Experimental and theoretical study of tautomerism in 1,4-bis-[methoxyamino]anthracene-9,10-diones and their reduced forms

John. O. Morley,[a] A. Paul Krapcho[b] and Douglas S. Cummings[b]

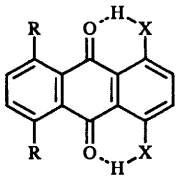
[a] *Department of Chemistry, University of Wales Swansea, Singleton Park, Swansea, UK SA2 8PP*

[b] *Department of Chemistry, University of Vermont, Burlington, VT 05405, USA*

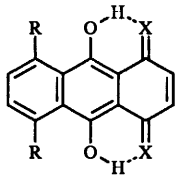
Treatment of leucoquinizarin 4a with methoxylamine hydrochloride (*O*-methylhydroxylamine hydrochloride) in pyridine led to tautomer 4e. Oxidation of 4e in refluxing nitrobenzene led to 1,4-diaminoanthracene-9,10-dione 1e while oxidation with manganese dioxide yielded 1,4-bis(methoxyimino)-2,3-dihydroanthracene-9,10-dione 6. Attempted diplacement of the fluorides from 1,4-difluoroanthracene-9,10-dione by methoxylamine in dimethyl sulfoxide led to 9,10-dihydroxy-1,4-bis(methoxyimino)anthracene 2h instead of the anticipated bis(methoxyamino) tautomer 1h. Calculations have been carried out on some of these derivatives using the 3-21G basis set and the results for 2h compared with X-ray data from a single crystal. The calculated results show that that 1h is marginally preferred over 2h by 0.68 kcal mol^{-1}. The reduced forms show the opposite trend with 4e preferred by 11.3 kcal mol^{-1} over 3e in line with NMR data recorded in chloroform. The presence of an oxygen atom adjacent to the nitrogen atom in the methoxyimine substituent forces a tetrahedral conformation at nitrogen resulting in a destabilization of the anthracene-9,10-dione tautomers 1h and 3e.

Introduction

There is considerable current interest in 1,4-dihydroxyanthracene-9,10-dione **1a** and 1,4,5,8-tetrahydroxyanthracene-9,10-dione **1b** because of their facile conversions into 1,4-bis[(aminoalkyl)amino]- and 1,4-bis[(aminoalkyl)amino]-5,8-dihydroxy-anthracene-9,10-diones.[1-6] Specifically substituted analogues such as ametantrone **1c** and mitoxantrone **1d** are potent anticancer drugs currently in clinical use.[7,8]

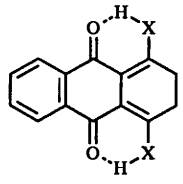


1

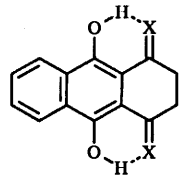


2

a X = O, R = H
b X = O, R = OH
c X = $N(CH_2)_2NH(CH_2)_2OH$, R = H
d X = $N(CH_2)_2NH(CH_2)_2OH$, R = OH
e X = NH, R = H
f X = NC_4H_9, R = H
g X = NNH_2, R = H
h X = $NOCH_3$, R = H

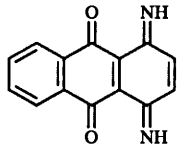


3

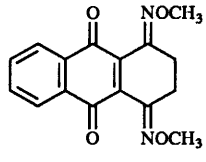


4

a X = O
b X = NH
c X = NC_4H_9
d X = NNH_2
e X = $NOCH_3$



5



6

The chemotherapeutic agents **1c** and **1d** are prepared by reduction of **1a** or **1b** to the so-called leuco compounds, addition of 2-(2-aminoethylamino)ethanol followed by an oxidative workup.[2-4] In principal, the leuco derivatives can exist in several tautomeric forms. In the reduction of **1a** only the tautomer, 9,10-dihydroxy-2,3-dihydroanthracene-1,4-dione **4a**, and not **3a**, was found experimentally by ^1H and ^{13}C NMR spectral analysis.[9] In contrast, the reduction of 1,4-diaminoanthracene-9,10-dione **1e** leads to the leuco tautomer thought to be 1,4-diamino-2,3-dihydroanthracene-9,10-dione **3b** on the basis of ^1H and ^{13}C NMR studies in deuteriochloroform on the closely related leuco derivative **3c** formed from reduction of **1f**.[9]

However, ^{13}C NMR studies of leuco 1,4-bis(hydrazino)-anthracene-9,10-dione **1g** in [$^2H_6$]dimethyl sulfoxide solution appears to show only 1,4-bis(aminoimino)-9,10-dihydroxy-2,3-dihydroanthracene **4d**.[10]

In a drug development programme dealing with the synthesis and antitumour evaluations of anthracene-9,10-dione chemotypes, we wished to prepare O-substituted hydroxyamino analogues such as **1h**. This analogue under cellular conditions could act as a bioreductive alkylator.[11] The intermediate **5**, which might be formed by enzymatic sequential two electron addition to **1h** followed by reductive elimination of the N–O bonds, might be expected to undergo attack by nucleophilic cellular components to form covalently bonded species. An event of this type could eventually lead to cellular destruction in hypoxic solid tumours.

Results

It was hoped that treatment of leucoquinizarin **4a** with methoxylamine would lead to the 1,4-bis-*O*-methyl substituted oxime which during workup would undergo oxidation to yield **1h**. Addition of methoxylamine hydrochloride (*O*-methylhydroxylamine hydrochloride) to a pyridine solution of leucoquinizarin **4a** led to the tautomer **4e** (74%). This structural assignment is based on ^1H and ^{13}C NMR spectral analysis. The

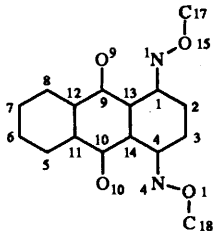


Fig. 1 Numbering scheme for the anthracene-9,10-diones **1**–**4**

^{13}C NMR spectrum for **4e** does not exhibit a C=O resonance peak in the δ 180 region.[9] The absorption at δ 157.8 is consistent with that previously reported for the C–OH carbon of leucoquinizarin **4a** (δ 154.9 for C–9 and C–10).[9]

Tautomer **4e** is stable when stored in the dark but gradually darkens when allowed to stand at room temperature for a few days. An attempt to oxidize **4e** to **1h** in refluxing nitrobenzene was unsuccessful. The product which was isolated from this reaction was 1,4-diaminoanthracene-9,10-dione **1e** (68%), which arises from two N–O bond cleavages.

The oxidation of **4e** with activated manganese dioxide in chloroform at room temperature led to tautomer **6**. The ^{13}C NMR chemical shifts for the C=O and C=N carbons occur at δ 182.1 and 150.6, respectively. Of additional interest is the stability of tautomer **6**, since attempts under acidic or basic conditions to tautomerize **6** into **1h** have proven unsuccessful.

Based on our prior formal sequential S_NAr displacements of fluoride from 1,4-difluoroanthracene-9,10-dione by (aminoalkyl)amines to form 1,4-bis[(aminoalkyl)amino]anthracene-9,10-diones,[1] we envisioned that displacements of the fluorides from this difluoroanthracenedione with methoxylamine would lead directly to **1h**. Treatment of 1,4-difluoroanthracene-9,10-dione with methoxylamine in dimethyl sulfoxide (DMSO) for long periods (2 weeks) followed by chromatography of the crude reaction product led to a tautomer **2h** and not tautomer **1h**. This structural assignment is based on ^1H and ^{13}C NMR spectral analysis and X-ray crystallographic analysis.† The ^{13}C NMR spectrum lacks a resonance for the C=O carbon, and the C=N and C–OH carbons occur at δ 148.6 and 151.6, respectively.

The theoretical studies described here have been carried out to help rationalise the experimental data in terms of the structural and electronic features of the stable tautomer of leuco 1,4-bis(methoxyamino)anthracene-9,10-dione which is found to be **4e** rather than **3e** in $CDCl_3$, and which differs from the closely related leuco 1,4-bis(butylamino)anthracene-9,10-dione which is found to exist as **3c**[9] rather than **4c** in the same solvent. The same theoretical approach has been applied to 1,4-bis(methoxyamino)anthracene-9,10-dione which, surprisingly, exists as **2h** rather than **1h** and which again differs from the favoured tautomers of the closely related 1,4-diaminoanthracene-9,10-dione and 1,4-bis(butylamino)-anthracene-9,10-dione which are clearly shown by X-ray crystallography to exist as **1e**[12] and **1f**[13] rather than **2e** and **2f**, respectively.

Methods of calculation

Both the AM1 method[14] and PM3[15] of the MOPAC 93 program[16] were used initially to optimise the structures of the molecules considered here (at the 'precise' level).[16] However, the AM1 method gave unsatisfactory results with the molecules either folded along an axis between the 9- and 10-carbon atoms or with the substituents at the 1- and 4-positions twisted from the ring plane. The hydrogen bonding distances between hydrogen atoms on either the hydroxy group in structures **2h** and **4e** or on the hydroxyamino group in structures **1h** and **3e** and the adjacent nitrogen or oxygen atom were found to be greater than 2.1 Å. Although the PM3 method gave improved results particularly with respect to the hydrogen bonding distances in all four molecules with values ranging from 1.78 to 1.80 Å, tautomers **1h** and **3e** were predicted to be folded along the axis between the 9- and 10-carbon atoms.

As a result, the structure optimisations were repeated with the 3-21G basis set[17] of the GAMESS program[18] using the usual gradient techniques. The resulting structures and energies obtained in the gas phase were then compared with the experimental data generated in $CDCl_3$. The numbering convention shown in Fig. 1 was used.

Discussion

Structural aspects

Recent theoretical results on the leuco-derivatives of both 1,4-dihydroxyanthracene-9,10-dione **1a** and 1,4-diaminoanthracene-9,10-dione **1e** using the 3-21G basis set have shown that 9,10-dihydroxy-2,3-dihydroanthracene-1,4-dione **4a** is preferred by 10.3 kcal mol^{-1}‡ over the alternative isomer **3a**, but 1,4-diamino-2,3-dihydroanthracene-9,10-dione **3b** is preferred by 12.5 kcal mol^{-1} over the alternative isomer **4b**[19] in line with the experimental data in chloroform. This preference for the amine–carbonyl structure rather than the imine–hydroxy combination is found generally[20] and rationalised by the better push–pull character of the former over that of the latter. However, the presence of an additional strongly electronegative oxygen atom at the amine or imine group is likely to have a considerable effect on the electronic properties and structure of the closely related leuco derivative of 1,4-bis(methoxyamino)anthracene-9,10-dione **1h**.

In the 2,3-dihydroanthracene-1,4-diimine **4e**, the aliphatic carbons at the 2- and 3-positions of the ring are twisted from the central aromatic ring plane, with one positioned approximately 10° below the molecular plane and the other 10° above (Table 1). Both the oxygen atoms at the imine nitrogens and the hydrogen atoms at the 9- and 10-hydroxy groups are almost co-planar with the central aromatic ring (Table 1). The bond lengths are fully consistent with the structure as drawn with values of 1.27 Å for the double bonds C(1)–N(1) and C(4)–N(4), and 1.36 Å for the single bonds C(9)–O(9) and C(10)–O(10) respectively (Table 2). A strong hydrogen bond is present between the hydrogen at the 9- and 10-positions and the imine nitrogens at the 1- and 4-positions, as shown by the interatomic distance of 1.76 Å.

The 2,3-dihydroanthracene-9,10-dione **3e** shows similar features to tautomer **4e** with respect to the aliphatic carbons at the 2- and 3-positions, with one positioned below the molecular plane and the other above (Table 1). However, the nitrogen atoms of the hydroxylamine groups are partly sp^3 hybridised so that the attached oxygen atoms are no longer in the plane of the aromatic ring, with one pushed above the plane and the other below (Table 1). The bond lengths are again fully consistent with the structure as drawn, with values of 1.24 Å for the double bonds C(9)–O(9) and C(10)–O(10), and 1.37 Å for the single bonds C(1)–N(1) and C(4)–N(4), respectively (Table 2). Despite the sp^3 hybridisation at the hydroxylamine nitrogen atom, the attached hydrogen atoms form a hydrogen bond with the oxygens at the 9- and 10-positions although this is weaker than in the previous case as shown by the interatomic distance here of 1.88 Å (Table 2).

In the fully aromatic 9,10-dihydroxyanthracene-1,4-diimine there is a good correlation between the calculated results and

† Kindly determined by Debra Decosta and Jon Bordner, Pfizer Central Research, Groton CT 06340, Pfizer ID Number DSC-X-RAY-100.

‡ 1 cal = 4.184 J.

Table 1 Calculated angles of the tautomeric forms of the 1,4-bis(hydroxyamino)anthracene-9,10-diones (**3e** and **4e**) and 9,10-dihydroxyanthracene-1,4-diimines (**1h** and **2h**), obtained using the 3-21G basis set, compared with crystallographic data for **2h**[a]

	Calculated results				
Angle	**4e**	**3e**	**1h**	**2h**	X-Ray[b] **2h**
C(2)–C(1)–C(13)	117.1	119.2	118.4	117.8	119.4
C(1)–C(2)–C(3)	110.4	110.3	121.3	122.7	121.9
C(2)–C(3)–C(4)	110.4	110.2	121.4	122.7	121.6
C(4)–C(14)–C(13)	119.9	120.0	120.2	119.5	119.4
C(1)–C(13)–C(14)	119.9	119.9	120.2	119.5	
C(1)–C(2)–H(2)	108.7	109.1	117.8	116.0	
H(2)–C(2)–H(2′)	108.3	107.8			
C(14)–C(10)–C(11)	120.7	117.1	118.2	120.7	121.6
C(10)–C(14)–C(13)	119.7	120.2	120.4	119.7	119.0
C(10)–C(11)–C(12)	119.6	121.9	121.2	119.6	119.3
C(5)–C(11)–C(12)	119.7	119.8	120.1	119.7	119.7
C(6)–C(5)–C(11)	120.0	120.3	119.9	119.9	119.3
C(5)–C(6)–C(7)	120.4	119.9	120.0	120.4	120.9
C(6)–C(7)–C(8)	120.4	119.9	120.0	120.4	120.1
C(7)–C(8)–C(12)	120.0	120.3	119.9	119.9	120.5
C(8)–C(12)–C(11)	119.7	119.8	120.1	119.6	118.6
C(9)–C(12)–C(11)	119.6	121.9	121.3	119.6	119.0
C(9)–C(13)–C(14)	119.7	120.3	120.4	119.7	119.6
C(12)–C(9)–C(13)	120.7	117.5	118.2	120.7	121.6
C(13)–C(9)–O(9)	124.8	123.3	122.9	124.8	123.6
C(13)–C(1)–N(1)	118.3	124.4	121.9	119.3	117.3
C(9)–O(9)–H	111.3		111.5		
C(1)–N(1)–H		117.7	115.7		
C(1)–N(1)–O(15)	115.0	112.3	113.0	113.9	112.0
N(1)–O(15)–C(17)	107.4	110.2	107.3	108.5	108.6
C(11)–C(9)–C(14)–C(2)	−170.3	−164.2	177.4	179.3	
C(13)–C(1)–N(1)–H		−14.5	27.4		
C(13)–C(9)–O(9)–H	−3.3		0.7		
C(13)–C(1)–N(1)–O(1)	−177.5	−151.0	158.4	179.2	

[a] Angles in degrees. [b] Average values from the two molecules in the unit cell, see ref. 12.

Table 2 Calculated bond lengths of the tautomeric forms of the 1,4-bis(hydroxyamino)anthracene-9,10-diones (**3e** and **1h**) and 9,10-dihydroxyanthracene-1,4-diimines (**4e** and **1h**), obtained using the 3-21G basis set, compared with crystallographic data for **2h**[a]

	Calculated results				
Bond	**4e**	**3e**	**1h**	**2h**	X-Ray[b] **2h**
C(1)–C(2)	1.506	1.510	1.410	1.465	1.445
C(2)–C(3)	1.538	1.529	1.355	1.319	1.339
C(3)–C(4)	1.506	1.509	1.410	1.465	1.453
C(4)–C(14)	1.481	1.352	1.387	1.475	1.468
C(1)–C(13)	1.481	1.354	1.387	1.475	1.464
C(2)–H(2b)	1.082	1.082	1.067	1.066	
C(10)–C(11)	1.428	1.485	1.481	1.427	1.418
C(5)–C(11)	1.409	1.387	1.385	1.408	1.412
C(5)–C(6)	1.362	1.379	1.381	1.362	1.363
C(6)–C(7)	1.409	1.387	1.388	1.407	1.403
C(7)–C(8)	1.362	1.379	1.380	1.362	1.373
C(8)–C(12)	1.409	1.387	1.385	1.408	1.419
C(11)–C(12)	1.393	1.385	1.381	1.393	1.412
C(9)–C(12)	1.428	1.485	1.480	1.427	1.422
C(9)–C(13)	1.365	1.447	1.471	1.364	1.382
C(13)–C(14)	1.450	1.487	1.426	1.448	1.437
C(9)–O(9)	1.356	1.238	1.229	1.355	1.362
C(1)–N(1)	1.270	1.371	1.388	1.273	1.306
O(9)–H	0.978	0.976			
N(1)–H		1.006	1.004		
N(1)–O(15)	1.437	1.443	1.488	1.433	1.398
O(15)–C(17)	1.450	1.451	1.447	1.447	1.424
H-bond[c]	1.755	1.881	1.861	1.771	1.861

[a] Bond lengths in Å. [b] Average values from the two molecules in the unit cell, see ref. 12. [c] Distance between the acidic hydrogen at the hydroxy or the hydroxyamino group and the adjacent oxygen or nitrogen atom.

those determined experimentally by X-ray crystallography (Tables 1 and 2). This is especially true of the angles at the nitrogen and oxygen atoms with calculated values of 113.9° for C(1)–N(1)–C(15) and 108.5° for N(1)–O(15)–C(17) *vs.* 112.0° and 108.6° for the X-ray structure (Table 1). While the calculated C(9)–O(9) single bond length at 1.36 Å matches the experimental data, the calculated C(1)–N(1) double bond at 1.27 Å is somewhat shorter than that found experimentally (Table 2). The aromatic ring of the tautomeric 1,4-bis(methoxyamino)anthracene-9,10-dione **1h**, is also fully planar, but the nitrogen atoms of the hydroxylamine groups are sp^3 hybridised as for structure **3e** so that the attached oxygen atoms are no longer in the plane of the aromatic ring, with one pushed above the plane and the other below (Table 1). The predicted bond lengths are similar to those found in the related crystal structures of 1,4-diaminoanthracene-9,10-dione **1e**[12] and 1,4-bis(butylamino)anthracene-9,10-dione **1f**[13] although the value at the C–N bond of 1.39 Å is longer than that found experimentally at 1.35 Å,[12,13] reflecting the sp^3 character of the nitrogen atom. The C=O bond is somewhat shorter at 1.23 Å than that found experimentally at 1.25 Å, but the hydrogen bond length at 1.86 Å lies between the experimental values of 1.78 Å for **1f**[13] and 1.93 Å for **1b**.[12] These results strongly suggest that the 3-21G basis set gives a good account of the geometry of all the molecules considered here.

Relative stabilities

The calculated molecular energies of the two tautomers of the 2,3-dihydroanthracenes **3e** and **4e** clearly show that the latter is preferred over the former by 11.3 kcal mol^{-1} (Table 3), fully in line with the experimental data. The explanation for the change in tautomer preference in moving from leuco 1,4-diaminoanthracene-9,10-dione **1e** to leuco 1,4-bis(methoxyamino)anthracene-9,10-dione **1h** where the anthracene-9,10-dione is preferred for the former **3b** but not for the latter **3e**, appears to be due to the change in hybridization of the nitrogen atom from a planar sp^2 conformation to a

Table 3 Calculated energies and electronic properties of the tautomeric forms of 1,4-bis(methoxyamino)anthracene-9,10-diones (**3e** and **4e**) and 9,10-dihydroxyanthracene-1,4-diimines (**1h** and **2h**), obtained using the 3-21G basis set[a]

Tautomer	E_m	E_r	μ	Atomic charges O(9)	H	N(1)	O(15)	Ref.
3b	−791.366 629		5.38	−0.365	0.240	−0.352		19
3e	−1017.744 121	11.34	3.39	−0.343	0.227	−0.132	−0.246	
4e	−1017.762 189	0.00	2.48	−0.361	0.275	−0.102	−0.256	
2h	−1016.585 118	0.00	2.25	−0.357	0.275	−0.089	−0.254	
1h	−1016.586 202	0.68	1.04	−0.306	0.212	−0.147	−0.255	

[a] E_m is the molecular energy (in au; 1 au ≈ 4.359 75 × 10^{-18} J), μ is the dipole moment (in D); E_r is the energy of each tautomer relative to the lowest energy form (in kcal mol^{-1}); the atomic charges were obtained by the Lowdin method.[21]

tetrahedral sp^3 conformation, respectively. In the imine **4e**, the oxygen atom attached to the imine nitrogen is constrained to lie in the same plane because of the double bond. There is no such constraint in the amine **3e**, however, where the nitrogen can adopt either a planar or tetrahedral conformation.

The atomic charge at the nitrogen atom of 1,4-diamino-2,3-dihydroanthracene-9,10-dione **3b** is strongly negative with a value of −0.352, but the replacement of one hydrogen atom of the planar amino group by an oxygen atom has a substantial impact on the charge. Thus in 1,4-bis(methoxyamino)-2,3-dihydroanthracene-9,10-dione **3e**, the charge on nitrogen is reduced and partly transferred to the oxygen atom to give values of −0.132 and −0.246, respectively (Table 3). In the structure optimisation, both atoms were placed in a planar sp^2 conformation at the starting point, but as the optimisation proceeds, the two adjacent overlapping lobes of the electron rich P_Z orbitals on nitrogen and oxygen will repel one another very strongly. As a result, the molecule will attempt to accommodate this repulsion either by stretching the N–O bond or by changing its conformation. The lowest energy option is clearly a switch from a planar sp^2 conformation on both nitrogen and oxygen, to a tetrahedral sp^3 conformation where the lone pairs of electrons on each atom are now pointing away from one another. The calculated torsion angle C(13)–C(1)–N(1)–O(15) and bond angle N(1)–O(15)–C(17) fully support this argument with values of around 151° for the former and 110° for the latter (Table 1).

A similar picture emerges in the fully aromatic structures **2h** and **1h**. In the former, the oxygen atom attached to the imine nitrogen is constrained to lie in the same plane because of the double bond, while in the latter **1h** there is no such constraint and the nitrogen can now adopt either a planar or tetrahedral conformation. Crystallographic data[12] clearly shows that 1,4-diaminoanthracene-9,10-dione **1e** is preferred over the tautomeric 1,4-diimine **2e**, but the introduction of an oxygen atom in place of one hydrogen would be expected to distort the fully planar conformation of **1e** and result in a tetrahedral sp^3 conformation at both nitrogen and oxygen in the same way as for **3e**. The atomic charges at the nitrogen and oxygen atoms are again consistent with this argument with both negatively charged (Table 3). The energy barrier between the two possible tautomers **1h** and **2h** would be expected to narrow significantly as a result of the destabilisation of the planar conformation of **1h**. This is reflected in the calculated energies where there is little to choose between the 1,4-diimine **2h** and 9,10-dione **1h** with the latter predicted to be marginally more stable by 0.68 kcal mol^{-1} than the former (Table 3).

Conclusions

Calculations on the gas phase structures and tautomeric preferences of 1,4-bis(methoxyamino)anthracene-9,10-dione and its reduced form have shown that 1,4-bis-(methoxyamino)anthracene-9,10-dione **1h** is marginally preferred over 9,10-dihydroxy-1,4-bis(methoxyimino) anthracene (**2h**) by 0.68 kcal mol^{-1}. The reduced forms show the opposite trend with 9,10-dihydroxy-1,4-bis(methoxyimino)-2,3-dihydroanthracene **4e** preferred by 11.3 kcal mol^{-1} over 1,4-bis(methoxyamino)-2,3-dihydroanthracene-9,10-dione **3e** in line with experimental data recorded in chloroform. The presence of an oxygen atom adjacent to the nitrogen atom in the methoxylamine substituent results in a loss of planarity and hence destabilisation of the anthracene-9,10-dione tautomers **1h** and **3e**.

Experimental

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Proton and ^{13}C NMR were recorded on a Bruker WP-270SY or WM-250 pulsed Fourier transform spectrometer. The mass spectra were run on a Finnagan MAT 4610 instrument. Microanalyses were performed by Robertson Laboratories, Madison, NJ.

1,4-Diaminoanthracene-9,10-dione (1e)

A solution of the diimine **4e** (0.14 g, 0.47 mmoles) in nitrobenzene (2 cm^3) was refluxed for 19 h. The nitrobenzene was removed by steam distillation. The purple residue was collected by filtration, washed with water and air dried. The solid was recrystallised from chloroform to yield the title compound **1e** as violet crystals (68%), mp 266–269 °C; $\delta_H(CDCl_3)$ 8.34 (2 H, m), 7.71 (2 H, m), 7.06 (4 H, br s) and 6.90 (2 H, br s).

9,10-Dihydroxy-1,4-bis(methoxyimino)anthracene (2h)

A mixture of 1,4-difluoroanthracene-9,10-dione (0.5 g, 2 mmol) and methoxylamine (1.0 g, 20 mmol) in anhydrous DMSO (5 cm^3) was stirred at room temperature for 14 days. The resultant brick red mixture was quenched with ice and the red solid was collected by filtration. The solid was chromatographed over silica gel (30:70 pentane–chlorofom) to yield the title compound **2h** (0.02 g, 6%) as a metallic red solid. Analytical and X-ray samples were prepared by recrystallisation from chloroform to yield metallic red needles, mp 174–175 °C; $\delta_H(CDCl_3)$ 11.95 (2 H, s), 8.34 (2 H, m), 7.58 (2 H, m), 7.47 (2 H, s) and 4.11 (6 H, s); $\delta_C(CDCl_3)$ 151.5, 148.6, 127.4, 126.5, 123.1, 121.5, 103.9 and 63.2; *m/z* 299.2 (M^+, 100%); ν_{max}(KBr)/cm^{-1} 3463, 1633 and 1593 (Found: C, 63.7; H, 4.5; N, 9.2. Calc. for $C_{16}H_{14}N_2O_4$: C, 64.43; H, 4.73; N, 9.39%).

X-Ray structure determination of compound 2

The X-ray structural data for **2h** have been deposited at the Cambridge Crystallographic Data Centre, University Chemical Labs, Lensfield Road, Cambridge, UK CB2 1EW.§

§ For details of the deposition scheme, see 'Instructions for Authors', *J. Chem. Soc., Perkin Trans. 2*, 1996, Issue 1.

9,10-Dihydroxy-1,4-bis(methoxyimino)-2,3-dihydroanthracene (4e)

A mixture of leucoquinizarin (**4a**, 1.0 g, 4.1 mmol) and methoxylamine hydrochloride (1.4 g, 16.5 mmol) in pyridine (6 cm^3) was stirred at room temperature under a nitrogen atmosphere for 72 h. The red–orange mixture was quenched with ice water and the resultant orange–yellow solid was collected by filtration, washed with cold ethanol and dried under vacuum to yield to title compound **4e** (quantitative) as an amorphous yellow solid. The product was recrystallised from ethanol to yield the title compound **4e** (0.91 g, 74%) as metallic gold plates, mp 165–166 °C; $\delta_H(CDCl_3)$ 12.06 (2 H, s), 8.30 (2 H, m), 7.56 (2 H, m), 4.05 (6 H, s) and 2.98 (4 H, s); $\delta_C(CDCl_3)$ 157.8, 148.0, 127.0, 126.8, 123.5, 105.0, 62.6 and 19.9; *m/z* 301 (44.9%, M^+) and 300.2 (100). ν_{max}(KBr)/cm^{-1} 1631 and 1596. Analytical data could not be obtained as compound **4e** decomposes partially on standing at room temperature.

1,4-Bis(methoxyimino)-2,3-dihydroanthracene-9,10-dione (6)

Activated manganese(IV) dioxide (0.5 g, 5.9 mmol) was added to a solution of diimine of **4** (0.35 g, 1.2 mmol) in chloroform (3 cm^3). The mixture was flushed with nitrogen and stirred at room temperature for 45 h. The manganese dioxide was removed by filtration and the filtrate was concentrated by rotary evaporation to yield the title compound **6** (0.28 g, 79%) as an amorphous red–orange solid. The analytical sample was obtained as red–orange rhombs, mp 130.5–131.5 °C; $\delta_H(CDCl_3)$ 8.08 (2 H, m), 7.71 (2 H, m), 4.12 (6 H, s) and 2.84 (4 H, s); $\delta_C(CDCl_3)$ 182.1, 150.2, 135.8, 133.6, 132.5, 126.4, 63.0 and 21.3; ν_{max}(KBr)/cm^{-1} 1675, 1633 and 1587 (Found: C, 64.36; H, 4.67; N, 9.39. Calc. for $C_{16}H_{14}N_2O_4$: C, 64.36; H, 4.37; N, 9.39%).

References

1 A. P. Krapcho, Z. Getahun, K. L. Avery, Jr., K. J. Vargas, M. P. Hacker, S. Spinelli, G. Pezzoni and C. Manzotti, *J. Med. Chem.*, 1991, **34**, 2373.
2 R. K.-Y. Zee-Cheng and C. C. Cheng, *J. Med. Chem.*, 1978, **21**, 291.
3 R. K.-Y. Zee-Cheng, E. G. Podrebarac, C. S. Menon and C. C. Cheng, *J. Med. Chem.*, 1979, **22**, 501.
4 K. C. Murdock, R. G. Child, F. F. Fabio, R. B. Angier, R. E. Wallace, F. E. Durr and R. V. Citarella, *J. Med. Chem.*, 1979, **22**, 1024.
5 C. C. Cheng and R. K.-Y. Zee-Cheng, *Prog. Med. Chem.*, 1983, **20**, 83.
6 R. K.-Y. Zee Cheng and C. C. Cheng, *Drugs Future*, 1983, **8**, 229.
7 T. D. Shenkenberg and D. D. Von Hoff, *Ann. Int. Med.*, 1986, **105**, 67.
8 D. Faulds, J. A. Balfour, P. Chrisp and H. D. Lantry, *Drugs*, 1991, **41**, 400.
9 M. Kikuchi, T. Yamagishi and M. Hida, *Dyes Pigm.*, 1981, **2**, 143.
10 A. P. Krapcho, K. L. Avery, Jr., K. J. Shaw and J. D. Andrews, *J. Org. Chem.*, 1990, **55**, 4960.
11 D. L. Kirkpatrick, *Drugs Today (Barcelona)*, 1990, **26**, 91.
12 S. Kahino, K. Senoo and M. Maisa, *Acta Crystallogr. Sect. C (Cryst. Struct. Commun.)*, 1988, **44**, 1044.
13 A. M. Chippendale, A. Mathias, R. S. Aujla, R. K. Harris, K. J. Packer and B. J. Say, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1357.
14 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
15 J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209; 221.
16 MOPAC 93, J. J. P. Stewart and Fujitsu Limited, Tokyo, Japan, Copyright Fujitsu Limited, 1993. Obtained from QCPE, Department of Chemistry, Indiana University, Bloomington, Indiana 47405, USA.
17 See for example: W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley, New York, 1986.
18 M. F. Guest and P. Sherwood, GAMESS, an *ab initio* program, The Daresbury Laboratory, Warrington, UK.
19 J. O. Morley, *J. Phys. Chem.*, 1995, **99**, 5956.
20 See for example, J. V. Greenhill, *J. Chem. Soc. B.*, 1969, 299.
21 P.-O. Lowdin, *J. Phys. Chem.*, 1950, **18**, 365.

Paper 5/05702G
Received 29*th August* 1995
Accepted 2*nd October* 1995