H (DMSO-d_6) 3.20 (12H, s), 3.30 (4H, t), 3.50 (4H, q), 7.35 (2H, s), 7.65 (2H, s), 10.10 (2H, *NH*, t), δ_C 179.91, 144.45,136.03, 132.23, 132.09, 124.66, 109.78, 55.55, 51.74, 46.79.

1,4-Bis{[2-(diethylamino)ethyl]amino}-5,8-dichloroanthracene-9,10-dione hydrochloride (1k)

A similar procedure using *N*,*N*-diethylethylenediamine (2.80 g, 24 mmol) place of *N*,*N*-dimethylethylenediamine (2.80 g, 28 mmol) gave the title compound (0.30 g, 22%), mp 265 °C, δ_H (DMSO-d_6) 1.25 (12H, t), 3.20 (8H, q), 3.40 (4H, t), 3.90 (4H, q), 7.60 (2H, s), 7.80 (2H, s), 9.90 (2H, *NH*, t), 10.90 (2H, *HCl*), δ_C 180.51, 144.04, 136.61, 132.54, 132.26, 124.20, 111.04, 49.94, 46.75, 37.36, 8.69.

1,4-Bis(phenylamino)-5,8-dichloroanthracene-9,10-dione (1l)

A mixture of 2,3-dihydro-9,10-dihydroxy-5,8-dichloroanthracene-1,4-dione (1.00 g, 3.2 mmol), aniline (3.00 g, 32 mmol) and boric acid (0.40 g, 6.4 mmol) was heated for 4 h at 90–95 °C. The solution was allowed to cool, the precipitate was filtered off, and purified by column chromatography using an eluant of toluene 95% and chloroform 5% to yield the title compound (0.35 g, 24%), mp 230 °C (lit., 234–235 °C[58]), δ_H ($CDCl_3$) 7.00–7.30 (10H, m), 7.40 (2H, s), 7.50 (2H, s), 11.40 (2H, *NH*, s), δ_C 182.26, 142.77, 139.97, 136.43, 133.60, 133.26, 129.92, 126.51, 125.30, 123.92, 113.42.

1,4-Bis(*n*-propylamino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (1f)

1,4-Bis(*n*-propylamino)-5,8-dichloroanthracene-9,10-dione (0.43 g, 1.1 mmol) was added to a solution of ethanethiol (0.68 g, 11 mmol) and potassium hydroxide (0.62 g, 11 mmol) in DMF (25 ml) and the solution was heated under reflux for 2 h. The DMF was removed under vacuum distillation and the resulting solid was washed with 10% potassium hydroxide solution (50 ml) and then methanol. The crude product was purified by column chromatography using an eluant of 90% toluene and 10% chloroform to yield the title compound (0.30 g, 62%), mp 235 °C, δ_H ($CDCl_3$) 1.00 (6H, t), 1.30 (6H, t), 1.70 (4H, m), 2.80 (4H, q), 3.20 (4H, q), 6.90 (2H, s), 7.25 (2H, s), 10.30 (2H, *NH*, t).

1,4-Bis(isobutylamino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (1o)

A similar procedure using 1,4-bis(isobutylamino)-5,8-dichloroanthracene-9,10-dione (0.43 g, 1.1 mmol) in place of the *n*-propyl derivative gave the title compound (0.20 g 41%), mp 230 °C, δ_H 0.95 (12H, d), 1.30 (6H, t), 1.90 (2H, m), 2.80 (4H, q), 3.05 (4H, t), 6.95 (2H, s), 7.30 (2H, s), 10.40 (2H, t, *NH*), δ_C 182.17, 137.02, 131.11, 128.23, 127.34, 124.48, 108.4, 49.63, 29.79, 28.79, 19.53, 11.80.

1,4-Bis[2-(hydroxyethyl)amino]-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (1q)

A similar procedure using 1,4-bis[2-(hydroxyethyl)amino]-5,8-dichloroanthracene-9,10-dione (0.43 g, 1.1 mmol) in place of the *n*-propyl derivative gave the title compound (0.25 g, 51%), mp 254 °C, δ_H ($CDCl_3$) 1.10 (6H, t), 2.70 (4H, q), 3.30 (4H, q), 3.50 (4H, t), 7.20 (2H, s), 7.4 (2H, s), 10.10 (2H, NH); *m/z* (EI) 446.1336, $C_{22}H_{26}N_2O_4S_2$ requires 446.1334.

1,4-Bis(phenylamino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (1s)

A similar procedure using 1,4-bis(phenylamino)-5,8-dichloroanthracene-9,10-dione (0.50 g, 1.1 mmol) in place of the *n*-propyl derivative gave the title compound (0.30 g, 52%), mp 215 °C, δ_H ($CDCl_3$), 1.35 (6H, t), 2.90 (4H, q), 7.00–7.50 (14H, m), 11.75 (2H, *NH*, s), δ_C 184.74, 140.26, 139.77, 132.77, 132.22,

129.89, 129.79, 128.50, 124.85, 124.79, 112.43, 26.79, 13.23; *m/z* (EI) 510.1434, $C_{30}H_{26}N_2O_2S_2$ requires 510.1436.

1,4-Bis(*n*-propylamino)-5,8-bis(phenylsulfanyl)anthracene-9,10-dione (1m)

1,4 - Bis(*n* - propylamino) - 5,8 - dichloroanthracene - 9,10 - dione (0.43 g, 1.1 mmol) was added to a solution of thiophenol (1.20 g, 11 mmol) and potassium hydroxide (0.62 g, 11 mmol) in DMF (25 ml). The solution was heated under reflux for 2 h and the solvent was removed by vacuum distillation. The solid was washed with 10% potassium hydroxide solution (50 ml) and then methanol. The crude solid was purified *via* column chromatography using an eluant of 90% toluene and 10% chloroform to yield the title compound (0.40 g, 66%), mp 240 °C, δ_H ($CDCl_3$) 1.00 (6H, t), 1.8 (4H, m), 3.30 (4H, q), 6.60 (2H, s) 7.40 (12H, m), 10.50 (2H, *NH*, t); *m/z* (EI) 538.1747, $C_{32}H_{30}N_2O_2S_2$ requires 538.1749. In an alternative procedure, the same reactants were refluxed in ethanol (25 ml) for 2 h rather than DMF. The solvent was removed under vacuum distillation, the residual solid was treated as before and purified *via* column chromatography using an eluant of 90% toluene and 10% chloroform to yield the title compound (0.25 g, 41%), mp 240 °C.

1,4-Bis(isobutylamino)-5,8-bis(phenylsulfanyl)anthracene-9,10-dione (1n)

A similar procedure using 1,4-bis(isobutylamino)-5,8-dichloroanthracene-9,10-dione (0.43 g, 1.1 mmol) in place of the *n*-propyl derivative in DMF yielded the title compound (0.22 g, 37%), mp 240 °C, δ_H ($CDCl_3$) 1.00 (12H, d), 2.10 (2H, m), 3.30 (4H, t), 6.60 (2H, s), 7.50 (12H, m), 10.60 (2H, *NH*, t).

1,4-Bis[2-(hydroxyethyl)amino]-5,8-bis(phenylsulfanyl)anthracene-9,10-dione (1p)

A similar procedure using 1,4-bis[2-(hydroxyethyl)amino]-5,8-dichloroanthracene-9,10-dione (0.43 g, 1.1 mmol) in place of the *n*-propyl derivative in DMF gave the title compound (0.40 g, 67%), mp 260 °C, δ_H (DMSO) 3.40 (4H, q), 3.75 (4H, t), 5.10 (2H, *OH*, s), 6.70 (2H, s), 7.50 (12H, m), 10.50 (2H, *NH*, s), δ_C 181.64, 145.64, 139.88, 135.95,133.33, 130.50, 130.45, 129.87, 129.17, 124.56, 108.77, 60.27, 45.19.

1,4-Bis(phenylamino)-5,8-bis(phenylsulfanyl)anthracene-9,10-dione (1r)[68]

A similar procedure using 1,4-bis(phenylamino)-5,8-dichloroanthracene-9,10-dione (0.50 g, 1.1 mmol) in place of the *n*-propyl derivative in DMF gave the title compound (0.40 g, 60%), mp 225 °C, δ_H ($CDCl_3$) 6.65 (2H, s), 7.00–7.50 (22H, m), 11.85 (2H, *NH*, s), δ_C 184.56, 143.46, 141.60, 137.44, 133.51, 131.34, 130.32, 130.29, 129.85, 129.49, 129.43, 127.91, 125.03, 124.38, 112.25.

1,4-Bis(amino)-5,8-bis(ethylsulfanyl)anthracene-9,10-dione (1u)

In a similar procedure and work up to that described for (**1i**) but with an extended reaction time of 24 h resulted in de-amination of the initial product to give the title compound (0.13 g, 25%), mp 256 °C, δ_H (DMSO) 1.40 (6H, t), 3.00 (4H, q), 7.20 (2H, s), 7.65 (2H, s), 8.20 (4H, s); *m/z* (EI) 358.0813, $C_{18}H_{18}N_2O_2S_2$ requires 358.0810. The same product (0.01 g, 22%) was isolated also from the same procedure and work up to that described for (**1e**) but with an extended reaction time of 24 h.

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