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Polycyclic Hydroxyquinones. XXVII[1]. Tautomerism in 1,4-Dihydroxy-9,10-anthraquinone Monoimines. Cycloaddition Reactions of Their 1,4-Anthraquinonoid Tautomers

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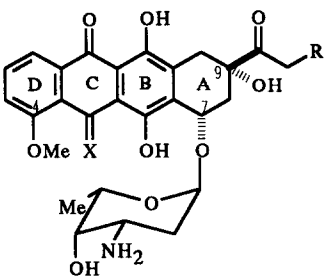
Abstract 1,4-Dihydroxy-9,10-anthraquinone monoimine and differently substituted derivatives thereof (**6a-i**) have been prepared by ammonolysis of the corresponding 1,4-dihydroxy-9,10-anthraquinones. ^{1}H- and ^{13}C-n.m.r. studies show the existence of a rapid tautomeric equilibrium in quinone imines of type **6**. Diels-Alder reaction with the 1,4-anthraquinonoid tautomer of quinone monoimines **6a,e** affords ABCD tetracyclic systems related to those existing in anthracyclinones.

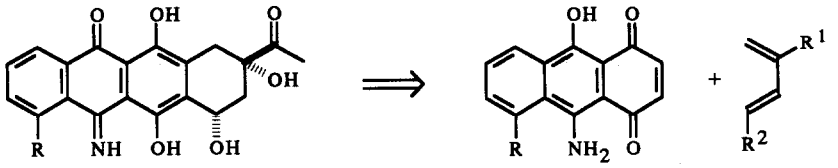
INTRODUCTION

During the past decade, the anthracycline antibiotics such as daunomycin (**1**) and adriamycin (**2**) have emerged as the most effective drugs for the treatment of a variety of human cancers. However, these "first generation anthracyclines" display a cumulative dose dependent cardiotoxicity as the most serious side effect[2]. In 1979, Acton et al. reported[3] that the 5-imino derivatives of daunomycin and adriamycin (**3** and **4**, respectively), obtained by derivatization of the natural anthracyclines, retain the antitumor activity and are significantly less toxic than the clinically important **1** and **2**.



1, R = H, X = O
2, R = OH, X = O
3, R = H, X = NH
4, R = OH, X = NH

A retrosynthetic analysis shows that the corresponding aglycone, 5-iminodaunomycinone (**5a**) and its 4-demethoxyderivative (**5b**), could be constructed from a Diels-Alder adduct of a 10-amino-9-hydroxy-1,4-anthraquinone, used as a BCD ring synthon, with an adequately substituted 1,3-diene. However, the 1,4-anthraquinones of type **6** bearing OH and/or NH_2 groups in 9 and 10 positions, can exist in two main tautomeric forms. Thus, quinizarin **7a** (1,4-dihydroxy-9,10-anthraquinone) exists entirely in the 9,10-anthraquinonoid form **A**, which is much more energetically favoured than the 1,4-anthraquinonoid form **B**.

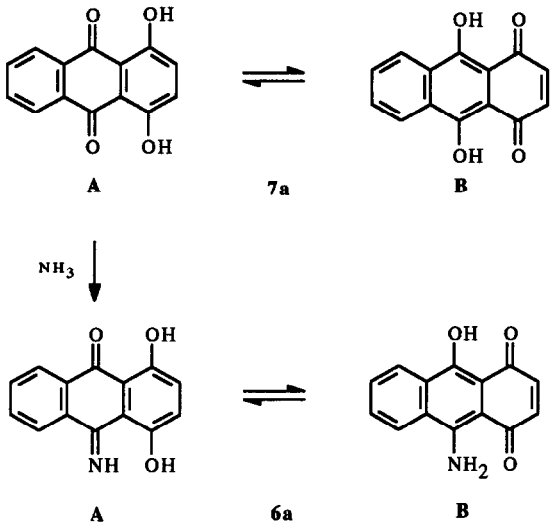


5a, R = OCH_3

5b, R = H

6B

Recently, we have reported[4a] that quinizarin **7a**, by treatment with aqueous ammonia in methanol, at room temperature, is converted into 1,4-dihydroxy-9,10-anthraquinone monoimine **6a**. The tautomeric form **A** of the monoimine **6a** is not necessarily more stable than the 1,4-anthraquinonoid form **B**, since the presence of the =NH group in position 10 modifies the relative stabilities of the **A** and **B** forms and causes a certain destabilisation of the **A** form. However, the tautomeric equilibrium can be shifted to the **A** or the **B** side by various factors, especially by the presence of substituents.



A **7a** **B**

A **6a** **B**

The present work reports the synthesis of differently substituted 1,4-dihydroxy-9,10-anthraquinone monoimines (**6a-i**), investigations on the tautomerism that exists in these quinone monoimines and the Diels-Alder reaction of the anthraquinonoid tautomeric form of quinone imines **6a,e** with simple dienes. Preliminary accounts of this work and on the synthesis of **5a** and **5b** by using the above approach have appeared[4].

RESULTS AND DISCUSSION

The preparation of quinone monoimines **6a-i** was achieved by treatment of the corresponding 1,4-dihydroxy-9,10-anthraquinones **7** with aqueous ammonia in methanol at room temperature . The results of the reactions are summarized in Table 1.

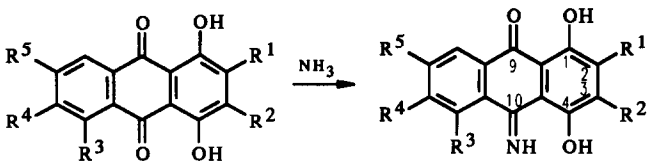


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Table 1. Preparation of 1,4-dihydroxy-9,10-anthraquinone monoimines

Comp.	R^1	R^2	R^3	R^4	R^5	Time	Yield, %
6a	H	H	H	H	H	6 d	75
6b	H	Bu	H	H	H	1 d	83*
6b'	Bu	H	H	H	H		
6c	H	OH	H	H	H	12 h	79*
6c'	OH	H	H	H	H		
6d	H	OMe	H	H	H	4 d	74
6e	H	H	OMe	H	H	3 h	97
6f	Cl	H	H	H	H	18 h	73
6g	Cl	Cl	H	H	H	48 h	65
6h	H	H	H	Me	Me	4 d	70
6i	H	H	OMe	OMe	H	3 h	86

* Mixture of regioisomers

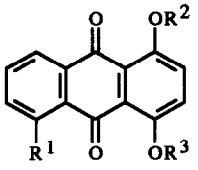
The formation of quinone monoimines of type **6** was evidenced by their elemental analyses and mass spectra, which confirmed the existence of only one N atom, and from the ^{1}H-n.m.r. spectra (DMSO-d_6) which indicated the presence of a strongly chelated OH group (sharp singlet at δ ca. 15 ppm) and showed two broad singlets (at δ ca. 13 and 9 ppm) assigned to the OH and =NH groups of the quinone imine, respectively.

The ammonolysis reaction afforded a single regioisomer in the formation of **6d-f** and **6i**. In contrast, the quinizarins **7b** and **7c** were converted into a mixture of regioisomers **6b** + **6b'** and **6c** + **6c'**, in a 2:1 and 3:1 ratio, respectively, although in both cases we could not assign the structure of the major component.

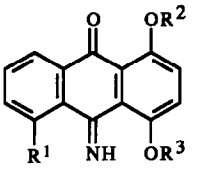
We have tentatively assigned the structure **6d** to the product of the ammonolysis of **7d**, on the basis of the expected deactivating effect of the OCH_3 group at C-2 on the C-10 carbonyl group. Structures **6e** and **6i** were unequivocally established by using n.O.e. experiments. Moreover, the formation of a single regioisomer

6e is in accord with previous results of Acton et al.[3] in the ammonolysis of daunomycin (1) and adriamycin (2) indicating that the presence of a *peri* OMe group favours the formation of the corresponding quinone monoimine. The proposed regiochemistry of compound **6f** was based on the fact that the H-3 proton is long-range coupled ($^3J_{CH}$=3Hz) with the C-1.

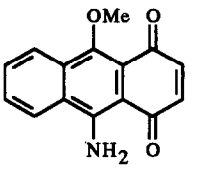
We have also studied the ammonolysis reaction in several *O*-substituted derivatives of quinizarin. Thus, quinizarin diacetate reacts readily under the above mentioned ammonolysis conditions to afford the quinone imine **6a**, the first step of the reaction presumably being the hydrolysis of the OAc groups.



8a-c



9a,c



10

a, $R^1=R^3=H$, $R^2=Me$

b, $R^1=H$, $R^2=R^3=Me$

c, $R^1=OH$, $R^2=R^3=Me$

The ammonolysis of quinizarin monomethyl ether **8a** occurs readily under similar conditions and gives a single regiosomeric monoimine **9a** in 75% yield. The structure **9a** was supported by the i.r. spectrum in $CHCl_3$, which showed a non chelated quinone carbonyl band at 1665 cm^{-1}. In addition, the ^{1}H-n.m.r. spectrum showed a sharp singlet at δ 16.14 attributable to a OH group chelated with the *peri* =NH group, which appeared as a broader singlet at δ 11.05 ppm. It is to point out that quinizarin dimethyl ether **8b** does not react with ammonia under the mild conditions described above. However, the 5-hydroxy substituted quinizarin dimethyl ether **8c** reacts with ammonia to yield the 5-hydroxy-1,4-dimethoxy-9,10-anthraquinone-10-imine **9c**. The regiochemical assignment of **9c** was established by using n.O.e. experiments. These results indicate that the presence of *peri* OH groups favours the reaction, presumably by activation of the carbonyl group and by intramolecular hydrogen bonding with the imine group of the product.

The presence of a fast tautomeric equilibrium on the ^{1}H-n.m.r. time scale in 1,4-dihydroxy-9,10-anthraquinone monoimines **6** between the 9,10- and 1,4-anthraquinonoid forms (**A** and **B**, respectively)[5] was evidenced from the ^{1}H-n.m.r. data summarized in the Table 2. Compounds **9a**, **9c** and **10** can be used as fixed derivatives of the 9,10- and 1,4-anthraquinonoid tautomers **A** and **B** and their ^{1}H-n.m.r. data are also included in Table 2. In fact, in anthraquinone imine **6a** the H-2 and H-3 protons resonate about midway compared to the values expected for aromatic and quinonoid protons. As mentioned above, the corresponding quinizarin exhibit only one principal tautomer in solution, represented by the 9,10-anthraquinone structure **7A**.

Table 2. Chemical shifts and coupling constants of the H-2 and H-3 protons in anthraquinone monoimines*

Comp.	H-2	H-3	J_{AB}
6a	7.24	7.09	9.8
6d	6.79	-	-
6e	7.24	7.12	9.8
6f	-	7.60	-
6h	7.17	7.02	9.8
6i	7.22	7.09	9.7
9a	7.50	7.17	9.6
9c	7.66	7.56	9.5
10	6.88	6.96	10.2

*DMSO-d_6, 300 MHz

Table 3. ^{13}C Chemical shifts of C-1, C-4, C-9 and C-10 in anthraquinone monoimines*.

Comp.	C-1	C-4	C-9	C-10
6a	178.8	176.4	164.7	153.2
6d	183.5	181.3	160.7	156.7
6e	180.0	174.5	162.5	155.3
6f	155.2	161.5	180.0	169.0
6g	141.3	154.3	174.3	164.8
6h	179.7	176.0	163.4	153.6
6i	180.1	175.0	163.5	155.5
9a	152.6	161.4	180.0	167.7
9c	153.5	163.3	181.7	170.4
10	183.6	184.1	149.6	148.7

*DMSO-d_6, 300 MHz

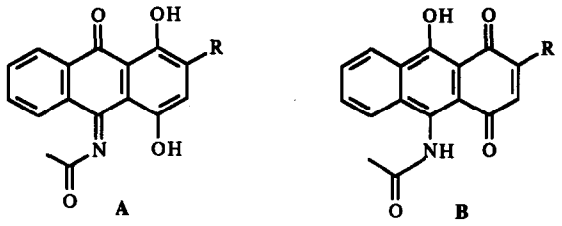
In quinone monoimine **6d**, bearing a methoxy substituent on the 3-position, the H-2 proton resonates at δ 6.79 ppm. This fact may be interpreted by the donor ability of the MeO group, which results in a modification of the relative stabilities of the **A** and **B** forms and causes a displacement of the tautomeric equilibrium towards the 1,4-anthraquinonoid form **B**. In contrast, the introduction of a chlorine atom into the 2-position destabilises the **B** form and markedly increases the amount of the 9,10-anthraquinone imine tautomer **A** in **6f**, as deduced from the H-3 proton resonance at δ 7.60 ppm.

The above conclusions are confirmed by the ^{13}C-n.m.r. spectral data (Table 3). The ^{13}C-n.m.r. study of the tautomeric equilibrium depends on the comparison of the chemical shifts of the quinone imines **6** under investigation with those of model molecules (**9a** and **10**) with fixed 9,10-anthraquinone imine and 1,4-anthraquinonoid structure, **A** and **B**, respectively. Thus, in quinone monoimines **6a**, **6e**, **6h** and **6i**, unsubstituted at positions 2 and 3, the C-1, C-4, C-9 and C-10 carbons, directly involved in the tautomeric equilibrium **A**⇌**B**, show averaged chemical shifts between those expected for the 9,10- and 1,4-anthraquinonoid tautomers (**A** and **B**, respectively).

In the parent quinone imine **6a**, the C-4 observed chemical shift is 176.4, which is intermediate between that found for C-4 in the model compound **9a** and that of the model compound **10**. Assuming that the chemical shifts of C-4 are 160.4 in the 9,10-anthraquinone imine tautomer **A**[6] and 183.5 in the 1,4-anthraquinoid tautomer **B**[7], it can be estimated that the 1,4-anthraquinone **B** represents ca. 69% of **6a** (in DMSO-d_6 solution at room temperature). In the quinone imines **6e**, **6h**, and **6i**, the chemical shifts of the C-1, C-4, C-9, and C-10 resemble those of the parent quinone imine **6a**. Therefore, the presence of substituents on the 5-, 6-, and 7-positions does not appear to affect significantly the relative percentages of the **A** and **B** forms in the tautomeric equilibrium.

On the other hand, the ^{13}C-n.m.r. spectrum of **6d**, bearing a MeO substituent on the 3-position, shows two signals at δ 183.5 and 181.3 ppm attributable to quinonoid carbonyl groups. This fact confirms that the tautomeric equilibrium has been displaced towards more **B** tautomer than in the parent quinone monoimine **6a**, as previously suggested from the ^{1}H-n.m.r. data. In contrast, the ^{13}C-n.m.r. spectra of the chloro substituted quinone imines **6f** and **6g**, show a sole carbonyl signal (δ 180.0 and 174.3 ppm, respectively) consistent with a displacement of the tautomeric equilibrium towards more **A** form in both compounds.

After establishing the effect of the presence of substituents on the anthraquinone nucleus, we wish to report the first results obtained on the *N*-acylation of the anthraquinone monoimines. We have found that the reaction of the quinone monoimine **6a** with an excess of acetic anhydride at 60 °C for 24 h afforded the *N*-acetyl derivative **11** in 75% yield. The preparation of the *N*-acetyl derivative from **6f** was best achieved by treatment with an excess of isopropenyl acetate in the presence of *p*-toluenesulfonic acid at 72 °C for 2h (70% yield)[8]. The relevant signals of the ^{1}H- and ^{13}C-n.m.r. spectra of **11** and **12** are summarized in Table 4.



A B

11, R = H

12, R = Cl

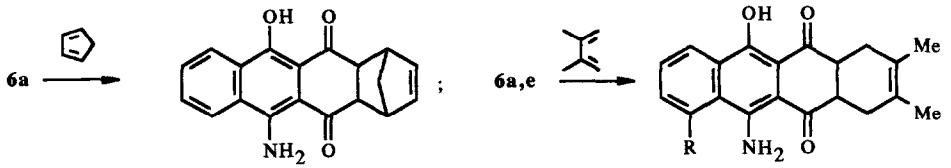
Table 4. Chemical shifts of H-2, H-3 protons and C-1, C-4, C-9 and C-10 carbons of the *N*-acetyl derivatives **11** and **12***.

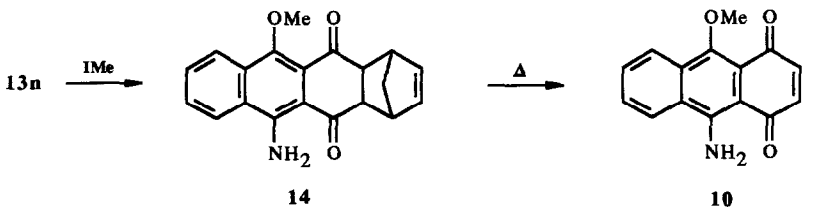
Comp.	H-2	H-3	J_{AB}	C-1	C-4	C-9	C-10
11	7.01	6.93	10.2	186.7	188.0	162.6	134.4
12	-	7.29	-	179.4	185.6	163.0	136.3

*$CDCl_3$, 300MHz

It should be pointed out that the presence of the *N*-acyl group in **11** switches the tautomeric equilibrium in favour of the **B** form. In fact, **11** exists predominantly in the 1,4-anthraquinonoid form as evidenced from a comparison of its n.m.r. data with those of **6a**. Thus, the chemical shifts of C-1, C-4, C-9 and C-10 of the *N*-acetyl derivative **11** indicate that the tautomeric equilibrium lies far on the side of the 1,4-anthraquinonoid form **11B**. Similar conclusions could be obtained for the 2-chloro derivative **12**.

The presence of the 1,4-anthraquinonoid tautomer in the quinone monoimines of type **6** favours the cycloaddition reactions, which occur readily. In contrast, quinizarin (**7a**), which exists predominantly in the **A** form, reacts only under drastic conditions[9]. The Diels-Alder reaction of the quinone imine **6a** with cyclopentadiene was effected at room temperature, in toluene as solvent, to give the expected adduct **13** in 70% yield, as a ca. 8:1 mixture of the *endo* and *exo* isomers (**13n** and **13x**, respectively). The diastereoisomers were readily separable by chromatography and their assignment could be made on the basis of their ^{1}H-n.m.r. spectra. The major *endo* isomer shows the *exo* protons at δ 3.37 ppm, while the *endo* protons of the minor *exo* isomer resonate at δ 2.68 ppm.





Treatment of the *endo* adduct with methyl iodide and potassium carbonate in acetone afforded the *O*-methyl ether **14** in 70% yield. Its ^{1}H-n.m.r. spectrum was consistent with the proposed structure and, as expected, showed the disappearance of the low field OH signal and the presence of a new singlet at δ 3.92, attributable to the MeO group. The methyl ether **14**, by refluxing in toluene, undergoes a retro Diels-Alder reaction to afford compound **10**, which we have used above as a fixed derivative of 1,4-anthraquinonoid structure.

The Diels-Alder reactions of quinone monoimines **6a** and **6e** with 2,3-dimethylbuta-1,3-diene were conducted in refluxing toluene over a period of 4 days, to afford the corresponding adducts **15** and **16**, respectively, in good yield.

In summary, the monoimines **6** of 1,4-dihydroxy-9,10-anthraquinones exist in equilibrium with their 1,4-anthraquinonoid tautomers **6B** and the latter can be captured in Diels-Alder reactions. The use of the quinone imines **6** as BCD synthons offers a promising approach to the synthesis of anthracyclinones.

EXPERIMENTAL

M.p.s are uncorrected. Microanalyses were performed with a Heraeus analyzer. UV-Vis spectra were determined on a Perkin-Elmer model 402 spectrophotomer, λ values in nm. I.r. spectra were recorded on a Perkin-Elmer model 681 grating spectrophotometer as nujol mulls, ν values in cm^{-1}. ^{1}H-n.m.r. spectra were determined with either a Varian EM-390, a Bruker AM-200 or a Varian XL-300 spectrometer, in DMSO-d_6 solution (unless otherwise stated). ^{13}C-n.m.r. spectra were determined with either a Varian XL-300 or a Bruker AM-200 in DMSO-d_6 solution (unless otherwise stated). Chemical shifts are reported in δ (ppm) downfield from

Me_4Si. Mass spectra were determined on a VG-12-250 spectrometer. Silica gel Merck 60 (70-230 mesh), 60 (230-400 mesh) and DC-Alufolien 60 F_{254} were used for conventional, flash column chromatography and analytical t.l.c., respectively.

Synthesis of 1,4-dihydroxy-9,10-anthraquinone-10-imines. General Procedure

A suspension of the dihydroxyanthraquinone **7** (5 mmol), methanol (100 ml) and 30% aqueous ammonia (150 ml), was stirred at room temperature until the starting material was consumed (disappearance of the anthraquinone was monitored by t.l.c.). The reaction mixture was then poured into ice-water and the precipitate obtained was collected, washed with water and purified by column chromatography on silica gel under pressure.

1,4-Dihydroxy-9,10-anthraquinone monoimine (6a)

From commercially available quinizarin **7a**. Purified by columm chromatography (chloroform-ethyl acetate, 3:1), m.p. 278 °C (75%). (Found: C, 66.99; H, 4.09; N, 6.01. $C_{14}H_9NO_3$ requires C, 70.29; H, 3.79; N, 5.86). λ_{max} ($CHCl_3$) 258, 304, 500, 538 , 572 (log ϵ 4.52, 3.77, 3.76, 4.04 , 4.07). ν_{max} 3300, 1630, 1580 . ^{1}H-n.m.r. 15.20 (1 H, s, OH), 13.30 (1 H, br s, OH), 9.70 (1 H, br s, NH), 8.59 (1 H, d, $J_{5,6}$ 8.0 Hz, H-5), 8.40 (1 H, dd, $J_{8,7}$ 7.6 Hz, $J_{8,6}$ 0.8 Hz, H-8), 7.99 (1 H, t, $J_{6,5}$ 7.6 Hz, $J_{6,7}$ 7.6 Hz, H-6), 7.90 (1 H, t, $J_{7,6}$ 7.6 Hz, H-7), 7.24, 7.09 (2 H, AB q, $J_{2,3}$ 9.8 Hz, H-2 , H-3). ^{13}C-n.m.r. 178.8, 176.4, 164.7, 153.2, 139.3, 133.7, 132.3, 131.0, 130.9, 129.8, 126.6, 125.1, 109.7, 104.5 . *m/z* 239 (M^+) (100), 211, 182, 154, 128.

3-Butyl-1,4-dihydroxy-9,10-anthraquinone-10-imine (6b) and 2-Butyl-1,4-dihydroxy-9,10-anthraquinone-10-imine (6b')

From the anthraquinone **7b** prepared according to the method previously reported[10]. Purified by column chromatography (ethyl acetate-n-hexane, 3:1), m.p. 240-242 °C (83%). λ_{max} (MeOH) 258, 308, 350, 500, 536, 574 (log ϵ 4.55, 3.90, 3.37, 3.85, 4.13, 4.20). ν_{max} 3340, 1620 , 1565 . ^{1}H-n.m.r. 16.03, 15.55 (1 H, s, OH), 13.00 (1 H, br s, OH), 9.30 (1 H, br s, NH), 8.56 (1 H, m, H-5), 8.38 (1 H, m, H-8), 7.97-7.80 (2 H, m, H-6, H-7), 7.07, 6.92 (1 H, s, H-2, H-3), 2.63-2.40 (2 H, m, CH_2), 1.65-1.45 (4 H, m, CH_2), 0.91 (3 H, t, J 7.1 Hz, CH_3).

1,3,4-Trihydroxy-9,10-anthraquinone-10-imine (6c) and 1,2,4-Trihydroxy-9,10-anthraquinone-10-imine (6c')

From the commercially available anthraquinone **7c**. Purified by column chromatography (ethyl acetate-n-hexane, 4:1), m.p. 155 °C. λ_{max} (MeOH) 257, 304, 351, 500, 536, 572 (log ϵ 4.07, 3.77, 3.22, 3.64, 3.60, 3.65). ν_{max} 3400, 3300, 1630, 1590 . ^{1}H-n.m.r. 15.35, 15.26 (1 H, s, OH), 13.46, 13.31 (1 H, br s, OH), 9.86, 9.26 (1 H, br s, NH), 8.24 (2H, m, H-5, H-8), 7.85 (2 H, m, H-6, H-7), 7.75, 7.65 (1H, d, $J_{OH,3}$ 8.0 Hz, $J_{OH,2}$ 8.0 Hz, H-2, H-3), 5.80, 5.61 (1 H, m, OH). *m/z* 255 (M^+), 238 (100), 210, 154, 97, 57.

1,4-Dihydroxy-3-methoxy-9,10-anthraquinone-10-imine (6d)

From the anthraquinone **7d** prepared according to the method previously reported[11]. Purified by column

chromatography (ethyl acetate-n-hexane, 4:1), m.p. 260-261.5°C (74%). (Found: C, 66.89; H, 4.42; N, 5.10. $C_{15}H_{11}O_4N$ requires C, 66.91; H, 4.12; N, 5.20). λ_{max} (MeOH) 301, 372, 514, 546, 588 (log ε 3.80, 2.76, 3.84, 4.22, 3.28). ν_{max} 3420, 3260, 1670, 1620, 1580 .^{1}H-n.m.r. 14.68 (1H, s, OH), 12.48 (1H, br s, OH), 9.40 (1H, br s, NH), 8.25-8.20 (2H, m, H-5, H-8), 7.89-7.83 (2H, m, H-6, H-7), 6.79 (1H, s, H-2), 4.00 (3H, s, OCH_3).^{13}C-n.m.r. 183.5, 181.3, 160.7, 156.7, 140.2, 134.7, 133.9, 133.0, 132.7, 126.3, 125.4, 106.4, 106.3, 104.7, 56.9.

1,4-Dihydroxy-5-methoxy-9,10-anthraquinone-10-imine (6e)

From the anthraquinone **7e** prepared according to the method previously reported[12]. Purified by column chromatography (chloroform-ethyl acetate, 1:4), m.p. 263-265°C (97%). (Found: C, 66.80; H, 4.20; N, 5.10. $C_{15}H_{11}O_4N$ requires C, 66.92; H, 4.10; N, 5.20). λ_{max} ($CHCl_3$) 249, 302, 510, 552, 594 (log ε 4.38, 3.82, 3.81, 4.13, 4.21). ν_{max} 3410, 1580 . ^{1}H-n.m.r. 15.00 (1H, s, OH), 14.35 (1H, br s, OH), 10.00 (1H, br s, NH), 8.08 (1H, dd, $J_{8,7}$ 7.8 Hz, $J_{8,6}$ 1.0 Hz, H-8), 7.89 (1H, dd, $J_{7,8}$ 7.8 Hz, $J_{7,6}$ 7.3 Hz, H-7), 7.68 (1H, dd, $J_{6,7}$ 7.3 Hz, $J_{6,8}$ 1.0 Hz, H-6), 7.24, 7.12 (2H, AB q, $J_{2,3}$ 9.8 Hz, H-2, H-3), 4.14 (3H, s, OCH_3).^{13}C-n.m.r. 180.0, 174.5, 162.5, 160.0, 155.3, 139.3, 133.8, 132.9, 129.4, 128.6, 119.3, 117.4, 109.9, 104.5, 56.89, *m/z* 269 (M^+) (100), 252, 225, 239, 196, 170, 115.

2-Chloro-1,4-dihydroxy-9,10-anthraquinone-10-imine (6f)

From the anthraquinone **7f** prepared according to the method previously reported[13].Purified by column chromatography (chloroform-ethyl acetate, 4:1), m.p. 311-316°C (73%). (Found: C, 61.15; H, 3.10; N, 4.85. $C_{14}H_8O_3NCl$ requires C, 61.44; H, 2.95; N, 5.12).λ_{max} (MeOH) 307, 504, 538, 578 (log ε 4.83, 4.83, 5.13, 5.47).ν_{max} 3310, 1640, 1610, 1580. ^{1}H-n.m.r. 14.93 (1H, s, OH), 13.35 (1H, br s, OH), 10.20 (1H, br s, NH), 8.59 (1H, d, $J_{5,6}$ 7.7 Hz, H-5), 8.37 (1H, dd, $J_{8,7}$ 7.79 Hz, $J_{8,6}$ 1.45 Hz, H-8), 8.02-7.79 (1H, m, H-6 or H-7), 7.94-7.88 (1H ,m, H-7 or H-6), 7.60 (1H, s, H-3). ^{13}C-n.m.r. 180.0, 169.0, 161.5, 155.2, 142.6, 132.9, 131.7, 131.3, 129.0, 126.7, 125.3, 125.0, 109.3, 104.4. *m/z* 275 (M^++2) (30), 273 (M^+) (100), 254, 238.

2,3-Dichloro-1,4-dihydroxy-9,10-anthraquinone-10-imine (6g)

From the anthraquinone **7g** prepared according to the method previously reported[13]. Purified by column chromatography (chloroform-ethyl acetate, 1:4), m.p. 320°C (65%). λ_{max} (MeOH) 261, 309, 508, 542, 580 (log ε 3.20, 2.50, 2.51, 2.74, 2.78). ν_{max} (KBr) 3425, 1630, 1590. ^{1}H-n.m.r. 12.78 (1H, s, OH), 12.07 (1H, br s, OH), 10.02 (1H, br s, NH), 8.30 (1H, m, H-5 or H-8), 8.16 (1H, m, H-8 or H-5), 8.10-7.95 (2H, m, H-6, H-7). ^{13}C-n.m.r. 174.3, 164.8, 154.3, 141.3, 142.2, 135.0, 134.9, 134.0, 133.8, 132.9, 128.9, 126.3, 125.2. *m/z* 312 (M^++4) (10), 310 (M^++2) (66), 308 (M^+) (100).

1,4-Dihydroxy-6,7-dimethyl-9,10-anthraquinone-10-imine (6h)

From the anthraquinone **7h** prepared according to the method previously reported[14]. Purified by column chromatography (ethyl acetate-n-hexane, 4:1), m.p. 275°C (70%). (Found : C, 71.70; H, 4.60; N, 5.15. $C_{16}H_{13}O_3N$ requires C, 71.90; H, 4.90; N, 5.24. λ_{max} ($CHCl_3$) 258, 267, 368, 516, 554, 590 (log ε 4.21, 4.20,

3.34, 3.62, 3.79, 3.67). ν_{max} 3310, 1640, 1580. ^{1}H-n.m.r. 15.11 (1H, s, OH), 13.27 (1H, br s, NH), 9.15 (1H, br s, NH), 8.21 (1H, s, H-5), 7.95 (1H, s, H-8), 7.17, 7.02 (2H, AB q, $J_{2,3}$ 9.8 Hz, H-2, H-3), 2.36 (3H, s, CH_3), 2.35 (3H, s, CH_3). ^{13}C-n.m.r. 179.7, 176.0, 163.4, 153.6, 143.7, 142.0, 138.9, 130.6, 129.0, 127.6, 126.9, 125.6,109.7, 104.5, 20.0, 19.6. *m/z* 227 (M^+) (100),239, 210, 168, 133, 77, 44.

1,4-Dihydroxy-5,6-dimethoxy-9,10-anthraquinone-10-imine (6i)

From the anthraquinone **7i** prepared according to the method previously reported[15]. Purified by column chromatography (ethyl acetate-n-hexane, 4:1), m.p. 240-243 °C (86%). (Found: C, 64.17; H, 4.56; N, 4.61. $C_{16}H_{13}O_5N$ requires C, 64.21; H, 4.34; N, 4.68). ν_{max} 3360, 1610, 1570. ^{1}H-n.m.r. 14.87 (1H, s, OH), 14.26 (1H, br s, OH), 10.04 (1H, br s, NH), 8.24 (1H, d, $J_{8,7}$ 9.0 Hz, H-8), 7.65 (1H, d, $J_{7,8}$ 9.0 Hz, H-7), 7.22, 7.09 (2H, AB q, $J_{2,3}$ 9.7 Hz, H-2, H-3), 4.03 (3H, s, OCH_3), 4.02 (3H,s,OCH_3). ^{13}C-n.m.r. 180.1, 175.0, 163.5, 160.7, 157.4, 155.5, 138.3, 135.0, 129.9, 124.8, 117.1, 109.6, 105.1, 40.8, 40.3. *m/z* 299 (M^+) (100), 284, 256, 241.

Reaction of 1,4-diacetoxy-9,10-anthraquinone with ammonia

A suspension of 1,4-diacetoxy-9,10-anthraquinone[16] (1 mmol), methanol (25 ml) and 30% aqueous ammonia (30 ml), was stirred at room temperature. After the usual work-up, the precipitate was estimated by ^{1}H-n.m.r. to be a mixture of quinizarin **7a**, the quinone monoimine **6a** and the 9,10-anthraquinone **8a**.

4-Hydroxy-1-methoxy-9,10-anthraquinone-10-imine (9a)

From the anthraquinone **8a** prepared according to the method previously reported[12]. Purified by column chromatography (ethyl acetate-n-hexane, 4:1), m.p. 238-240 °C (75%). (Found: C, 71.16; H, 4.25; N, 6.30. $C_{15}H_{11}O_3N$ requires C, 71.14; H, 4.38; N, 5.53). λ_{max} ($CHCl_3$) 274, 317, 444, 546, 588 (log ϵ 4.07, 4.58, 4.67, 4.54, 2.76). ν_{max} (KBr) 3305, 1665, 1615, 1595. ^{1}H-n.m.r. 16.14 (1H, s, OH), 11.05 (1H, s, NH), 8.50 (1H, dd, $J_{5,6}$ 7.7 Hz, $J_{5,7}$ 2.2 Hz, H-5), 8.21 (1H, dd, $J_{8,7}$ 7.7 Hz, $J_{8,6}$ 2.2 Hz, H-8), 7.90 (1H, td, $J_{6,5}$= $J_{6,7}$ 7.7 Hz, $J_{6,8}$ 2.2 Hz, H-6), 7.84 (1H, td, $J_{7,6}$=$J_{7,8}$ 7.7 Hz, $J_{7,5}$ 2.2 Hz, H-7), 7.50 , 7.17 (2H, AB q, $J_{2,3}$ 9.6 Hz, H-2, H-3), 3.89 (3H, s, OCH_3). ^{13}C-n.m.r. 180.0, 167.7, 161.4, 152.6, 133.3, 133.0, 132.8, 130.6, 129.1, 126.9, 124.3, 124.0, 116.8, 110.7, 56.6. *m/z* 253 (M^+) (100), 238, 224, 210.

1,4-Dimethoxy-5-hydroxy-9,10-anthraquinone-10-imine (9c)

From the anthraquinone **8c** prepared according to the method previously reported[12]. Purified by column chromatography (ethyl acetate-dichlorometane, 1:2), m.p. 204-205 °C (75%). (Found: C, 67.50; H, 4.58; N, 5.30. $C_{16}H_{13}O_4N$ requires C, 67.84; H, 4.59; N, 4.94). λ_{max} (MeOH) 277, 420, 520, 556 (log ϵ 3.97, 3.63, 3.88, 3.70). ν_{max} 3565, 3360, 1660, 1615 . ^{1}H-n.m.r. 15.44 (1H, s, OH), 11.36 (1H, br s, NH), 7.66, 7.56 (2H, AB q, $J_{2,3}$ 9.55 Hz, H-2, H-3), 7.46 (1H, t, $J_{7,6}$= $J_{7,8}$ 8.1 Hz, H-7), 7.25 (1H, d, $J_{8,7}$ 8.1 Hz, H-8), 7.00 (1H, d, $J_{6,7}$ 8.1 Hz, H-6), 4.08 (3H, s, OCH_3) , 3.88 (3H, s, OCH_3). ^{13}C-n.m.r. 181.7, 170.4, 163.3, 154.6, 153.5, 133.9, 133.4, 126.6, 120.2, 119.7, 117.2, 114.4, 112.1, 56.9, 56.6. *m/z* 283 (M^+) (100), 266, 253, 237, 197, 149, 63, 44.

Attempted reaction of 1,4-dimethoxy-9,10-anthraquinone (8b) with ammonia

A suspension of 1,4-dimethoxy-9,10-anthraquinone[12] (**8b**) (1 mmol), methanol (50 ml) and 30% aqueous ammonia (70 ml), was stirred at room temperature for 10 days. After the usual work-up the precipitate obtained was only recovered anthraquinone **8b**.

10-Acetylamino-9-hydroxy-1,4-anthraquinone (11)

A mixture of **6a** (200 mg, 0.84 mmol), sodium acetate (200 mg, 2.44 mmol) and acetic anhydride (2.4 ml) was heated at 60 °C for 24 h. The resulting solution was poured into ice/water to give a red precipitate, which was collected, washed with water and purified by chromatography on silica gel under pressure (chloroform), m.p. 205-207 °C (75%). (Found: C, 68.08; H, 3.84; N. 4.77. $C_{16}H_{11}O_4N$ requires C, 68.32; H, 3.94; N, 4.98). λ_{max} ($CHCl_3$) 253, 300, 330, 490, 520, 560 (log ϵ 4.23, 3.41, 3.31, 3.50, 3.58, 3.63). ν_{max} 3250, 1660, 1635, 1590. ^{1}H-n.m.r. ($CDCl_3$) 14.72 (1H, s, OH), 10.67 (1H, br s, NH), 8.50 (1H, m, H-5, or H-8), 8.00 (1H, m, H-8 or H-5), 7.72 (2H, m, H-6, H-7), 7.01, 6.93 (2H, AB q, $J_{2,3}$ 10.2 Hz, H-2, H-3), 2.37 (3H, s, OCH_3). ^{13}C-n.m.r. ($CDCl_3$) 188.0, 186.7, 170.9, 162.6, 141.3, 138.9, 134.4, 132.2, 130.9, 130.2, 128.9, 128.4, 124.8, 116.5, 107.6, 24.75. *m/z* 281 (M^+) (9), 239 (100), 211, 182, 43.

10-Acetylamino-2-chloro-9-hydroxy-1,4-anthraquinone (12)

A solution of **6f** (273 mg, 1 mmol) in isopropenyl acetate (10 ml) and a catalytic amount of *p*-toluenesulfonic acid was heated at 72 °C for 2 h and the acetone formed was removed by azeotropic distillation. After 2 h, celite was added, the solvent was removed and the residue was purified by chromatography on silica gel under pressure (chloroform-ethyl acetate, 4:1), m.p.168-169 °C (70%). λ_{max} ($CHCl_3$) 252, 296sh, 340sh, 496sh, 530, 574sh (log ϵ 4.54, 3.93, 3.48, 3.79, 3.74, 3.57). ν_{max} 3220, 3170, 1670, 1635. ^{1}H-n.m.r. ($CDCl_3$) 14.67 (1H, s, OH), 10.49 (1H, s, NH), 8.50 (1H, dd, J 6.4 Hz, J 3.4 Hz, H-5 or H-8), 8.01 (1H, dd, J 6.8 Hz, J 3.4 Hz, H-8 or H-5), 7.75 (2H, m, H-6, H-7), 7.29 (1H, s, H-3), 2.41 (3H, s, $COCH_3$). ^{13}C-n.m.r. ($CDCl_3$) 185.6, 179.4, 170.9, 163.0, 147.7, 136.5, 136.3, 132.0, 131.3, 130.8, 129.1, 128.8, 125.0, 116.0, 107.3, 24.8. *m/z* 275 (M^++2-42), 273 (M^+-42),102, 43 (100).

6-Amino-11-hydroxy-2,3-dimethyl-1,4,4a,12a-tetrahydronaphthacene-5,12-dione (15)

A solution of 2,3-dimethylbuta-1,3-diene (2 mmol) and the quinone imine **6a** (1 mmol) in toluene (50 ml) was heated under reflux for 4 days. The solvent was removed and the residue was recrystallized from benzene-hexane, m.p.175-176 °C (85%). (Found: C, 74.66; H, 5.97; N, 3.91. $C_{20}H_{19}O_3N$ requires C, 74.74; H, 5.96; N, 4.36). ν_{max} 3480, 1640, 1595. ^{1}H-n.m.r. ($CDCl_3$) 13.98 (1H, s, OH), 8.60-8.40 (1H, m, H-10), 8.05-7.82 (1H, m, H-7), 7.80-7.60 (2H, m, H-8, H-9), 7.45 (2H, br s, NH_2), 3.40-3.05 (2H, m, H-4a, H-12a), 2.80-1.90 (4H, m, H-1, H-4), 1.65 (6H, br s, CH_3). *m/z* 321 (M^+) (82), 288, 278, 239 (100).

6-Amino-11-hydroxy-7-methoxy-2,3-dimethyl-1,4,4a,12a-tetrahydronaphthacene-5,12-dione (16)

A solution of 2,3-dimethylbuta-1,3-diene (2 mmol) and the quinone monoimine **6e** (1 mmol) in toluene was heated under reflux for 4 days. The solvent was removed and the residue was recrystallized from benzene-hexane, m.p. 290-292 °C (80%). (Found: C, 71.50; H, 5.77; N, 3.79.$C_{21}H_{21}O_4N$ requires C, 71.79; H, 5.98;

N, 3.99). ν_{max} 3460, 1640, 1610. ^{1}H-n.m.r. ($CDCl_3$) 13.72 (1H, s, OH), 8.07 (1H, d, $J_{9,10}$ 9.0 Hz, H-10), 7.52 (1H, t, $J_{8,9}=J_{9,10}$ 9.0 Hz, H-9), 7.04 (1H, d, $J_{8,9}$ 9.0 Hz,H-8), 4.03 (3H, s, OCH_3), 3.40-2.85 (2H, m, H-4a, H-12a), 2.60-1.90 (4H, m, H-1, H-4), 1.66 (6H, br s, CH_3). *m/z* 315 (M^+) (30), 272, 270, 269, 149, 57 (100).

6-Amino-11-hydroxy-1,4,4a,12a-tetrahydro-1,4-methanonaphthacene-5,12-dione (13)

A mixture of freshly distilled cyclopentadiene (4 mmol), the quinone monoimine **6a** (2 mmol) and benzene (100 ml) was stirred at room temperature for 6 days. The solvent was removed to afford a mixture of the adducts **13n**+**13x** (70%).(Found C,74.45; H, 5.04; N, 4.68. $C_{19}H_{15}O_3N$ requires C, 74.74; H, 4.95; N, 4.59). The mixture was separated by column chromatography on silica gel (benzene-ethyl acetate, 3:1) to give **13n**, m.p. 294-296 °C (60%). ν_{max} 3420, 1590. ^{1}H-n.m.r. ($CDCl_3$) 14.89 (1H, s, OH), 8.60-8.30 (1H, m, H-10), 8.00-7.50 (5H, m, H-7, H-8, H-9, NH_2), 6.00 (2H, m, H-2,H-3), 3.67 (2H, m, H-1, H-4), 3.37 (2H, m, H-4a, H-12a), 1.57 (2H, m, CH_2) .*m/z* 305 (M^+) (10), 239 (100), 211; and **13x**, m.p. 289-292 °C (7%). ν_{max} 3410, 1590. ^{1}H-n.m.r. ($CDCl_3$) 15.00 (1H, s, OH), 8.65-8.35 (1H, m, H-10), 8.10-7.50 (5H, m, H-7, H-8, H-9, NH_2), 6.40 (2H, m, H-2,H-3), 3.43 (2H,m, H-1,H-4), 2.68 (2H, m, H-4a, H-12a), 1.57 (2H, m, CH_2). *m/z* 305 (M^+) (8), 239 (100).

6-Amino-11-methoxy-1,4,4a,12a-tetrahydro-1,4-methanonaphthacene-5,12-dione (14)

To a solution of **13n** (300 mg, 1 mmol) in acetone (20 ml) was added K_2CO_3 (300 mg) and methyl iodide (4 ml). The mixture was magnetically stirred at 60 °C for 24 h. The reaction mixture was filtered, washed with acetone and the residue was purified by preparative t.l.c. (chloroform-ethyl acetate, 4:1) to give **14n** 168-170 °C (70%). (Found: C,75.43; H, 5.24; N, 4.67.$C_{20}H_{17}O_3N$ requires C, 75.22; H, 5.37; N, 4.39). ν_{max} 3420, 1690, 1610. ^{1}H-n.m.r. ($CDCl_3$) 8.37-8.13 (1H, m, H-10), 8.03-7.80 (1H, m, H-7), 7.80-7.50 (4H,m, H-8,H-9, NH_2), 6.01 (2H, m, H-2, H-3), 3.92 (3H, s, OCH_3), 3.58 (2H, m, H-1. H-4), 3.45 (2H, m, H-4a, H-12a), 1.51 (2H, m, CH_2). *m/z* 319 (M^+) (2), 253 (100), 238, 224, 210.

10-Amino-9-methoxy-1,4-anthraquinone (10)

A solution of **14n** (200 mg, 0.63 mmol) in toluene (20 ml) was heated under reflux for 72 h.The solvent was removed and the residue was purified by preparative t.l.c. (chloroform-ethyl acetate, 9:1) to yield **10**, m.p. 175-178 °C (75 %).(Found: C, 71.49; H, 4.54; N, 6.01.$C_{15}H_{11}O_3N$ requires C, 71.15; H, 4.38; N, 5.53). ν_{max} 3380, 3165, 1655, 1640, 1610. ^{1}H-n.m.r. 9.40 (2H, br s, NH_2), 8.70-8.40 (1H,m ,H-5), 8.40-8.02 (1H, m, H-8), 8.00-7.60 (2H, m, H-6, H-7), 6.96, 6.82 (2H, AB q, $J_{2,3}$ 10.2 Hz, H-2, H-3), 3.87 (3H, s, OCH_3). ^{13}C-n.m.r. 184.1, 183.6, 149.6, 148.7, 140.5, 138.3, 131.7, 130.9, 129.3, 127.0, 124.8, 124.4, 118.1, 103.8, 61.4. *m/z* 253 (M^+) (100), 238, 224, 210, 182.

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5. We have ignored the less probable 1,10- or 4,9-anthraquinonoid tautomeric forms, although their presence is not excluded.
6. Calculated chemical shift, based on the experimental value of C-4 in the model compound **9a** (161.4) modified by the correction parameter (-1.0 ppm) corresponding to the change (OCH_3) → (OH) obtained from available substituent chemical shifts for related compounds.
7. Calculated chemical shift, based on the experimental value of C-4 in the model compound **10** (184.1) modified by the correction parameter (-0.6 ppm) corresponding to the change (OCH_3) → (OH) obtained from available substituent chemical shifts for related compounds.
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