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Amination of 5,8-Dihydroxy-1,4-naphthoquinone

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SUMMARY

The reaction of naphthazarin (**1**) *with butylamine selectively gave 2-butylaminonaphthazarin* (**2a**) *in 70% yield at low temperature, but it gave complex mixtures of aminated products in very low yields at higher temperature. The similar reactions of* **1** *with ethylenediamine afforded the ring-closure product, 7-10-dihydroxy-2,3,4-trihydrobenzo[f]quinoxalin-6-one* (**9a**) *in 46% yield. It was proposed that the reaction was initiated by the direct 2-amination of* **1** *followed by the intramolecular nucleophilic substitution of the 2-amino group on the 2-alkylamino substituent, and then followed by oxidation to give the ring-closure product* **9a**. *The role of atmospheric oxygen as an oxidant, and the redox system of* **1** *in the reaction of* **1** *with amines, are discussed.*

1. INTRODUCTION

Amination of 1,4-naphthoquinone derivatives has been widely studied in connection with potential colouring matters[1] and from the point of view of biological activities.[2] Recently, Griffiths *et al.*[3] have reported a series of syntheses of some interesting naphthoquinone colouring matters by means of thermal and photochemical aminations of naphthoquinone derivatives. Kallmayer *et al.*[4] have also reported the amination of naphthoquinones from the standpoint of the pharmaceutical interest. We

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have also studied the direct amination of 1,4-dihydroxyanthraquinone to give 2-alkylaminoquinizarins,[5] one of which has antitumour activity.[6] The naphthoquinone analogue of these is most interesting with regard to biological activity, and the direct amination of 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin, **1**) has been examined. In our previous paper,[7] the direct amination of **1** at ambient temperature with and without copper salts has been described but the selective 2-amination of **1** failed. In the present paper, the amination of **1** is re-examined in detail with a view to obtaining its selective 2-amination. The reaction of **1** with 1,2-alkylenediamines has been studied also with a view to the synthesis of the quinoxalin derivative, **9**. A possible mechanism for these aminations is also proposed.

2. RESULTS AND DISCUSSION

2.1. Direct 2-amination of 1

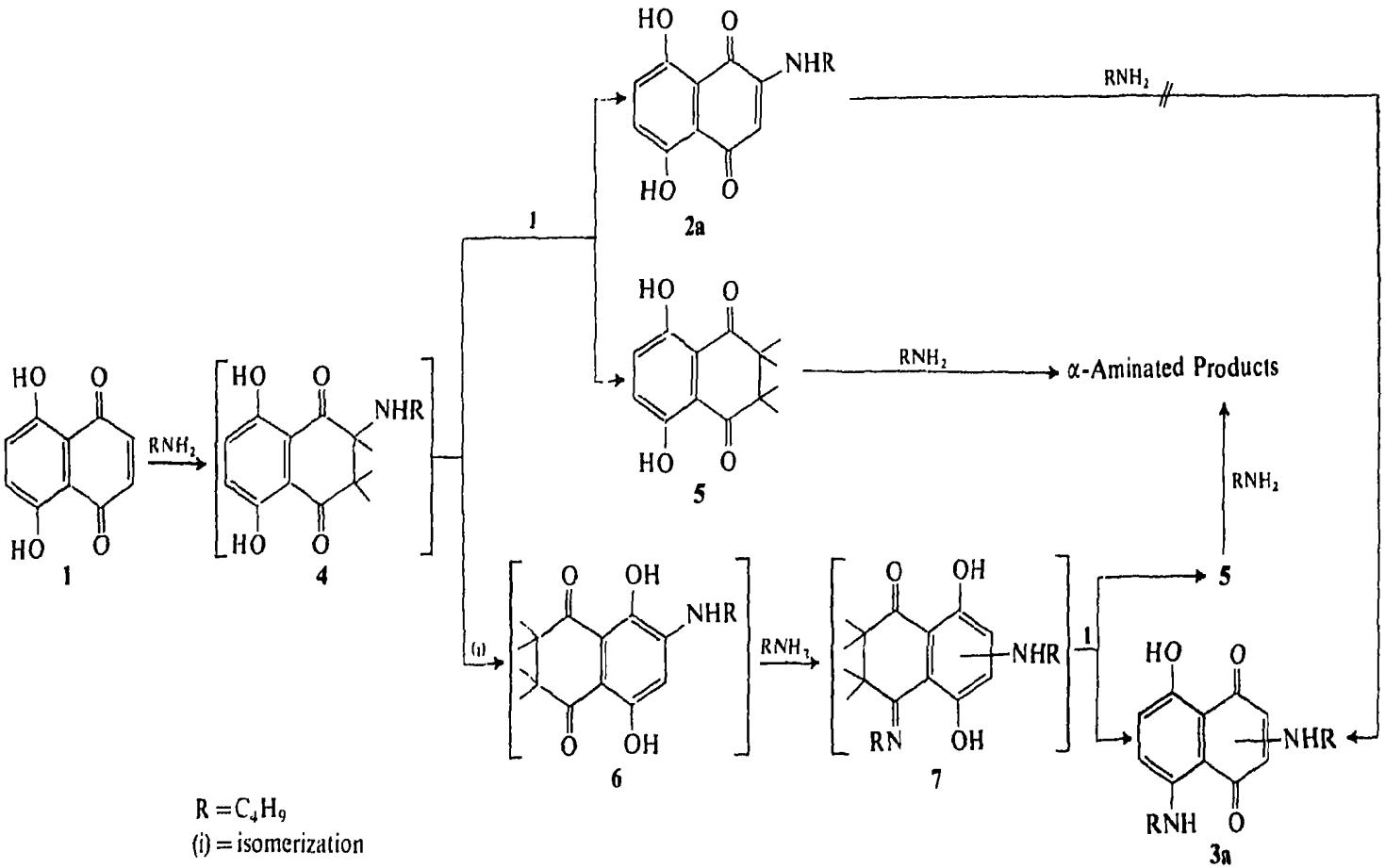
The reaction of **1** with butylamine at 50 °C for 16 h gave complex mixtures of aminated products in very low yields (Run 1), but at 25 °C, 8-hydroxy-2,5 (or 3,5)-bisbutylaminonaphthoquinone (**3a**) was obtained in 31·6 % yield together with a small amount of **2a** (Run 2). It was found that **1** was very reactive toward the alkylamine at ambient temperatures, and it was necessary to control the temperature for selective 2-amination. At 0 °C for 1 h, **2a** was selectively obtained in 61·5 % yield and **1** was recovered in 7.9 % yield (Run 3). The yield of **2a** was less than 50 % under nitrogen (Run 4), and it is proposed that unreacted **1** plays a role as an oxidant under these conditions. Atmospheric oxygen also acts effectively as an oxidant and the yield of **2a** in Run 4 was improved in its presence (Run 3). The reverse addition of **1** to amine solution improved the yield of **2a** to 69·5 %. In this system the Michael adduct **4** might be effectively oxidized to **2a** by atmospheric oxygen. Gaseous ammonia did not react with **1** because of its low basicity under the conditions described above. 2-Aminonaphthazarin (**2b**) was obtained in 6·3 % yield when the reaction of **1** with aqueous ammonia was carried out in a glass tube autoclave at 70 °C for 3 h (Run 6). Direct 2-arylamination of **1** hardly occurs at all at ambient temperatures but gives 78 % yield at 110 °C for 3 h.[8] However, the reaction is easily achieved at low temperatures by using arylimino-dimagnesium bromide as amine. 2-(4-Methoxyphenylamino)-naphth-

TABLE 1
2-Amination of Naphthazarin

Run	*Amine*	*System*[a]	*Temp.* (°C)	*Time* (*h*)	*Yield*(%)[b] 1[c]	**2a**	**3**
1	$C_4H_9NH_2$	1	50	16	0	0	3[d]
2	$C_4H_9NH_2$	1	25	24	0	1	31·6[d]
3	$C_4H_9NH_2$	2	0	1	7·9	61·5	0
4	$C_4H_9NH_2$	3	0	1	4·2	40·2	0
5[e]	$C_4H_9NH_2$	2	0	2·5	trace	69·5	0
6[f]	NH_3	—	70	3	0	6·3[g]	0
7[i]	p-$CH_3OC_6H_4N(MgBr)_2$	3	10	3	trace	32·0[h]	0

[a] The reaction was carried out under the following conditions (Method A): 1, with atmospheric oxygen; 2, under a stream of air; 3, under a stream of nitrogen.
[b] Isolated yield.
[c] Recovery.
[d] A number of aminated products were isolated in very low yields.
[e] An ethanolic solution of **1** was added dropwise to amine in ethanol (Method B).
[f] The reaction was carried out in a glass tube autoclave.
[g] **2b**, R = H.
[h] **2c**, R = p-$CH_3OC_6H_4$.
[i] p-Methoxyphenyliminodimagnesium bromide was used.

azarin (**2c**) was obtained in 32% yield by this method (Run 7). On the basis of these results, the proposed mechanism for selective 2-alkylamination of **1** is presented as Scheme 1. The initial Michael addition of amine to the quinone ring gives the adduct **4**, which is oxidized by **1** or atmospheric oxygen to give **2a**. Oxidation of **4** to **2a** by **1** accompanies the formation of leuconaphthazarin (**5**) which is subsequently aminated at the α-position to give a number of α-aminated naphthoquinone derivatives. On the other hand, the isomerization of **4** to **6** easily proceeds at higher temperatures (Runs 1 and 2), and α-amination of **6** was followed by oxidation to give **3a**. The further butylamination of **2a** does not proceed at all under these conditions (Run 2) and **2a** is recovered in 93% yield. The formation of **3a** via **2a** has been neglected. The selective synthesis of **2a** is achieved by keeping the reaction temperature below 0 °C to avoid the isomerization of **4** to **6**, and using atmospheric oxygen as an oxidant to prevent the formation of **5** which can be aminated to give unwanted α-aminated by-products. These observations have been further confirmed by results obtained from the reaction of **1** with 1,2-alkylenediamines.



R = C_4H_9

(i) = isomerization

Scheme 1

2.2. The ring-closure reaction between 1 and 1,2-alkylenediamines

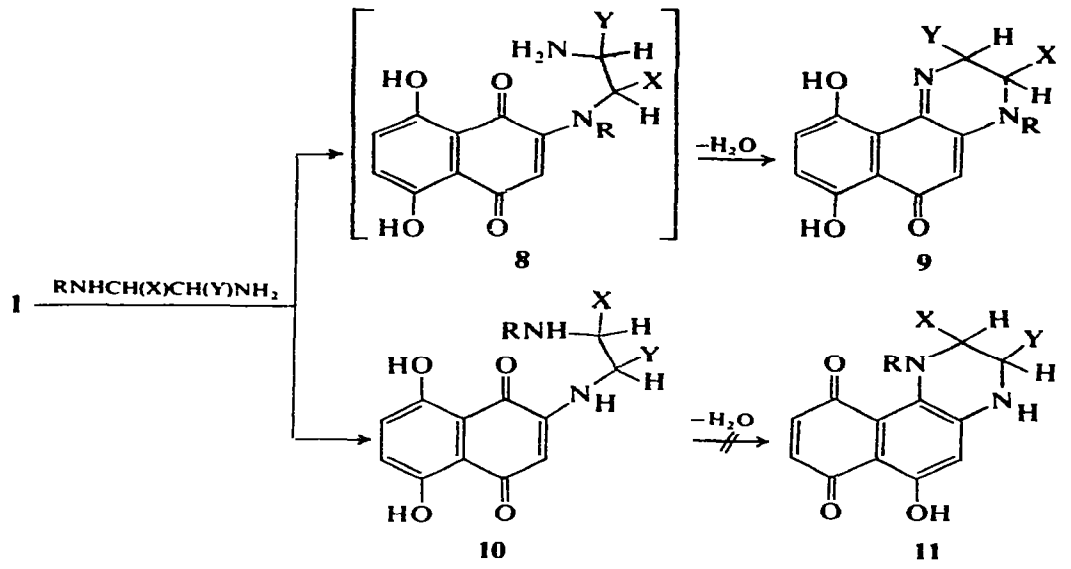
The reaction of **1** with ethylenediamine at 0 °C for 1 h gave the ring-closure product **9a** (7,10-dihydroxy-2,3,4-trihydrobenzo[*f*]quinoxalin-6-one) in 45·7% yield (Run 8). Similar reactions of **1** with other 1,2-alkylenediamines also afforded the corresponding ring-closure products **9b–9e** (Runs 9–12). The ring-closure reaction was not inhibited by the alkyl substituents at the 1- and/or 2-positions of ethylenediamine (Runs 9 and 10), but was greatly inhibited when the amino group was alkylated because of steric hindrance. The *N*-alkyl substituent markedly inhibited both the 2-amination and the ring-closure reactions. The reactions of **1** with *N*-methyl- and *N*-ethyl-ethylenediamine gave 28·9% yield of **9d** and 8% yield of **9e**, respectively (Runs 11 and 12). The yields were greatly decreased in comparison with that of **9a** (Run 8).

TABLE 2
The Reaction of **1** with Ethylenediamines[a]

Run	*Diamine*	*Products (Yield, %)*[b]	
8	$H_2N(CH_2)_2NH_2$	**9a** (45·7)	
9	$H_2NCH(CH_2)_4CHNH_2$	**9b** (46·1), (59·9)[c]	
10	$H_2NCH(CH_3)CH_2NH_2$	**9c** (39·3)[c]	
11	$H_2N(CH_2)_2NHCH_3$	**9d** (28·9)	**10d** (—)[d]
12	$H_2N(CH_2)_2NHC_2H_5$	**9e** (8·0)	**10e** (—)[d]
13	$H_2N(CH_2)_2NHC_6H_5$	**9f** (0)	**10f** (49·0)
14	$H_2N(CH_2)_2NHCOCH_3$	**9a** (trace)	**10g** (44·8)[c]

[a] The reaction was carried out under atmospheric oxygen (Method A).
[b] Isolated yield.
[c] Method B.
[d] Isolation from the reaction mixture was very difficult because of its high solubility.

As shown in Scheme 2, the formation of **8** and **10** should be obtained in the 2-amination of **1** and *N*-alkylethylenediamine. The formation of **8** was much less probable than that of **10** because of steric hindrance by the *N*-alkyl group. The intermediate **8** could be subsequently cyclized to give **9**, and no **8** was obtained. On the other hand, **10** could not give the ring-closure product **11** because of steric hindrance by the *N*-alkyl group. Consequently, only **9a–9e** were isolated. Compounds **10d** and **10e** were not isolated from the reaction mixture because of their high solubility. A

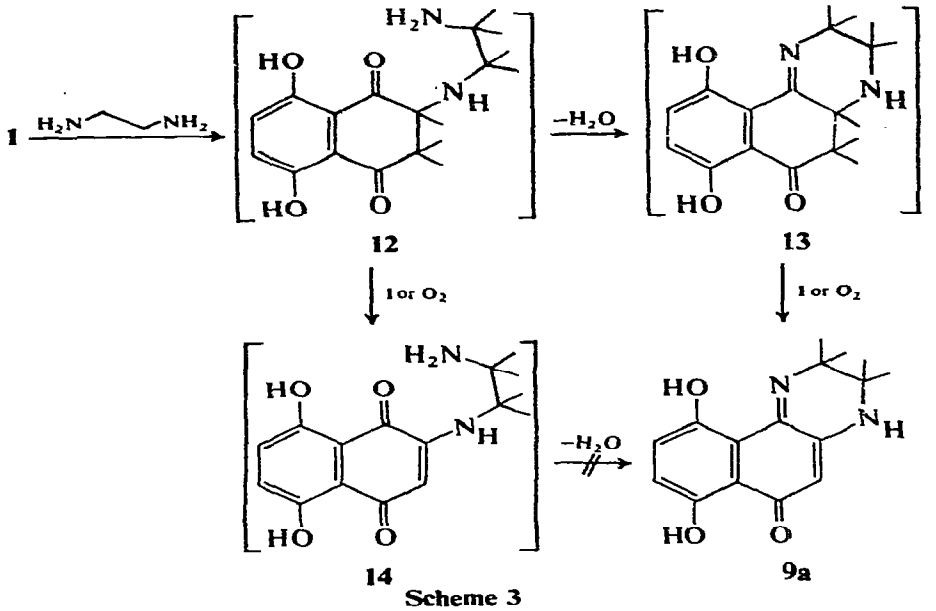


	a	b	c	d	e	f	g
X	H	C_4H_8	H	(CH_3)	H	H	H	H
Y	H		(CH_3)	(H)	H	H	H	H
R	H	H	H		CH_3	C_2H_5	C_6H_5	$COCH_3$

Scheme 2

similar substituent effect has been observed in the reactions of quinizarin with *N*-alkylethylenediamines to give the corresponding 6-hydroxy-1,2,3,4-tetrahydronaphtho[2,3-*f*]quinoxalin-7,12-dione derivatives.[5(b)] The reaction of **1** with *N*-phenylethylenediamine afforded the corresponding **10f** in 49 % yield but not **9f** (Run 13). The initial formation of **8f** might be completely inhibited because of steric hindrance by the *N*-phenyl group. In the case of *N*-acetylethylenediamine, **10g** was obtained in 44-8 % yield together with a trace amount of **9a** which might be formed after the hydrolysis of the *N*-acetylamino group during the reaction (Run 14).

A possible mechanism of formation of **9a** is proposed in Scheme 3. It is suggested that the reaction is initiated by the direct 2-amination of **1** to give the Michael adduct **12**. Two possible paths to **9a** are considered: *Path A*, the initial intramolecular nucleophilic substitution of the 2-



Scheme 3

aminoethylamino group to the carbonyl group at the 1-position to give the ring-closure leuco compound **13**, followed by oxidation to give **9a**. *Path B*, oxidation of **12** to give 2-(2-aminoethylamino)naphthazarin (**14**) followed by a ring-closure reaction to give **9a**. Path B is considered to be improbable for the following reasons: (i) **2a**, which corresponds to **14**, does not react with butylamine under the conditions described; (ii) the carbonyl group at the 1-position of **12** is likely to be much more reactive to amines than that in **14** because it is not conjugated as it is in **14**.

3. EXPERIMENTAL

All the melting points are uncorrected. Visible spectra in chloroform 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 $CDCl_3$ 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 chloroform as eluent.

3.1. Materials

Naphthazarin was synthesized by the method described in the literature[9] and was purified by recrystallization from benzene. Amines were reagent grade and were used without further purification. Solvents were purified by the usual method.

3.2. Reaction of 1 with amine (general procedures)

The reaction was carried out in a three-necked flask equipped with a magnetic stirrer, a dropping funnel, a thermometer and a reflux condenser.

Method A
Amine (30 mmol) was added dropwise to an ethanol solution (150 ml) of naphthazarin (1 mmol) under the conditions described. The mixture was poured into water and the solution was neutralized with aqueous dilute hydrogen chloride solution. The solution was extracted with two 50 ml portions of chloroform and the extract was dried by anhydrous sodium sulphate, concentrated and then chromatographed. Products were identified by the usual methods. The yield was determined by isolation by column chromatography.

Method B
A solution of **1** was added to the amine solution. The other procedures were the same as those of Method A.

3.3. Reaction of 1 with gaseous ammonia

Ammonia gas was preliminarily introduced into an ethanol solution (25 ml) of **1** (1 mmol) in a glass tube autoclave and the reaction was carried out at 70 °C for 3 h. The subsequent procedures were the same as those of Method A.

3.4. Reaction of 1 with *p*-methoxyphenyliminodimagnesium bromide

The reaction was carried out in the equipment described in Section 3.2. The aryliminodimagnesium reagent was previously prepared by the method described.[10] A solution of **1** (5 mmol) in tetrahydrofuran (50 ml)

was added dropwise to a solution of *p*-methoxyphenyliminodimagnesium bromide (25 mmol) in tetrahydrofuran (20 ml) at 10 °C. The mixture was hydrolysed with saturated aqueous ammonium chloride solution and was neutralized with aqueous dilute hydrogen chloride solution. The solution was filtered and the filtrate was extracted with benzene. The extract was dried by anhydrous sodium sulphate, concentrated, and then chromatographed. Compound **2c** was isolated in 32% yield.

3.5. Characterization and identification of products

Compounds **2a** and **3a** were already known[7] and these were identified by the data described in the literature[7] and by those following.

2a PMR($CDCl_3$): $\delta = 13{\cdot}58$(1H,s), 11·97(1H,s), 7·23(1H,d), 7·08(1H,d), 6·15(1H,broad), 5·75(1H,s), 3·24(2H,q); u.v. max. nm, benzene ($\varepsilon \times 10^{-4}$): 474(0·78), 500(0·86), 534(0·65).

3a PMR($CDCl_3$): $\delta = 14{\cdot}80$(1H,s), 10·10(1H,broad), 7·24(1H,s), 7·15(1H,s), 6·42(1H,broad), 5·73(1H,s); u.v. max.: 555(1·25), 599(1·16).

2-Aminonaphthazarin, **2b**
M.p. 276–8 °C ($CHCl_3$); u.v. max.: 472(0·75), 498(0·78), 535^{sh}(0·51); mass: 205(M^+) PMR(D_6-DMSO): 13·59(1H,s), 11·7(1H,broad), 7·58(2H,broad), 7·24(2H,d), 5·8(1H,s). Analysis: Found (%), C, 58·02; H, 3·19; N, 6·54; Calculated for $C_{10}H_7NO_4$: C, 58·54; H, 3·41; N, 6·83.

2-(4-Methoxyphenylamino)naphthazarin, **2c**
M.p. 188–90 °C($CHCl_3$); u.v. max.: 512(1·04), 541^{sh}(0·96); mass: 311(M^+), 296($M^+ - 15$); PMR: 13·3(1H,s), 11·9(1H,s), 7·5(1H,broad), 7·3(2H,d), 7·1(2H,s), 7·0(2H,d), 6·1(1H,s), 3·8(3H,s). Analysis: Found(%), C, 65·09; H, 3·96; N, 4·37; Calculated for $C_{17}H_{13}NO_5$: C, 65·59; H, 4·18; N, 4·50.

7,10-Dihydroxy-2,3,4-trihydrobenzo[f]quinoxalin-6-one, **9a**
M.p. >320 °C($CHCl_3$); u.v. max.: 443^{sh}(0·36), 477(0·41), 508(0·48), 544(0·67), 584(0·94), 631(0·69); mass: 230(M^+), 229($M^+ - 1$), 215($M^+ - 15$); PMR(D_6–DMSO), 14·6(1H,s), 12·6(1H,broad), 8·3(1H,broad), 6·9(2H,s), 5·7(1H,s), 3·8(2H,m), 3·4(2H,m). Analysis: Found(%), C, 62·51; H, 4·10; N, 12·16; Calculated for $C_{12}H_{10}N_2O_3$, C, 62·61; H, 4·35; N, 12·17.

7,10-Dihydroxy-2,3,4-trihydro-2,3-butanobenzo[f]quinoxalin-6-one, **9b**
M.p. 219–21 °C($CHCl_3$); u.v. max.: 448^{sh}(0·39), 476(0·43), 506(0·48), 547(0·72), 588(1·06), 637(0·73); mass: 284(M^+), 241($M^+ - 43$); PMR: 14·3(1H,s), 12·3(1H,broad), 6·8(2H,s), 5·8(1H,s), 5·2(1H,broad), 3·7(2H,m), 1·7(8H,m). Analysis: Found(%), C, 67·75; H, 5·63; N, 9·43; Calculated for $C_{16}H_{16}N_2O_3$, C, 67·61; H, 5·63; N, 9·86.

7,10-Dihydroxy-2,3,4-trihydro-2(or 3)-methylbenzo[f]quinoxalin-6-one, **9c**
M.p. 202–204 °C($CHCl_3$); u.v. max.: 443^{sh}(0·31), 474(0·35), 509(0·39), 544(0·63), 583(0·99), 632(0·65); mass, 244(M^+), 229($M^+ - 15$); PMR: 14·47(1H,s), 12·2(1H,broad), 6·95(2H,s), 5·92(1H,s), 5·00(1H,broad), 3·99(1H,m), 3·52(2H,d), 1·4(3H,d). Analysis: Found(%), C, 63·49; H, 4·67; N, 10·97; Calculated for $C_{13}H_{12}N_2O_3$, C, 63·93; H, 4·92; N, 11·48.

7,10-Dihydroxy-2,3-dihydro-4-methyl-benzo[f]quinoxalin-6-one, **9d**
M.p. 214–16 °C(C_6H_6); u.v. max.: 446^{sh}(0·63), 473(0·71), 502(0·69), 539(0·66), 583(0·70), 627(0·48); mass: 244(M^+), 243($M^+ - 1$); PMR: 13·7(1H,s), 13·1(1H,broad), 6·8(2H,s), 5·6(1H,s), 3·9(2H,t), 3·4(2H,t), 2·9(3H,s). Analysis: Found(%), C, 63·87; H, 4·76; N, 11·54; Calculated for $C_{13}H_{12}N_2O_3$: C, 63·93; H, 4·92; N, 11·48.

7,10-Dihydroxy-2,3-dihydro-4-ethylbenzo[f]quinoxalin-6-one, **9e**
M.p. 194–95 °C(C_6H_6); u.v. max.: 446^{sh}(0·49), 476(0·6), 506^{sh}(0·57), 543(0·49), 586(0·52), 634(0·3); mass: 258(M^+), 243($M^+ - 15$), 229($M^+ - 29$); PMR: 14·0(1H,s), 13·4(1H,broad), 7·0(2H,s), 5·8(1H,s), 4·0(2H,t), 3·5(2H,q), 3·4(2H,t), 1·3(3H,t). Analysis: Found(%), C, 64·91; H, 5·35; N, 10·85; Calculated for $C_{14}H_{14}O_3N_2$, C, 65·12; H, 5·43; N, 10·85.

2-(2-Phenylaminoethylamino)naphthazarin, **10f**
M.p. 179–80 °C(C_6H_6); u.v. max.: 476^{sh}(0·80), 503(0·85), 541^{sh}(0·56); mass: 324(M^+), 219($M^+ - 105$); PMR: 13·3(1H,s), 11·8(1H,s), 7·0–7·3(4H,m), 6·5–6·8(3H,m), 6·3(1H,broad), 5·72(1H,s), 3·5(4H,m). Analysis: Found(%), C, 66·88; H, 4·92; N, 8·57; Calculated for $C_{18}H_{16}N_2O_4$, C, 66·67; H, 4·94; N, 8·64.

2-(2-Acetylaminoethylamino)naphthazarin, **10g**
M.p. 241–42 °C($CHCl_3$); u.v. max.: 473^{sh}(0·68), 500(0·74), 543^{sh}(0·50);

mass: 290(M^+), 231($M^+ - 59$), 218($M^+ - 72$); PMR(D_6—DMSO): 13·6(1H,s), 11·67(1H,s), 7·9(2H,broad), 7·23(2H,d), 5·7(1H,s), 3·3(4H,m), 1·8(3H,s). Analysis: Found(%), C, 57·97; H, 4·73; N, 9·26; Calculated for $C_{14}H_{14}N_2O_5$, C, 57·93; H, 4·83; N, 9·66.

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