A NOVEL 2-AMINATION OF QUINIZARIN PROMOTED BY COPPER IONS†

MASARU MATSUOKA,[a] KATSUHIRA YOSHIDA,[b] YOSHINOBU MAKINO[a] and TEIJIRO KITAO[a]

[a] *Department of Applied Chemistry, University of Osaka Prefecture, Sakai, 591 Japan* [b] *Department of Chemistry, Faculty of Science, Kochi University, Akebono, Kochi, 780 Japan*

SUMMARY

Direct amination of the anthraquinone nucleus was studied as a substitute for the Ullmann amination to synthesize aminoanthraquinone derivatives. In the presence of copper chlorides, 2-butylamination of 1,4-dihydroxyanthraquinone (DHAQ) proceeded quantitatively at ambient temperature. The effects of temperature, atmosphere, mole ratio of copper ions and the kinds of amines on the 2-amination of DHAQ were studied. The mechanism was proposed as follows: 2-amination of DHAQ was initiated by the formation of a copper complex between a DHAQ dianion and copper ions, which was disproportionated to give quinizarinquinone (QZQ) and metal copper by a redox system. The final Michael type addition of amine to QZQ gave a 2-aminated product. Both quantitative 2-amination of QZQ and reduction of copper ion to metal copper supported the mechanism.

1. INTRODUCTION

Aminoanthraquinone derivatives are the most important compounds as dyes and dye intermediates. A large number of papers and patents have been reported to introduce amino groups to the anthraquinone nucleus. The most popular method is the Ullmann amination of halogenoanthraquinones. But, in principle, the Ullmann amination is carried out under high temperature, and undesirable side reactions such as dehalogenation, dealkylation and polymerization usually occur. If direct amination of the anthraquinone nucleus were available, halogenation would not be necessary and one step of the process could be omitted. Therefore, it could be a useful method for the preparation of aminoanthraquinone derivatives.

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In our preliminary papers, we reported metal-promoted new aminations between 1-aminoanthraquinone[1] or 1,4-dihydroxyanthraquinone (DHAQ)[2] and butylamine. In these reactions, direct butylamination proceeded with a good yield at ambient temperature. In the case of DHAQ, butylamination at the 2-position proceeded exclusively in the presence of copper ions. Fokin *et al.*[3] have already reported the direct 2-amination of DHAQ in the presence of atmospheric oxygen and presented the mechanism, but the details were still ambiguous. In this paper, we wish to report the details of this metal-promoted new direct amination of DHAQ, and present the mechanism for this reaction.

2. RESULTS AND DISCUSSION

The reaction of DHAQ 1 with alkylamine affords three types of products; these are 1-hydroxy-4-alkylamino- 2, 1,4-bisalkylamino- 3 and 2-alkylamino-1,4-dihydroxyanthraquinone 4. Compounds 2 and 3 are obtained by the usual nucleophilic substitution of α-hydroxyl by an amino group. Compound 4 should be obtained by direct amination at the 2-position of an anthraquinone nucleus.

Direct 2-amination of 1 has already been reported by Fokin *et al.*[3] who found that in the presence of atmospheric oxygen, 1 reacted with amines without replacement of α-hydroxyl by amino groups, but by direct amination at the
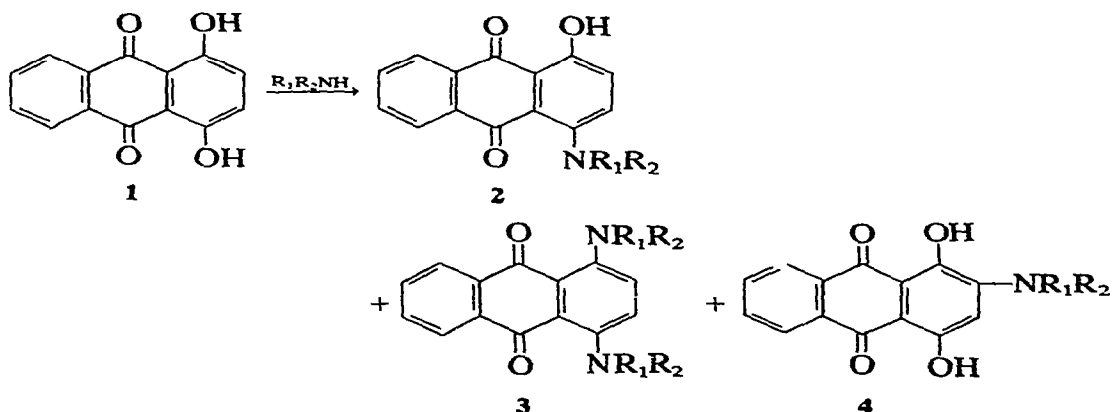
	a	b	c	d	e
R_1	H	H	H	CH_3	
R_2	CH_3	C_4H_9	C_8H_{17}	CH_3	C_5H_{10}

Scheme 1

TABLE 1
THE REACTION OF 1 WITH VARIOUS AMINES

Run[a]	Amine	Yield (%)			
		1	2	3	4
1	NH$_3^b$	100	0	0	0
2	C$_6$H$_5$NH$_2$	100	0	0	0^c
3	CH$_3$NH$_2^d$	0	1·4	19·3	70·9
4	C$_4$H$_9$NH$_2$	0	7·3	21·4	48·1
5	C$_8$H$_{17}$NH$_2^e$	0	0	0	88·8
6	(CH$_3$)$_2$NH^f	16·9	0	0	74·6
7	(C$_2$H$_5$)$_2$NH^g	100	0	0	0
8	C$_5$H$_{10}$NH	0	0	0	89·3^h

[a] Reactant 1 (5 mmol) was stirred in pyridine (8 ml) with amine (228 mmol) at room temperature for 24 h.
[b] 25% aqueous solution.
[c] 71% yield of 4 was reported[3] in the reaction of 1 with p-toluidine at 160°C for 30 h.
[d] 40% aqueous solution.
[e] 2 mole ratio of copper (II) chloride was added.
[f] 50% aqueous solution.
[g] Dibutylamine also did not react at all.
[h] 86% yield of 4e was reported[3] under the conditions at 40°C for 4·5 h.

2-position of the anthraquinone nucleus. The reaction of 1 with various amines was studied at room temperature. Results are summarized in Table 1.

Aqueous ammonia and aniline did not react with 1 and the reactant was recovered quantitatively. Methylamine (run 3) and butylamine (run 4) gave three products. Competitive α- and β-amination was observed. Both dimethylamine (run 6) and piperidine (run 8) gave 4 in good yields but did not give the α-aminated product. The basicity of the amine affected very much both the components and yields of products. It was found that the increase in basicity of the amine improved the yield of 4 and depressed the formation of α-aminated products. Diethylamine and dibutylamine did not react at all because of steric hindrance. Similar steric hindrance has been already reported by Greenhalgh and Hughes[4] in the β-cyclization reaction of leucoquinizarin with N-ethylethylenediamine. However the long chain primary amine easily reacted with 1 in the presence of copper (II) chloride to give 4 in a good yield (run 5). From the preliminary results[1,2], some of the metal salts were found to be effective for the direct amination of the anthraquinone nucleus. The effect of metal salts on the 2-butylamination of 1 was studied therefore and the results are summarized in Table 2.

Without metal salts, competitive α- and β-amination proceeded at ambient

TABLE 2
THE EFFECT OF METAL SALTS ON THE 2-BUTYLAMINATION OF 1

Run[a]	Metal salt	Temperature (°C)	Time (h)	Yield (%)			
				1	2b	3b	4b
1[b]	none	30	24	0	7·3	21·4	48·1
2	none	80	24	0	0	50·4[c]	0
3	$CuCl_2.2H_2O$	34	24	0	0	0	100
4[b]	CuCl	34	24	0	0	0	100
5	$CoCl_2$	34	24	70·5	0	0	24
6	$CoCl_2$	70	24	0	0	0	70·9
7[b]	$FeCl_3$	30	24	20·7	0	0	74·6
8	$NiCl_2.6H_2O$	30	120	81·2	0	0	3·1

[a] Reactant 1 (5 mmol) was stirred in butyl alcohol (7·5 ml) with butylamine (228 mmol) and metal salt (10 mmol).
[b] Pyridine (8 ml) was used as solvent instead of butyl alcohol.
[c] Dealkylation depressed the yield of 3^{2a}.

temperature (run 1), but α-amination predominantly proceeded at 80°C (run 2). An addition of metal salts changed the distribution of products completely and **4b** was obtained in a quantitative yield in the presence of copper chlorides (runs 3 and 4). In the case of cobalt (II) chloride, 2-amination proceeded predominantly both at low and high temperature but the yield of **4b** was improved at higher temperature (run 6). Iron (III) chloride was also effective (run 7) but nickel (II) chloride was inactive (run 8).

From the results in Table 2, it was found that β-amination proceeded exclusively in the presence of metal salts. The preferential β-amination of quinizarindimetaborate has been already reported,[5] and in our cases, the formation of metal complex between **1** and metal salts was also proposed. Recently, Pierport[6] reported some physical properties of copper complexes between **1** and copper salts. From the results in Table 2, it can be concluded that copper chlorides were the most effective metal salts for the preparation of **4b**, and some details of the reaction between **1** and butylamine in the presence of copper chlorides were studied. The yield of **4b** and the recovery of **1** against the reaction time are plotted in Fig. 1. The yield of **4b** increased together with prolonged reaction time and decrease of **1**. After 5h, **4b** was obtained quantitatively and no other product was obtained. In the reaction of **1** with butylamine in the presence of copper salts, reduction of copper ion to metal copper was observed. No reduction of copper salts was observed when copper salts in pyridine as solvent were treated with butylamine without **1**; therefore, oxidation of **1** by copper ions is proposed. Fokin et al.[3] reported that atmospheric oxygen played a great role in this amination of **1**, as an oxidizing agent. The effects of atmosphere and the mole ratio of copper salts on the 2-amination of **1** are summarized in Table 3.
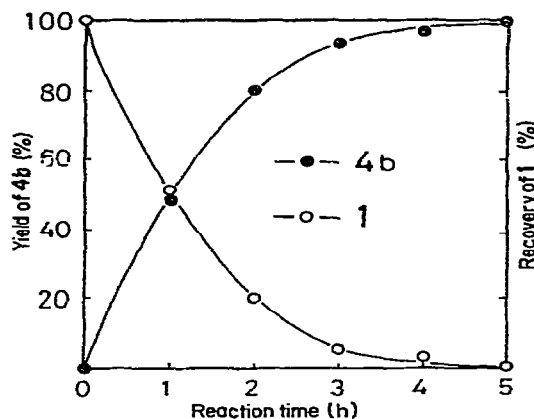
Fig. 1. The reaction of 1 with butylamine in the presence of $CuCl_2$(2 mole ratio)

The reaction was carried out under the conditions (systems A, B and C) of different atmosphere. Comparing the results of runs 1 and 2, the distribution of products differed very much. Without oxygen (run 2), α-amination was preferentially observed and 3b was obtained much more than 4b compared with the case of run 1, in which atmospheric oxygen was presented. The 13% yield of 4b even under the conditions without oxygen may be explained by the following

TABLE 3

THE EFFECTS OF ATMOSPHERE AND MOLE RATIO OF COPPER SALTS ON THE 2-BUTYLAMINATION OF 1

Run[a]	Copper salt	Mole ratio for 1	System	Temperature (°C)	Yield (%)				
					1	2b	3b	4b	Cu⁰
1	none	—	A	30	0	7·3	21·4	48·1	—
2	none	—	B	30	0	1·3	66·6	13·1	—
3	$CuCl_2 \cdot 2H_2O$	4	A	30	0	0	0	92·8	0
4	$CuCl_2 \cdot 2H_2O$	2	A	34	0	0	0	100	0
5	$CuCl_2 \cdot 2H_2O$	2	C	23	0	0	0	100	0
6	$CuCl_2 \cdot 2H_2O$	1	A	30	0	0·6	0	76·3	3·8
7	$CuCl_2$	1	B	30	1·2	15·7	0·3[b]	75	62·1
8	$CuCl_2 \cdot 2H_2O$	1/2	A	30	1·8	6·9	0	61·5	22·8
9	$CuCl_2$	1/2	B	30	0·5	32·7	9·0[b]	44·5	90·9
10	CuCl	2	A	34	0	0	0	100	30·8
11	CuCl	2	B	30	0	0	0	95	76·4

[a] Reactant 1 (5 mmol) was stirred in pyridine (8 ml) with butylamine (228 mmol) under the following conditions: A, with atmospheric oxygen; B, without oxygen under reduced pressure; C, under nitrogen atmosphere.
[b] 1-Hydroxy-(2 or 3),4-bisbutylaminoanthraquinone 7 was obtained in 3·6% (run 7) and 4·4% (run 9) yield, respectively.

results. Even under the conditions without oxygen, some of **1** was considered to be disproportionated to give quinizarinquinone **5** and leucoquinizarin by a redox system. In fact, the reaction of **1** with ethylenediamine without copper salt in system A gave leucoquinizarin in 15% yield, but not aminoleucoquinizarin, together with the aminated cyclization product of 6-hydroxy-1,2,3,4-tetrahydronaphtho(2,3-f)-quinoxaline-7,12-dione **6** in 47% yield. Similar results with the formation of **4e** were also found in the reaction of **1** with piperidine under the conditions of systems B and C. In these cases, 28·3% and 28% yields of **4e** were obtained, respectively.[2b] From these results, it was concluded that competitive α-and β-amination of **1** proceeded during the reaction, but α-amination proceeded preferentially under the conditions in which oxidizing agents such as atmospheric oxygen were not present. An addition of oxidizing agents such as metal ions should improve the yield of **4** and consequently depress the yield of α-aminated products **2** and **3**. In fact, an addition of two mole ratio of copper (II) chloride for **1** gave **4b** in a quantitative yield and none of the α-aminated product was obtained (run 4). As **1** has two sites for chelate formation, an addition of two mole ratio of copper (II) chloride might lead to the formation of a 2:1 copper complex (I) (Scheme 2). If enough (two mole ratio) of copper (II) chloride was present, **4b** was obtained quantitatively even if no atmospheric oxygen was present (run 5). An excess of copper (II) chloride was not necessary and rather depressed the yield of **4b** (run 3). When one mole ratio of copper (II) chloride was present, the 1:1 copper complex (II) might be formed and in this case, **4b** was obtained in 76% yield resulting in the deposition of metal copper in 3·8% yield (run 6). But if the same reaction was carried out without oxygen, in system B (run 7), only the copper (II) ion was available as an oxidizing agent, a larger amount of metal copper (62%) was deposited, and **4b** was obtained in 75% yield together with 16% of α-aminated product **2b**. It was obvious that both copper ions and atmospheric oxygen played a great role as oxidizing agents in this reaction, and the copper (II) ion was reduced to metal copper by two electron reductions of each chelate ring in the copper complex (II) (Scheme 2). It is reasonable to suggest that the copper (II) ion could not be trapped completely by **1** to form a 1:1 complex in the reaction mixture and some of free **1** was aminated at the α-position to give **2b** and **3b** (run 7). But in the case of run 6, atmospheric oxygen was also present and very little **2b** was obtained compared with the case of run 7. It was also reasonable that the yield of **2b** and **3b** were increased but that of **4b** was decreased together with the decrease in mole ratio of copper (II) chloride comparing the results of runs 6 and 8, or runs 7 and 9, respectively. In the case of run 9, almost all (91% yield) of the copper salt was recovered as metal copper and a 45% yield of **4b** and other α-aminated products was obtained. Neither oxidation nor reduction were necessary for α-amination, and the two electron reduction of the copper (II) ion to metal copper was explained
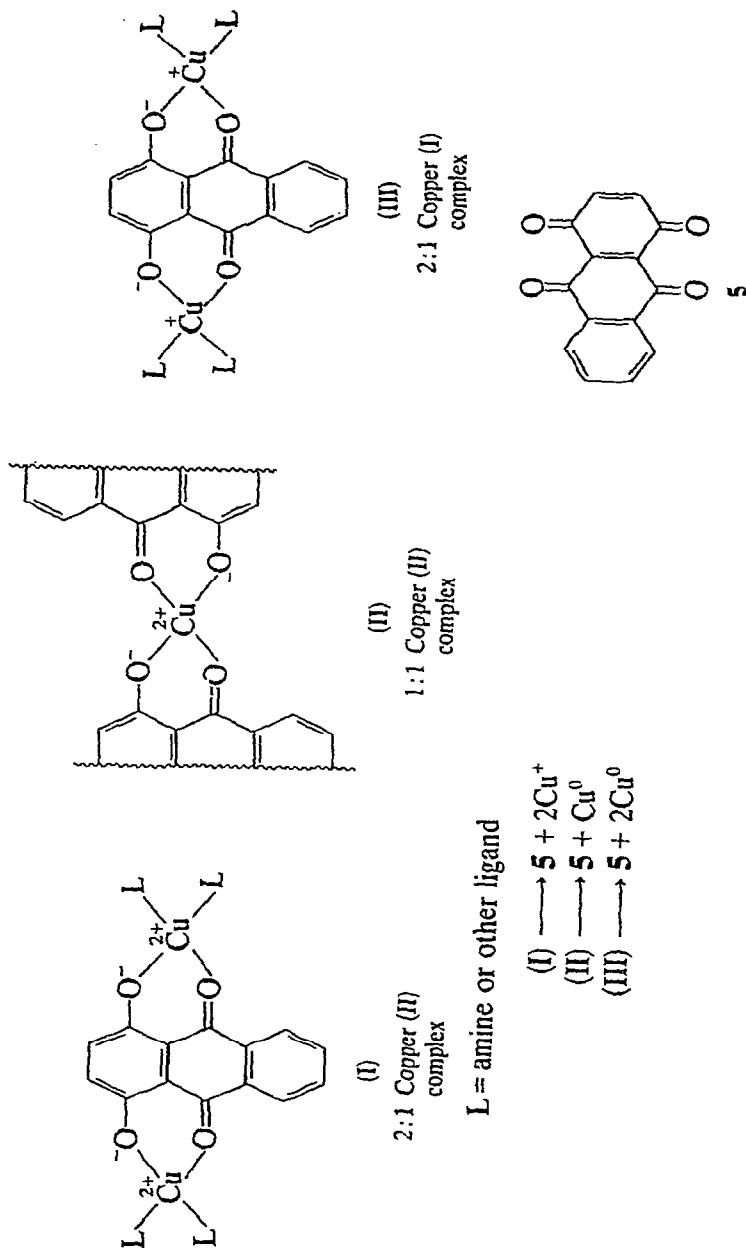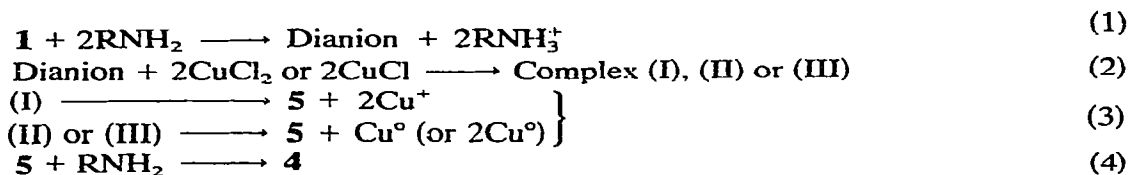
Scheme 2

stoichiometrically by the two electron redox systems of each chelate ring in complex (II) to give quinizarinquinone **5** and metal copper.

When a two mole ratio of copper (I) chloride was used as an oxidizing agent, the 2:1 copper complex (III) should be formed and one electron reduction of copper (I) ion should lead to the deposition of metal copper. In the case of run 11, where there was no oxygen in the reaction mixture and only a two mole ratio of copper (I) chloride was present as oxidizing agent, 76% yield of metal copper was isolated together with 95% yield of **4b**. Both of these values would be enough to justify the quantitative explanation of the redox system of copper complex (III) in Scheme 2.

On the other hand, the reaction of butylamine or piperidine with quinizarin-quinone **5**, which was prepared previously by the oxidation of **1** with lead tetraacetate,[7] gave **4b** or **4e** quantitatively at ambient temperature without any copper salts. These Michael type additions of amine to *p*-quinone were well known.[8] From the results described above, the mechanism of 2-amination of **1** was proposed as in Scheme 3. Without copper salts, **1** was oxidized to **5** by atmospheric oxygen or a redox system and gave three products, **2**, **3** and **4**.

$$1 + 2RNH_2 \longrightarrow \text{Dianion} + 2RNH_3^+ \tag{1}$$

$$\text{Dianion} + 2CuCl_2 \text{ or } 2CuCl \longrightarrow \text{Complex (I), (II) or (III)} \tag{2}$$

$$(I) \longrightarrow 5 + 2Cu^+ \left.\vphantom{\begin{matrix}a\\b\end{matrix}}\right\}$$

$$(II) \text{ or } (III) \longrightarrow 5 + Cu^\circ \text{ (or } 2Cu^\circ) \tag{3}$$

$$5 + RNH_2 \longrightarrow 4 \tag{4}$$

Scheme 3

3. EXPERIMENTAL

All the melting points are uncorrected. Visible spectra in benzene solution were recorded on a Hitachi EPS-3T spectrophotometer. The PMR spectra were taken on a Hitachi Perkin–Elmer Model R-20 spectrometer, unless otherwise stated in CDCl₃ solution with tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi RMU-6E spectrometer operating at 80 eV. Elemental analyses were recorded on a Yanaco CHN recorder MT-2. Column chromatography was carried out on silica gel (Wakogel C-300) using benzene as eluent.

3.1. *Materials*

Quinizarin was supplied by Mitsubishi Chemical Industry Co. Ltd and was purified by recrystallization from toluene. All the metal salts were reagent grade and used without further purification. Amines and solvents were purified by the ordinary methods.

3.2 *Reaction of 1 with amine (general procedures)*

System A: The reaction was carried out in an Erlenmeyer flask equipped with a magnetic stirrer. Reactant **1** (5 mmol) was stirred in butyl alcohol (7·5 ml) or pyridine (8 ml) with amine (228 mmol) and metal salt under the conditions described above. The mixture was poured into aqueous HCl solution (pH 1) and separated products were filtered, washed with water, dried and extracted with benzene. The filtrate was concentrated and chromatographed. Products were identified with the usual methods. The yields were determined by isolation from column chromatography.

System B: The reaction was carried out in a round bottom flask equipped with a magnetic stirrer. Deoxygenation was carried out three times by freezing the mixture of amine and pyridine in the flask with liquid nitrogen and deoxygenating under reduced pressure (2 Torr). The deoxygenated solution was transferred to the other flask to which the mixture of **1** and metal salts was previously added. Both flasks were connected with glass tube equipped with a stopcock and ball joint for attachment to the vacuum manifold. The reaction was carried out under reduced pressure.

System C: Nitrogen gas was passed into the mixture of butylamine and pyridine under reflux for 30 min. After cooling, the mixture of **1** and metal salt was added to the solution. Nitrogen gas was passed into the mixture during another 30 min. and then the reaction vessel was sealed with a cap.

Isolation of metal copper: The upper layer of the reaction mixture was decanted and the residual solid was washed several times with butylamine and ethanol. Metal copper was obtained in a pure state.

3.3. *Reaction of 1 with ethylenediamine*

Reactant **1** (5 mmol) was stirred in pyridine (8 ml) with ethylenediamine (228 mmol) at 30°C for 5 h. The mixture was treated as before. From silica gel chromatography, leucoquinizarin (14·6% yield) was isolated together with a 9·4% recovery of **1**. The main aminated product (46·7% yield) was not eluted by benzene and was extracted with methanol. The product was recrystallized from methanol and was identified with 6-hydroxy-1,2,3,4-tetrahydronaphtho-(2,3-f)-quinoxaline-7,12-dione(1,2-(ethylene-1',2'-diamino)-4-hydroxyanthraquinone) **6**.

An addition of CuCl₂ (two mole ratio to **1**) to the reaction mixture gave **6** quantitatively and no other products were obtained.

2.4. *Reaction of 5 with butylamine or piperidine*

Reactant **5** was obtained by the oxidation of **1** with lead tetraacetate.[7] Reactant **5** (5 mmol) was stirred in pyridine (8 ml) with butylamine (228 mmol)

at room temperature for 5 h. The mixture was treated as before. Compound **4b** was obtained in a quantitative yield.

The reaction of **5** with piperidine under the same conditions also gave **4e** in a quantitative yield.

3.5. *Characterization and identification of products*

Compounds **2a** and **3a** were identified with the authentic samples available as commercial products.

Some properties of the following compounds: **3b**,[1a] **4a**,[3] **4b**,[1a] **4d**,[3] **4e**[3] and **5**,[7] were already known, and these were identified by the data described in the literature and by the following data.

3b: PMR(CDCl$_3$); $\delta = 10 \cdot 74$(2H, broad), $8 \cdot 30$(2H, m), $7 \cdot 65$(2H, m), $7 \cdot 16$(2H, s), $3 \cdot 35$(4H, quartet), $1 \cdot 60$(8H, m), $1 \cdot 0$(6H, m).

4a; UVmax, nm, benzene ($\varepsilon \times 10^{-4}$), 485^{sh}(0·9), 516(1·16), 542^{sh}(0·9).

4d; UVmax, 535(1·21).

4e; UVmax, 522(1·22), PMR, 14·30(1H, s), 13·55(1H, s), 8·25(2H, m), 7·70(2H, m), 6·49(1H, s), 3·38(4H, m), 1·72(6H, m).

1-Hydroxy-4-butylaminoanthraquinone **2b**; m.p. 122–123°C(benzene); UVmax, 522^{sh}(0·63), 561(1·06), 602(1·0); Mass, 295(M$^+$), 252(M$^+$ − 43); PMR, 13·65(1H, s), 10·18(1H, broad), 8·30(2H, m), 7·70(2H, m), 7·15(2H, s), 3·35(2H, quartet), 1·62(4H, m), 1·0(3H, m). Analysis found(%): C, 73·22; H, 5·82; N, 4·49. Calculated for C$_{18}$H$_{17}$NO$_3$: C, 73·20; H, 5·80; N, 4·74.

2-Octylaminoquinizarin **4c**; m.p. 135–136°C(ethanol); UVmax, 485^{sh}(0·93), 515(1·23), 545^{sh}(0·95). Analysis found(%): C, 72·12; H, 7·05; N, 3·89. Calculated for C$_{22}$H$_{25}$NO$_4$: C, 71·93; H, 6·81; N, 3·81.

6 - Hydroxy - 1,2,3,4 - tetrahydronaphtho(2,3 - f) - quinoxaline - 7,12 - dione **6**: m.p. 274–275°C (pyridine : water = 9 : 1); UVmax, 510^{sh}(1·10), 544(1·95), 585(1·98); Mass, 280(M$^+$), 279(M$^+$ − 1); PMR(D$_6$-DMSO), 15·46(1H, s), 10·55(1H, broad), 8·11(2H, m), 7·95(1H, m), 7·70(2H, m), 6·06(1H, s), 3·5(4H, s).

4-N-benzoyl derivative of 6; m.p. 178–180°C(methanol); UVmax, 520^{sh}(0·97), 555(1·67), 597(1·64). Analysis found(%) C, 71·16; H, 4·12; N, 7·00. Calculated for C$_{23}$H$_{16}$N$_2$O$_4$: C, 71·69; H, 4·43; N, 7·27.

1-Hydroxy-(2 or 3),4-bisbutylaminoanthraquinone **7**; m.p. 131–133°C(ethanol); UVmax, ·523^{sh}(0·7), 556(1·13), 596(1·12); Mass, 366(M$^+$), 323(M$^+$ − 43); PMR, 15·32(1H, s), 11·07(1H, broad), 8·36(2H, m), 7·72(2H, m), 5·90(1H, s), 5·44(1H, broad), 3·28(4H, quartet), 1·62(8H, m), 1·0(6H, m). Analysis found(%): C, 71·59; H, 7·14; N, 7·24. Calculated for C$_{22}$H$_{26}$N$_2$O$_3$: C, 72·13; H, 7·10; N, 7·65.

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