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Reaction of Imines of Aminoanthraquinones with Formaldehyde and Alkenes

Patrice J. Gregoire, John M. Mellor* and Glynn D. Merriman

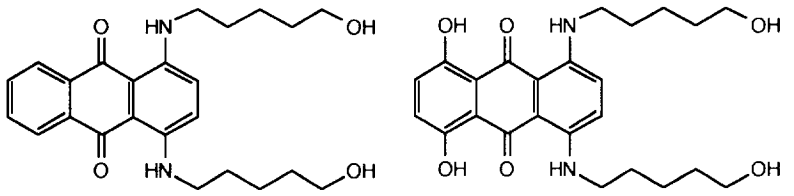
Department of Chemistry, Southampton University, Southampton, SO9 5NH, England

Abstract: *By reaction of mono- and di-aminoanthraquinones with formaldehyde and diverse electron rich alkenes in acetonitrile in the presence of trifluoroacetic acid cyclocondensation affords a series of tetrahydroquinolines. The resulting tetra-, penta- and hepta-cyclic products all contain the anthraquinone sub-structure. Aspects of regio- and stereo-selectivity are discussed and the potential of this series of aminoanthraquinones for metal ion chelation and binding in DNA are noted.*

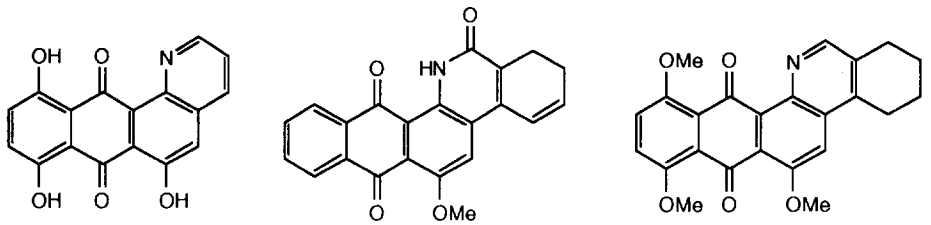
Interest in aminoanthraquinones has been reactivated. The use of mono- and di-aminoanthraquinones in the dyestuffs industry has been well established for many years. Recently a number of other features of aminoanthraquinone chemistry have attracted intense interest. A review[1] of the fascinating enediyne anticancer antibiotics details the role of anthraquinones such as dynemicin A in the cleavage of DNA. In certain cases[2] there is also evidence that an anthraquinone moiety can intercalate into DNA and a side arm of the anthraquinone, for example an alkylamino substituent, can bind to protein. In such cases due to disruption of DNA protein interactions there can be interference with topoisomerase II and antitumor activity is observed. Other important aspects of DNA cleavage by anthraquinones[3] have recently been discussed. The exciting biological results with the complex dynemicin A have stimulated synthesis of key sub-units. A tetracycle[4] having a core aminoanthraquinone portion related to dynemicin A has recently been synthesized, and related pentacycles[5] have also been prepared. Other aminoanthraquinones such as mitoxantrone and ametantrone are now used clinically. In particular mitoxantrone, a 1,4-diaminoanthraquinone, has shown clinical effectiveness[6] in the treatment of human malignancies. The specificity of binding[7] in DNA, in which it intercalates, has been examined. However a major limitation in anticancer therapy is cardiotoxicity, as found with the related daunomycin and adriamycin. The need for aminoanthraquinones with less toxic side effects has therefore stimulated further synthetic studies[8].

A second, but related, area of interest concerns the interaction of aminoanthraquinones with metal ions. These metal-aminoanthraquinone complexes constitute a different category of anticancer agent, where the interaction with DNA is different from that of the free drugs. Thus in binding studies with calf thymus DNA it is found[9] that such aminoanthraquinone - metal ion complexes cleave DNA. These biological studies further emphasize the need to establish efficient routes to a variety of aminoanthraquinones and related compounds. Earlier we have extended[10,11] the initial studies of Grieco and Bahsas[12], which permit the synthesis of a variety of

tetrahydroquinolines. In this paper we extend this chemistry to the elaboration of aminoanthraquinones to afford a rich diversity of modified aminoanthraquinones. The modifications extend to the creation of tetra-, penta- and heptacyclic structures containing aminoanthraquinone sub-structures of relevance to those programmes concerned with the biological activity of aminoanthraquinones.



Mitoxantrone Ametantrone

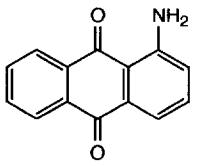
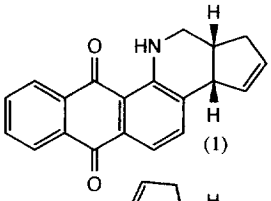
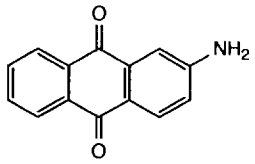
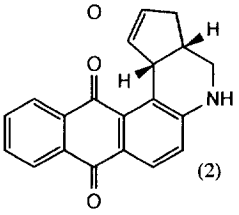
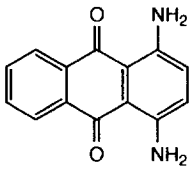
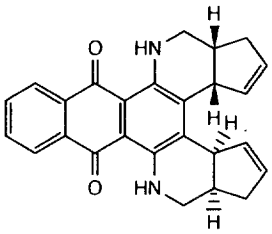
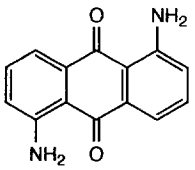
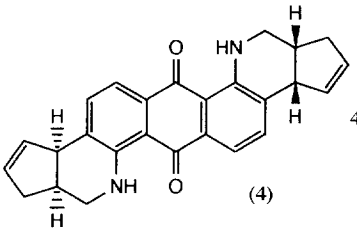


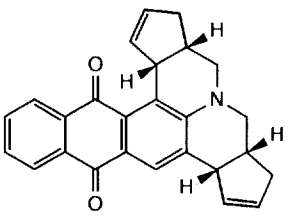
Recently synthesized anthraquinone substructures related to dynemicin A

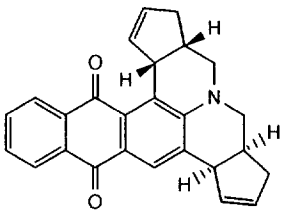
Studies with anthraquinones were initiated by an investigation of the reaction with formaldehyde and cyclopentadiene, under conditions analogous to those used by Grieco and Bahsas[12] in their study of anilines. Our results with cyclopentadiene are reported in Table 1. Reactions with 1-aminoanthraquinone, 2-aminoanthraquinone, 1,4-diaminoanthraquinone and 1,5-diaminoanthraquinone gave the respective adducts (1-4). 1-Aminoanthraquinone afforded the pentacycle (1) in 95% yield, the product being easily isolated by chromatography and purified by recrystallisation. The structural assignment is based on the spectroscopic data, and the stereochemical assignment by analogy with earlier related cyclocondensations[10-12]. The quinone (1) is deeply red and is isolated as very fine crystals. Reaction with 2-aminoanthraquinone is complicated by the possibility of reaction with either a single, or two equivalents of formaldehyde and cyclopentadiene. By appropriate selection of the reaction conditions the pentacycle (2) can be isolated in 74% yield, conditions which lead to minor quantities of the heptacycles (5) and (6). However by use of extra formaldehyde and cyclopentadiene the mixture of the products (5) and (6) of further reaction were isolated in 96% yield. However in this case the *cis* and *trans* products could not be separated by chromatography or fractional crystallisation. In each of the products (2), (5) and (6) there is a need to define the regiochemistry of cyclisation. Loss of a resonance in the three products, at about 8.1ppm, associated with an α-proton, readily permitted these assignments. No other regioisomers were observed and the regioselectivity is very high. The possibility that the isomers (5) and (6) might represent regioisomers, rather than stereoisomers, can be rejected by the close similarity of the ^{1}H and ^{13}C NMR spectra of the two compounds.

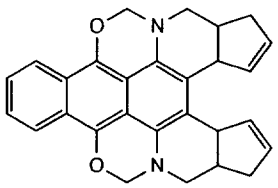
TABLE 1

Reaction of Aminoanthraquinones with Formaldehyde and Cyclopentadiene

Anthraquinone	Products	Yield (%)	Minor Products
	 (1)	95	None isolated
	 (2)	74	(5) and (6)
	 (3)	43	(7)
	 (4)	42	None isolated


(5)


(6)

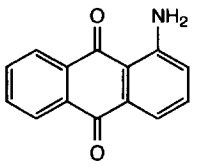
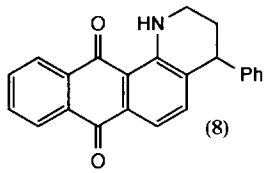
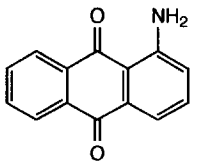
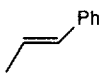
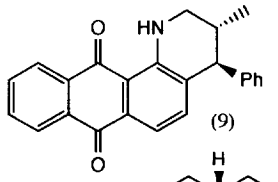
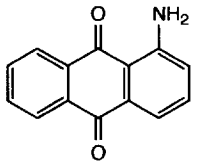
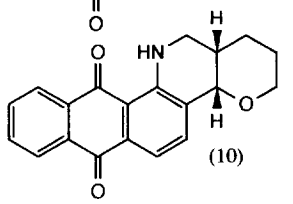
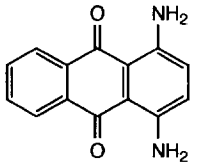
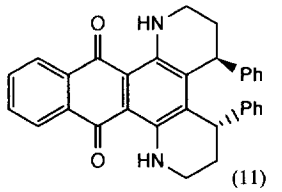
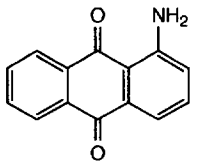
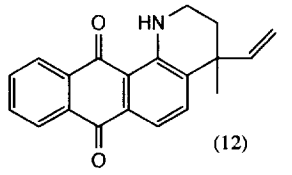

(7)

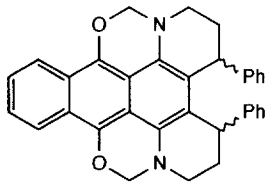
Reaction of 1,4- and 1,5-diaminoanthraquinone, using excess formaldehyde and cyclopentadiene, afforded in the former case a minor and major product, and in the latter case a single product. The minor product from 1,4-diaminoanthraquinone is tentatively assigned structure (7). Isolated as an orange solid in 4% yield this nonacycle has not been investigated to find whether it represents a mixture of diastereoisomers. However it is interesting to observe that the major product of dicyclocondensation (3) is isolated as a single diastereoisomer. On the grounds that the second cyclocondensation is likely to occur with the minimum steric repulsion we favour the *trans* stereochemistry as shown for the quinone (3). Reaction with 1,5-diaminoanthraquinone takes place in a similar manner, although we have not observed an analogue of the nonacycle (7). Again a single diastereoisomer, assigned on similar grounds the *trans* structure (4), is isolated. In this case minor chromatographic fractions suggest the formation of other minor products, but they represent insubstantial quantities. However this series of compounds is so highly coloured that observation of minor products is all too easy.

In Table 2 are described some cyclocondensations of styrene, *trans*-β-methylstyrene, 3,4-dihydro-2*H*-pyran and isoprene with aminoanthraquinones. The major products of cyclocondensation (8-12) were isolated and characterized in an analogous manner to those shown in Table 1. Although the product (8) from reaction of styrene with 1-aminoanthraquinone is obtained in 86% yield, the inefficient reaction of isoprene with 1-aminoanthraquinone to afford the quinone (12) suggests that satisfactory cyclocondensations are only observed with aminoanthraquinones and relatively electron rich alkenes. Reaction with *trans*-β-methylstyrene is efficient to afford a single major product, the adduct (9). The assignment of a *trans* stereochemistry in the tetracyclic (9) is possible by observation of the coupling constant (J 8.1Hz) between the C<u>H</u>-Ph proton at 3.7ppm and the C<u>H</u>-Me proton at 2.22ppm. It should be noted that neither a *cis* product was observed, nor any intermediate tricyclic alcohol, which might, on further reaction afford tetracyclic products. The absence of such an alcohol contrasts with the course of reaction[13] between 1-aminoanthraquinone, formaldehyde and α-methylstyrene. In the latter case an alcohol intermediate is isolated, but this, by further exposure to the reaction conditions, can be transformed to tetracyclic products. The difference in behaviour is attributed to formation of an intermediate secondary carbocation, in the case of *trans*-β-methylstyrene, whereas with α-methylstyrene the corresponding carbocation is tertiary and therefore less easily cyclized. Reaction of the enol ether, 3,4-dihydro-2*H*-pyran with 1-aminoanthraquinone and formaldehyde gave a single product (10) in a modest 36% yield. The low yield was attributed in part to the very poor solubility of the product, which created difficulties on chromatography. The question of the stereochemistry of the pentacycle (10) was resolved by observation of the C<u>H</u>-O proton at 4.53ppm (doublet J 2.7Hz), consistent with a *cis*, but not a *trans* stereochemistry. Finally the ability of a diaminoanthraquinone to undergo double cyclocondensation was assessed by reaction of 1,4-diaminoanthraquinone with formaldehyde and styrene. Three products could be isolated separately from this reaction, although the yields were diminished by solubility problems. A minor fraction is tentatively assigned the heptacyclic structure (13), and is probably a mixture of stereoisomers. The other two products are the diastereoisomers (11) and (14). On steric grounds the major product (11) is again assigned the *trans* stereochemistry, and the minor cyclocondensation product is assigned the *cis* stereochemistry (14). The products (11) and (14) show very similar spectroscopic features, and after recrystallisation appear as deeply blue solids.

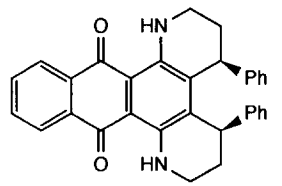
TABLE 2

Reaction of Aminoanthraquinones with Formaldehyde and Alkenes

Anthraquinone	Alkene	Products	Yield (%)	Minor Products
		 (8)	86	None
		 (9)	82	None
		 (10)	36	None
		 (11)	41	(13) (14)
		 (12)	15	None



(13)



(14)

The results in Tables 1 and 2 establish that the cyclocondensation procedure using formaldehyde to give in the presence of trifluoroacetic acid, an iminium cation, capable of being captured by a variety of electron rich alkenes, is a simple method of annelation to generate diverse novel monoamino- and diamino-anthraquinones. In particular the illustration that simple styrenes undergo cycloaddition efficiently highlights the potential of this procedure for generation of polycyclic quinones relevant to those programmes concerned with the medicinal chemical implications of related quinones. We are also interested in the interaction of metal ions with these aminoquinones and in preliminary investigations have established by electrochemical methods their complexation with a variety of metal ions. A wide variety of quinones are easily prepared by this one-pot procedure from simple precursors.

Experimental

General methods are described elsewhere[13]. The NMR data are reported using a conventional numbering system referring to aminoanthraquinones.

Reaction of 1-aminoanthraquinone with formaldehyde and cyclopentadiene

Trifluoroacetic acid (0.50 g, 1 eq) was added to 1-aminoanthraquinone 97% (1.00 g; 4.34 mmol) partially dissolved in acetonitrile (40 ml) to give a red brown heterogenous mixture. After stirring for 10min. under nitrogen, a mixture at 0°C of cyclopentadiene (0.59 g, 2 eq) and formalin solution (37% 0.70 ml., 2 eq) in acetonitrile (2 ml) was added to the former mixture which turned red purple while stirring under nitrogen at room temperature for 45 min. The dark mixture was added to saturated sodium bicarbonate (100 ml) and was extracted with dichloromethane (5x100 ml). The combined organic layers were dried over anhydrous magnesium sulfate and, after filtration, were concentrated under reduced pressure to give a dark purple solid (1.40 g). Flash chromatography on alumina (250 g) with ether/dichloromethane 10/0 to 0/10 as eluant gave one main fraction as a dark purple solid (1.24 g, 95%), Rf=0.65 (ether/petrol 1/1). Recrystallisation from methanol led to purple woolish crystals of 6,11-dioxo-3a,6,11,12,13,13a-hexahydro-1*H*-cyclopenta[1,2-*c*]-naphtho[2,3-*h*]quinoline (1), m.p.=165-167°C. δH(270 MHz,TMS,$CDCl_3$) 9.64 (1H, s, NH); 8.25 (1H, d,J7Hz, ArC_8-H); 8.22 (1H, d,J7Hz, ArC_5-H); 7.71 (2H, m, ArC_6-H, ArC_7-H); 7.58 (1H, d,J7.6Hz, ArC_4-H); 7.43 (1H, d,J7.6Hz, ArC_3-H); 5.78 (2H, m, HC=CH); 3.97 (1H, m, ArCH); 2.99 and 3.31 (2H, m, CH_2N); 2.18 and 2.70 (3H, m, CH and CH_2) δC(68 MHz,TMS,$CDCl_3$) 184.91 (ArC_9=O); 183.73 (ArC_{10}=O); 150.29 (ArC_1-N); 135.34, 135.17, 135.02, 133.91, 133.47, 133.28, 132.99, 132.39, 129.68, 126.82 (ArC and C=C); 116.23 (ArC_4-H); 113.20 (ArC_{9a}); 46.85 (Ar-CH); 42.27 (NCH_2); 37.27(CH_2); 34.16 (CH). $\nu_{max.}$ ($CHCl_3$) 3530, 3210, 3020, 2950, 2850, 1665, 1630, 1600, 1580, 1510, 1460, 1380, 1365, 1330, 1315 1270, 1185, 990cm.$^{-1}$. m/z Found: 301.1086 (M^+100%); 286 (18); 273 (21); 260 (31); 247 (6); 149 (7). $C_{20}H_{15}NO_2$ requires 301.1103.

Reaction of 2-aminoanthraquinone with formaldehyde and cyclopentadiene

Trifluoroacetic acid (0.61 g, 3 eq) was added to 2-aminoanthraquinone (0.40 g, 1.79 mmol) partially dissolved in acetonitrile (30 ml) to give a brown heterogenous mixture. After 15 min. of stirring under nitrogen, a mixture at 0°C of cyclopentadiene (0.36 g, 3 eq) and formalin solution 37% (0.44 g, 3 eq) in

acetonitrile (3 ml) was added to the former mixture which turned red very quickly while stirring under nitrogen at room temperature for 45 min. The dark red mixture was added to saturated sodium bicarbonate (150 ml) and was extracted with dichloromethane (2x150 ml). The combined organic layers were dried over anhydrous magnesium sulfate and after filtration, were concentrated under reduced pressure to give a dark red oil (0.80 g). Flash chromatography on alumina (100 g) with ether/ethyl acetate 10/0 to 5/5 as eluant gave a single main fraction as a red solid (0.65 g, 96% Rf=0.74; ether as eluant) the mixture of both diastereoisomers the 'd,l' isomer (6) ("M") and the 'meso' isomer (5) ("m") in relative ratios 80:20 respectively (deduced from the integration curves). Recrystallisation from ethanol led to cottonish red crystals, m.p.=169-171°C. δH(270 MHz, TMS, $CDCl_3$) 8.19 (2H, m, ArC_5-H, ArC_8-H); 8.06 (1H, s, ArC_4-H); 7.69 (2H, m, ArC_6-H, ArC_7-H); 5.84 (1H, m) and 5.73 (3H, m) HC=CH); 5.15 (1H, m, ArC-H); 4.04 (1H, m, ArC-H); 3.04 (2H, m, CH_2N), 2.65-2.90 (6H, m) and 2.29 (2H, m) (CH_2, CH). δC(68 MHz, TMS, $CDCl_3$) 186.05, 182.63 (CO); 151.44 (ArCN); 124.82-137.66 (18 resonances, ArC and C=C); 55.66 (NCH_2, M); 53.01 (NCH_2, m); 52.13 (NCH_2, M); 51.28 (NCH_2, m); 47.73 (ArCH, m); 47.44 (ArCH, M); 34.13-37.56 (8 resonances, CH and CH_2). $\nu_{max.}$($CHCl_3$) 3005, 2940, 2850, 1710, 1665, 1570, 1495, 1445, 1410, 1340, 1330, 1295, 1280, 1250cm.$^{-1}$ m/z Found: 379.1561 (M^+100%); 364 (6); 35 (10); 338 (14); 325 (5).$C_{26}H_{21}NO_2$ requires 379.1572.

In a second experiment trifluoroacetic acid (0.37 g, 3 eq) was added to 2-aminoanthraquinone (0.25 g, 1.12 mmol) partially dissolved in acetonitrile (110 ml) to give a brown heterogenous mixture which was warmed at reflux (~ 80°C) under stirring and nitrogen. A mixture at 0°C of cyclopentadiene (0.15 g, 2 eq) and formalin solution 37% (0.09 g, 1 eq) in acetonitrile (4 ml) was added in 20 min. to the former mixture. The homogenous reaction mixture was stirred under nitrogen at reflux for a further 25 min.. After cooling to room temperature, the dark red mixture was added to saturated sodium bicarbonate (200 ml) and was extracted with dichloromethane (2x150 ml). The combined organic layers were dried over anhydrous magnesium sulfate and, after filtration, were concentrated under reduced pressure to give a red solid (0.37 g). Flash chromatography on alumina (100 g) with ether/dichloromethane/ethyl acetate 10/0/0 to 0/8/2 as eluant gave two main fractions. The minor fraction (0.06 g, 14%, Rf=0.74) was the dicyclisation products and the major fraction, the quinone (2), was isolated as a purple solid (0.25 g, 74%, Rf=0.65). Recrystallisation from methanol led to cottonish purple crystals of 8,13-dioxo-3a,4,5,8,13,13c-hexahydro-3*H*-cyclopenta[1,2-*c*]-naphtho[2,3-*f*] quinoline (2). mp=169-171°C. δH(270 MHz,TMS,$CDCl_3$) 8.20 (2H, m, ArC_5-H, ArC_8-H); 8.10 (1H, d,J8.5Hz, ArC_4-H); 7.71 (2H, m, ArC_6-H, ArC_7-H); 6.80 (1H, d,J8.5Hz, ArC_3-H) 5.77 and 5.84 (2H, m, HC=CH); 4.97 (1H, m, ArC-H); 4.71 (1H, m. NH); 3.04 (1H, m) and 3.14 (1H, m) (CH_2N); 2.61-2.78 (2H, m) and 2.12 (1H, m) (CH_2 and CH) δC(68 MHz,TMS,$CDCl_3$) 186.34 (ArC_9=O); 182.42 (ArC_{10}=O); 151.47 (ArC_2); 137.15, 135.34, 135.17, 134.04, 133.37, 133.51, 129.41, 128.39, 128.08, 127.23, 126.39, 124.53, 119.13 (ArC, C=C); 45.01 (ArCH); 42.40 (NCH_2); 36.99 (CH_2); 34.85 (CH). $\nu_{max.}$ ($CHCl_3$) 3460, 3100-3000, 2960, 2870, 1680, 1590, 1580, 1510, 1340, 1310, 1300, 1290, 1100-1200 cm.$^{-1}$ m/z Found: 301.1107 (M^+100%); 286 (12); 272 (25); 260 (22); 247 (9); 167 (17); 149 (42). $C_{20}H_{15}NO_2$ requires 301.1103.

Reaction of 1,4-diaminoanthraquinone with formaldehyde and cyclopentadiene

Trifluoroacetic acid (0.93 g, 2 eq) was added to 1,4-diaminoanthraquinone (1.00 g, 4.07 mmol) partially dissolved in acetonitrile (40 ml) to give a purple heterogenous mixture. After 15 min. of stirring under nitrogen, a mixture at 0°C of cyclopentadiene (0.81 g, 3 eq) and formalin solution 37% (0.66 g, 2 eq) in acetonitrile (3 ml) was added to the former mixture, which turned blue very quickly while stirring under nitrogen at room temperature for 25 min. The dark blue mixture was added to saturated sodium bicarbonate (200 ml) and was extracted with dichloromethane (3x20ml). The combined organic layers were dried over anhydrous magnesium sulfate and, after filtration, were concentrated under reduced pressure to give a dark blue solid. Flash chromatography on alumina with eluant petrol/ether/dichloromethane 2/8/0 to 0/0/10 gave minor and major fractions. The former an orange brown solid (0.06 g, 4%, Rf=0.72) was tentatively identified as the nonacycle (7) m/z(e.i.) Found: 420 (M^+100%); 379 (15.6); 210 (6.9); 189 (10.7). ν_{max}($CHCl_3$) no bands for N-H and C=O. The major fraction a blue solid (0.69 g, 43%, Rf=0.65) was the single diastereoisomer (3). Recrystallisation from ethanol led to blue dark crystals of 9,14-dioxo-3a,3d,6a,7,8,9,14,15,16,16a-decahydro-1H,6*H*-dicyclopenta[2,1-*a*:1,2-*k*]-naphtho[2,3-*f*]-4,7-phenanthroline (3). mp=223-224°C. δH(270 MHz, TMS, $CDCl_3$) 8.32 (2H, m, ArC_5-H, ArC_8-H); 7.67 (2H, m, ArC_6-H, ArC_7-H); 5.87 (2H, m, HC=CH); 5.77 (2H, m, HC=CH); 4.15 (2H, m, ArCH); 3.13 and 3.30 (CH_2N); 2.21 and 2.75 (CH, CH_2). δC(68 MHz, TMS, $CDCl_3$) 180.90 (CO) 146.34 (ArCN); 134.76, 133.66, 133.08, 131.91, 131.76, 126.04, 108.30 (Ar C, C=C); 44.04, 41.53, 37.45, 34.45 (CH, CH_2). $\nu_{max.}$ ($CHCl_3$) 3460, 3070, 3010, 2940, 1850, 1580, 1560, 1505, 1455, 1380, 1360, 1320, 1270, 1210, 1020 $cm.^{-1}$ m/z Found: 394.1652 (M^+100%); 379 (4.5); 365 (4.0); 353 (16.3); 337 (5.0); 327 (3); 312 (3). $C_{26}H_{22}N_2O_2$ requires 394.1681

Reaction of 1,5-diaminoanthraquinone with formaldehyde and cyclopentadiene

Trifluoroacetic acid (0.93 g, 2 eq) was added to 1,5-diaminoanthraquinone (1.00 g, 4.07 mmol) partially dissolved in acetonitrile (25 ml) to give a purple heterogenous mixture. After 15 min. of stirring under nitrogen, a mixture at 0°C of cyclopentadiene (1.08 g, 4 eq) and formalin solution 37% (1,32 g, 4 eq) in acetonitrile (4 ml) was added and the solution was stirred under nitrogen at room temperature for 100 min. The dark purple mixture was added to saturated sodium bicarbonate (200 ml) and was extracted with dichloromethane (3x20 ml). The combined organic layers were dried over anhydrous magnesium sulfate and, after filtration, were concentrated under reduced pressure to give a dark purple solid (1.3 g). Flash chromatography on alumina with ether/ethyl acetate 10/0 to 0/10 as eluant gave as a single main fraction 6,14-dioxo-3a,6,7,8,8a,11a,14,15,16,16a-decahydrobenzo[1,2-*h*:4,5-*h*']bis-(cyclopenta[1.2-*c*]quinoline) (4) as a purple solid (0.67 g, 42%, Rf=0.74; ether as eluant) Recrystallisation in ethanol led to a purple powder, mp 240°C δH(270 MHz, TMS, $CDCl_3$) 9.57 (2H, m, NH); 7.53 (2H, d,J7.6Hz, ArC_4-H, ArC_8-H); 7.40 (2H, d,J7.6Hz, ArC_3-H, ArC_7-H); 5.75-5.80 (4H, m, HC=CH); 3.95 (2H, m, ArCH); 3.26-3.35 (2H, m) and 2,97 (2H, m) (CH_2N); 2.65-2.75 (4H,m) and 2.16 (2H, m) (CH_2 and CH). δC(68 MHz, TMS, $CDCl_3$) 185.39 (ArC_9=O); 149.88 (ArC_1-N, ArC_5-N); 135.57, 134.87, 134.26, 130.73, 129.48 (ArC; C=C); 115.36 (ArC_4-H, ArC_8-H); 113.40 (ArC_{9a}, ArC_{10a}); 46.73 (ArCH); 42.33 (NCH_2); 37.30 (CH_2); 34.28 (CH). $\nu_{max.}$ ($CHCl_3$ 3510, 3300, 3010, 2940,

2850, 1615, 1590, 1570, 1505, 1455, 1370, 1350, 1325, 1260, 1065cm.$^{-1}$ m/z Found: 394.1653 (M^+100%); 379 (5); 366 (13); 353 (14); 328 (7). $C_{26}H_{22}N_2O_2$ requires 394.1681.

Reaction of 1-aminoanthraquinone with formaldehyde and styrene

Trifluoroacetic acid (0.99 g, 1 eq) was added to 1-aminoanthraquinone (2.00 g, 8.68 mmol) partially dissolved in acetonitrile (45 ml) to give a red brown heterogenous mixture. After 10 min. of stirring under nitrogen, a mixture of styrene (1.81 g, 2 eq) and formalin solution 37% (1.41 g, 2 eq) in acetonitrile (2 ml) was added to the former mixture which was stirred under nitrogen at room temperature for 40 min. The same quantities of styrene and formaldehyde were then added to the dark red reaction mixture which was stirred at room temperature for a further 95 min. It was finally warmed to reflux (75-80°C) for 45 min. After cooling to room temperature, the dark mixture was added to saturated sodium bicarbonate (100 ml) and was extracted with dichloromethane (5x100 ml). The combined organic layers were dried over anhydrous magnesium sulfate and, after filtration, were concentrated under reduced pressure to give a dark red solid (3.0 g). Flash chromatography on alumina (250 g) with ether/dichloromethane 10/0 to 0/10 as eluant gave one main fraction 7,12-dioxo-4-phenyl-1,2,3,4,7,12-hexahydronaphtho[2,3-*h*]quinoline (8) as a red purple solid, (2.52 g, 86%, Rf=0.64 (ether/petrol 5/5). Recrystallisation from ethanol led to purple woolish crystals, m.p. 178.5-180°C. δH(270 MHz, TMS, $CDCl_3$) 10.11 (1H, brs, NH); 8.29 (1H, d,J7.4Hz, ArC_8-H); 8.23 (1H, d,J7.3Hz, ArC_5-H; 7.72 (2H, m, ArC_6-H, ArC_7-H); 7.45 (1H, d,J7.5Hz, ArC_3-H); 7.05-7.35 (6H, m, other ArH); 4.20 (1H, t,J7.5Hz, CHPh); 3.42 and 3.52 (2H, m, CH_2N); 2.05-2.25 (2H, m, CH_2). δC(68 MHz, TMS, $CDCl_3$) 184.93 (ArC_9=O); 183.76 (ArC_{10}=O); 149.51 (ArC_1-N); 144.28 (C_{quat}); 135.33, 135.28, 133.94, 133.30, 132.92, 132.30, 128.83, 128.50, 126.95, 126.79 (ArC); 115.64 (ArC_4-H); 111.94 (ArC_{9a}); 43.67 (CHPh); 38.34 (CH_2N); 28.48 (CH_2). $\nu_{max.}$ ($CHCl_3$) 3510, 3290, 3080, 3020, 2970, 2870, 1670, 1630, 1600, 1580, 1520, 1470, 1385, 1365, 1230, 1185, 1015 cm.$^{-1}$ m/z Found: 339.1239 (M^+100%); 324 (13); 260 (49); 248 (5); 91 (10). $C_{23}H_{17}NO_2$ requires 339.1259.

Reaction of 1-aminoanthraquinone with formaldehyde and *trans*-β-methylstyrene

1-Aminoanthraquinone (1.12g, 5mmol) was added to acetonitrile (25ml) containing one equivalent of trifluoroacetic acid (0.57g, 5mmol) to give a 0.2M amine concentration. To this deep red/brown suspension was added with stirring a heterogeneous mixture of *trans*-β-methylstyrene (1.78g, 15mmol) and 37% formalin solution (1.22ml, 15mmol). This deep red suspension was heated at reflux under nitrogen for 1h and then after cooling the mixture was worked up to give a deep red solid (2.75g) which was purified by chromatography on alumina to give (3α,4β)- 1,2,3,4,7,12-hexahydro-3-methyl-7,12-dioxo-4-phenylnaphtho[2,3-*h*]quinoline (9) as a deep red solid (1.46g, 82%, eluant 1/1 dichloromethane/ ether. Rf=0.65). (Rf of 1-aminoanthraquinone=0.35. Rf values for basic alumina, 1/1 ether/petrol). Recrystallisation of (9) from methanol gave a deep red crystalline powder (m.p. 214 - 216.5 °C). δH (270MHz) 10.10 (1H,br.s,NH); 8.29 (1H,br.d,J=7.5Hz,ArC_8-H); 8.22 (1H,br.d,J=7.7Hz,ArC_5-H); 7.71 (2H,m,ArC_6-H,ArC_7-H); 7.41 (1H, d,J=7.6Hz ArC_3-H); 7.24-7.36 (3H, m,Ar-H); 7.10 (2H,d,J=7.0Hz,Ar-H); 6.94 (1H,d,J=7.6Hz,ArC_4-H); 3.70 (1H, br.d,J=8.1Hz,CH-Ph); 3.52

(1H,dbr.t,J=12.7,3.8Hz,C$\underline{H}_2$-N); 3.23 (1H,ddd,J=12.7, 7.9,1.8Hz, C$\underline{H}_2$-N); 2.22 (1H,br.m,C$\underline{H}$-CH_3); 0.95 (3H,d,J=6.6Hz,C$\underline{H}_3$). δC (68MHz) 184.91 (Ar$\underline{C}_9$=O); 183.76 Ar$\underline{C}_{10}$=O); 149.22 (Ar$\underline{C}_1$-N); 143.59 (Cquat.); 135.83 (Ar$\underline{C}_3$-H); 135.33 (Ar$\underline{C}_{4a}$); 133.93 (Ar$\underline{C}_7$-H); 133.30 (Ar$\underline{C}_{8a}$); 133.04 (Ar$\underline{C}_{10a}$); 132.91 (Ar$\underline{C}_6$-H); 132.58 (Ar$\underline{C}_2$-C); 128.99 (Ar$\underline{C}$-H); 128.86 (Ar$\underline{C}$-H); 127.02 (Ar $\underline{C}_8$-H); 126.77 (Ar$\underline{C}_5$-H,Ar$\underline{c}$-H); 115.73 (Ar$\underline{C}_4$-H); 111.67 (Ar$\underline{C}_{9a}$); 51.57 ($\underline{C}$H-Ph); 45.65 ($\underline{C}H_2$-N); 32.28 ($\underline{C}$H-CH_3); 18.10 ($\underline{C}H_3$). $\nu_{max.}$($CHCl_3$):- 3285, 3080, 3020, 2970 ,2935, 2890 ,2860, 1665, 1626, 1598, 1578, 1517 cm^{-1}. m/z [Found:- 353.1412 (M^+ 100%); 338((M-CH_3)$^+$ 16); 324(16); 274(8); 260(28); 91 ($PhCH_2$)$^+$ 8). $C_{24}H_{19}NO_2$ requires 353.1416].

Reaction of 1-aminoanthraquinone with formaldehyde and 3,4-dihydro-2*H*-pyran

1-Aminoanthraquinone (1.12g, 5mmol) was added to acetonitrile (25ml) containing one equivalent of trifluoroacetic acid (0.57g, 5mmol) to give a 0.2M amine concentration. To this deep red/brown suspension was added with stirring a heterogeneous mixture at 0 °C of 3,4-dihydro-2*H*-pyran (0.50g, 6mmol) and 37% formalin solution (0.49ml, 6mmol). The mixture was heated at reflux under nitrogen for 1h and then after cooling the mixture was worked up to give a deep red oil (1.91g) which was purifiedby chromatography on alumina to give (4aα,14aα)- 2,3,4a,7,12,13,14,14a-octahydro-7,12-dioxo-1*H*-naphtho[2,3-*h*]pyrano[3,2-*c*] quinoline (10) as a deep red solid (0.57g, 36%, eluant 7/3 dichloromethane/petrol. Rf= 0.41). (Rf of 1-aminoanthraquinone=0.34. Rf values for basic alumina, 1/1 ether/petrol). Recrystallisation of (10) from methanol gave a deep red crystalline powder (m.p. 192.5 - 194 °C). δH (270MHz) 9.82 (1H,br.s,N$\underline{H}$); 8.22 (2H,m ,Ar$\underline{C}_5$-$\underline{H}$, Ar$\underline{C}_8$-$\underline{H}$); 7.70 (2H,m,Ar$\underline{C}_6$-$\underline{H}$, Ar$\underline{C}_7$-$\underline{H}$); 7.52 (2H,m,Ar$\underline{C}_3$-$\underline{H}$, Ar$\underline{C}_4$-$\underline{H}$); 4.53 (1H,d,J=2.7Hz,C$\underline{H}$O); 3.92 (1H,m,C$\underline{H}_2$-O); 3.60-3.76 (2H,m,C$\underline{H}_2$-O,C$\underline{H}_2$-N); 3.36 (1H,m,C$\underline{H}_2$-N); 2.15 (1H,m,C$\underline{H}$); 1.70-1.98 (3H,m,C$\underline{H}_2$); 1.55 (1H,m,C$\underline{H}_2$). δC (68MHz) 184.68 (Ar$\underline{C}_9$=O); 183.68 (Ar$\underline{C}_{10}$=O); 149.06 (Ar$\underline{C}_1$-N); 136.16 (Ar$\underline{C}_3$-H); 135.11 (Ar$\underline{C}_{4a}$); 134.49 (Ar$\underline{C}_{8a}$); 133.97 (Ar$\underline{C}_7$-H); 133.14 (Ar$\underline{C}_{10a}$); 132.95 (Ar$\underline{C}_6$-H); 128.37 (Ar$\underline{C}_2$-C); 126.79 (Ar$\underline{C}_8$-H); 126.75 (Ar$\underline{C}_5$-H); 115.51 (Ar$\underline{C}_4$-H); 112.56 (Ar$\underline{C}_{9a}$); 73.53 ($\underline{C}$HO); 67.02 ($\underline{C}H_2$-O); 40.97 ($\underline{C}H_2$-N); 30.84 ($\underline{C}$H); 24.70 ($\underline{C}H_2$); 22.79 ($\underline{C}H_2$). $\nu_{max.}$ ($CHCl_3$):- 3295, 3015, 2945, 2860, 1665, 1628, 1595, 1575, 1512cm^{-1}. m/z [Found:-319.1198 (M^+ 48%); 300(3); 291(5); 274(7); 260((M-C_3H_7O)$^+$ 100); 248 (4); 236(5). $C_{20}H_{17}NO_3$ requires 319.1208]. [Found:- C 74.8, H 5.25, N 4.3. $C_{20}H_{17}NO_3$ requires C 75.2, H 5.4, N 4.4%].

Reaction of 1,4-diaminoanthraquinone with formaldehyde and styrene

1,4-Diaminoanthraquinone (1.19g, 5mmol) was added to acetonitrile (50ml) containing two equivalents of trifluoroacetic acid (1.14g, 10mmol) to give a 0.1M amine concentration and the mixture heated to 80°C. To this deep purple solution was added with stirring a heterogeneous mixture of styrene (2.08g, 20mmol) and 37% formalin solution(1.63ml, 20 mmol) and the mixture was heated at reflux under nitrogen for 3h. After cooling the mixture was worked up [(10x100ml) of dichloromethane used] to give a deep blue oil (3.02g) which was purified by chromatography on alumina to give a mixture of the diastereoisomeric products 3,4-diphenyl-2,3,5,6-tetrahydro-1*H*,4*H*,7*H*,14*H* -6a,14a-diaza-8,13-dioxanaphtho[1,2,3,4-*ghi*]perylene (13) as a yellow/brown oil (0.35g, 14%, eluant 2/3 ether/petrol. Rf=0.80); as well as the two adducts 1,2,3,4,5,6,7,8,9,14-decahydro-

9,14-dioxo-4,5-diphenylnaphtho[2,3-*f*][4,7]phenanthroline [(4α,5β)- (11) and (4α,5α)- (14)]. The major fraction (11) was a deep blue crystalline solid (0.96g, 41%, eluant 3/2 ether/petrol. Rf=0.65) and the minor fraction (14) was also a deep blue crystalline solid (0.28g, 12%, eluant ether. Rf=0.46). (Rf of 1,4-diaminoanthraquinone=0.09. Rf values for basic alumina, 1/1 ether/petrol).

The heptacycle (13) is probably a mixture of two diastereoisomers. $\nu_{max.}$(CHCl$_3$):- 3075, 3015, 2940, 2845, 1624, 1605, 1586, 1489, 1417 cm^{-1}. m/z [Found:- 496.2157 (M$^+$ 100%); 467(4); 419(3); 391(2); 248(5); 209(5). $C_{34}H_{28}N_2O_2$ requires 496.2151]

Recrystallisation of(14) from absolute alcohol gave deep blue crystals (m.p. 252 - 255 °C). δH (270MHz) 11.87 (2H,d,J=4.1Hz,NH); 8.42 (2H,dd,J=5.8,3.3Hz,ArC$_5$-H,ArC$_8$-H); 7.71 (2H,dd,J=5.8,3.3Hz,ArC$_6$-H,ArC$_7$-H); 7.26-7.36 (6H,m,Ar-H); 7.09 (4H,m,Ar-H); 4.09(2H,br.m,CH); 3.38 (2H,m,CH$_2$-N); 3.20 (2H,m,CH$_2$-N); 1.96 (2H,tt,J=13.2,4.7 Hz,CH$_2$); 1.86 (2H,br.m,CH$_2$). Addition of three drops of D_2O with shaking caused the doublet at 11.87 (NH) to disappear and a singlet at 4.84 (H_2O) appeared (although exchange was very slow). δC (68MHz) 180.90 (ArC$_9$=O, ArC$_{10}$=O); 145.39 (ArC$_1$-N, ArC$_4$-N); 142.65 (Cquat.); 134.87 (ArC$_{8a}$, ArC$_{10a}$); 134.48 (ArC$_2$-C, ArC$_3$-C); 131.77 (ArC$_6$-H, ArC$_7$-H); 129.01 (ArC-H); 127.87 (ArC-H); 127.12 ArC-H); 126.07 (ArC$_5$-H, ArC$_8$-H); 107.90 (ArC$_{4a}$, ArC$_{9a}$); 39.04 (CH); 35.88 (CH$_2$-N); 28.48(CH$_2$). $\nu_{max.}$(CHCl$_3$):- 3410, 3087, 3012, 2968, 2937, 2872, 1596, 1576, 1560 cm^{-1}. m/z [Found:- 470.1991 (M$^+$ 100%); 391(5); 365(3); 235(2); 196(6); 157(5). $C_{32}H_{26}N_2O_2$ requires 470.1994].

Recrystallisation of (11) from absolute alcohol gave deep blue crystals (m.p. 254 - 258 °C). δH (270MHz) 12.08 (2H,d,J=4.1Hz,NH); 8.43 (2H,dd,J=5.9,3.4Hz,ArC$_5$-H,ArC$_8$-H); 7.71 (2H,dd,J=5.9,3.4Hz,ArC$_6$-H,ArC$_7$-H); 6.81 (6H,m,Ar-H); 6.65 (4H,m,Ar- H); 4.55 (2H,br.m,CH); 3.44 (2H,m,CH$_2$-N); 3.24 (2H,m,CH$_2$-N); 2.21 (2H,tt,J=12.8,4.7Hz,CH$_2$); 1.97 (2H,br.d,J=12.8Hz,CH$_2$). δC (68MHz) 180.54 (ArC$_{8a}$, ArC$_{10a}$); 134.30 (ArC$_2$-C, ArC$_3$-C); 131.68 (Ar C$_6$-H, ArC$_7$-H); 127.98 (ArC-H); 127.82 (ArC-H); 126.10 (ArC-H); 126.04 (ArC$_5$-H, ArC$_8$-H); 107.35 (ArC$_{4a}$, Ar C$_{9a}$); 39.53 (CH); 35.83 (CH$_2$-N); 28.52 (CH$_2$). $\nu_{max.}$(CHCl$_3$):- 3430, 3075, 3015, 2965, 2940, 2875, 1595, 1576, 1556cm^{-1}. m/z [Found:- 470(M$^+$ 100%); 391(8); 368(8); 351(4); 196(4); 157(6). $C_{32}H_{26}N_2O_2$ requires 470].

Reaction of 1-aminoanthraquinone with formaldehyde and isoprene

1-Aminoanthraquinone (1.12g, 5mmol) was added to acetonitrile (10ml) containing one equivalent of trifluoroacetic acid (0.57g, 5mmol) to give a 0.5M amine concentration. To this deep red/brown suspension was added with stirring a heterogeneous mixture at 0°C of isoprene (3.41g, 50mmol) and 37% formalin solution (1.63ml, 20mmol). This deep red suspension was stirred at room temperature under nitrogen for 5h and then worked up to give a deep red solid(1.65g) which was purified by chromatography on alumina to give 1,2,3,4,7,12-hexahydro-4-methyl-7,12-dioxo-4-vinylnaphtho[2,3-*h*]quinoline (12) as a deep red oil (0.15g, 10%, eluant 1/3 ether/petrol. Rf=0.69) and recovered 1-aminoanthraquinone (0.17g, 15%, eluant 1/1 ether/ethyl acetate. Rf=0.36). (Rf values for basic alumina, 1/1 ether/petrol). Recrystallisation of (12) from methanol gave a deep red crystalline powder (m.p. 107.5 - 109.5 °C). δH (270MHz) 10.22(1H,s,NH); 8.24 (2H,m,ArC$_5$-H,ArC$_8$-H); 7.70(2H,m,ArC$_6$-H,ArC$_7$-H); 7.51(1H,d,J=7.7Hz,ArC$_3$-H); 7.39 (1H,d,J=7.7Hz,ArC$_4$-H);

5.89(1H,dd,J=17.4,10.6Hz,HC=CH_2); 5.17 (1H,d,J=10.6Hz,HC=CH_2); 4.83 (1H,d,J=17.4Hz,HC=CH_2); 3.51 (2H,m,CH_2-N); 1.70-1.90 (2H,m,CH_2); 1.44 (3H,s,CH_3). δC (68MHz) 184.70 (ArC_9=O); 183.81 (ArC_{10}=O); 148.92 (ArC_1-N); 145.71 (HC=CH_2); 135.40 (ArC_{4a}); 135.24 (ArC_2-C); 133.90 (ArC_7-H); 133.24 (ArC_{8a},ArC_{10a}); 133.02 (ArC_3-H); 132.81 (ArC_6-H); 126.77 (ArC_8-H); 126.72 (ArC_5-H); 115.47 (ArC_4-H); 114.95 (HC=CH_2); 111.76 (ArC_{9a}); 39.81 (Cquat.); 37.48(CH_2-N); 33.18(CH_2); 26.45 (CH_3) $\nu_{max.}$($CHCl_3$):-3270, 3080, 3015, 2940, 1663, 1623, 1594, 1575,1515 cm^{-1}. m/z [Found:- 303.1257 (M^+ 99%); 288(100); 274(70); 260(50); 260(50); 247 (6); 236(7); 204(7). $C_{20}H_{17}NO_2$ requires 303.1259].

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