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SPECTROSCOPIC STUDY OF KETO-ENOL EQUILIBRIA—XII[1]

REDUCED AMINO-NAPHTHOQUINONES

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Abstract—The spectroscopic properties of several compounds related to 1,5-diamino-4,8-naphthoquinone and 1,4-*bis*-(methylamino)-5,8-naphthoquinone have been determined. The possibility of producing isomers during the synthesis and the tautomeric equilibria in the compounds have been investigated.

INTRODUCTION

The dye, napthazarin **1**, (Fig. 1), was first isolated by hydrolysis of a highly colored violet substance which is the direct product of the reaction of 1,5-dinitronaphthalene with sulfuric acid in the presence of a reducing agent.[2] Later, the structure **2** (Fig. 1) was proposed by Neudecker[3] for the violet intermediate. This violet intermediate is frequently referred to as the "naphthazarin intermediate product". A comprehensive, but non-critical review by Merian[4] last summarized the known chemistry of the amino-naphthoquinones.

These materials (**1** and **2**) are of interest because they are stable derivatives of 1,5-naphthoquinone, an unknown, presumably unstable compound and they have also served as starting materials for many dyes of commerce.

The synthetic procedures for producing 1,5-diamino-4,8-naphthoquinones from **1** and **2**, usually involve reducing them to the *leuco* forms and treating the reduced material with an amine. The material is then reoxidized without isolation, usually by atmospheric oxygen.

In this paper, we report the isolation and characterization of three of the reduced materials. As a result of this work, the structures of several previously reported compounds are re-assigned.

SYNTHESIS AND ASSIGNMENT OF STRUCTURE

The *leuco* form **3** on reaction with 40% aqueous methylamine in the presence of sodium dithionate and sodium carbonate, in an inert atmosphere gave three air sensitive compounds: **A**, m.p. 200° dec, $C_{12}H_{16}N_2O_2$; **B**, m.p. 172–3°, $C_{12}H_{14}N_2O_2$; and **C**, m.p. 163–4°, $C_{12}H_{14}N_2O_2$.*

Oxidation of **A** and **B** led to 1,5-*bis*-(methylamino)4,8-naphthoquinone **7** while oxidation of C led to 1,4-*bis*-(methylamino)5,8-naphthoquinone **8**. The evidence that provides the basis for assigning structures **4**, **5**, and **6** to **A**, **B**, and **C**, respectively, (Fig. 1) follows.

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* The mass spectrometric molecular ions are in agreement with these assignments.

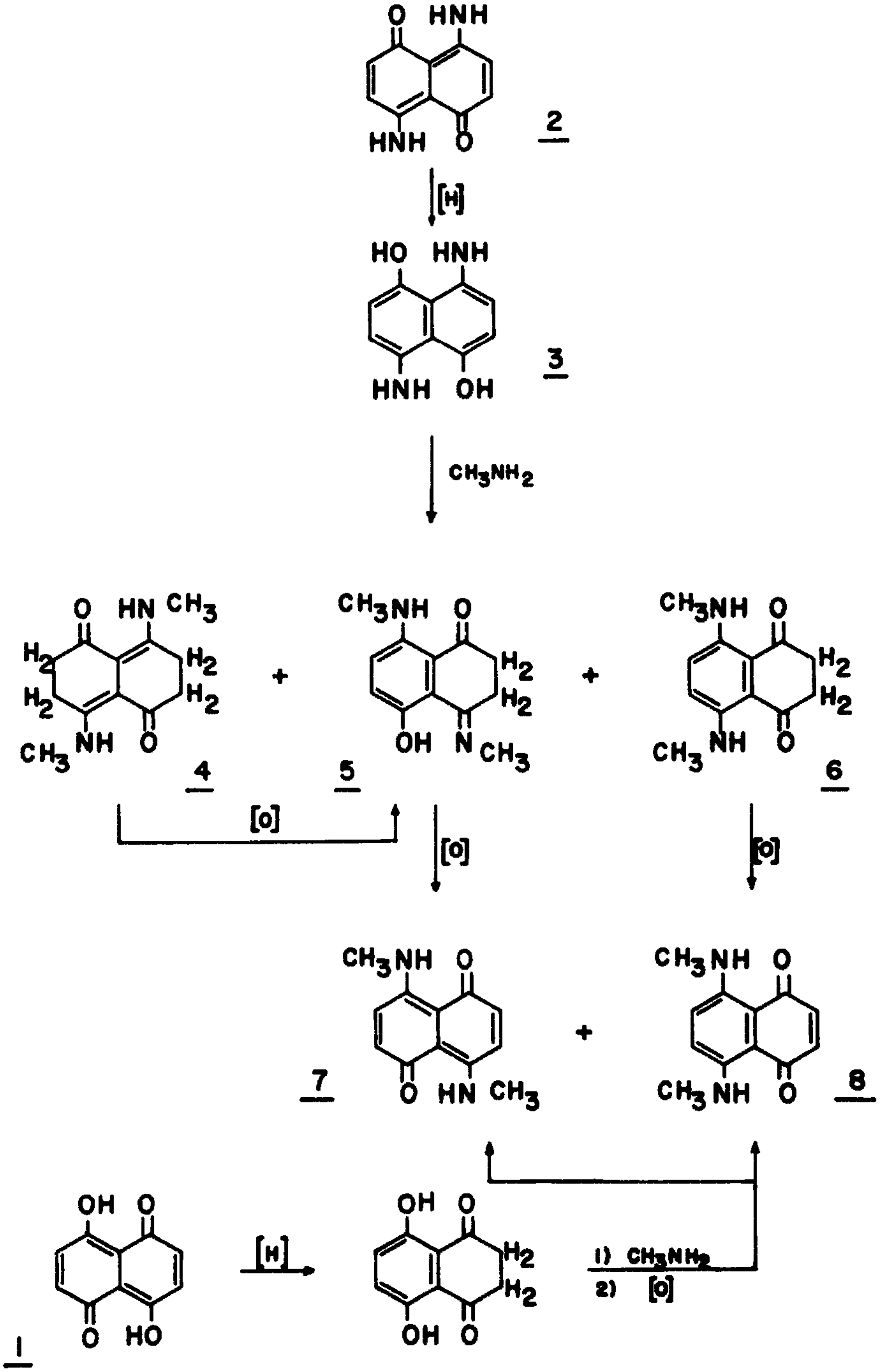
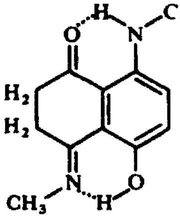


Fig. 1 Interrelationships among the various aminonaphthoquinones.

Mass spectrometric analyses establish that A contains 4 hydrogens and B contains 2 hydrogens more than the parent dye 7 to which they are converted by oxidation. The PMR spectrum of A indicates the presence of 2 H-bonded protons (δ = 11·27 ppm). The 6 protons of the two Me groups at 2·87 ppm are split into a doublet, J = 5·2 Hz, by the N-H, establishing the presence of the proton on nitrogen. The 8 additional hydrogens occur as complex methylene signals centred at δ = 2·51 ppm. The formulation of A as 4, *reduced* 1,5-*bis*-(methylamino)-4,8-naphthoquinone 7 is in agreement with the presented data.

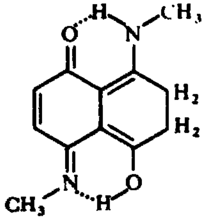
In chloroform solution, the PMR spectrum of B shows two markedly different acidic proton signals, strongly H-bonded, one at δ = 16·1 ppm and the other at 9·02 ppm. In the vinyl region, an AB quartet is observed at δ = 6·90 and 7·13 ppm (J = 9·4 Hz). The high field region is, however, complex. A 3 proton singlet at δ = 3·33 ppm can readily be assigned to an unsplit N-Me but a complex grouping at δ = 3 ppm cannot be unequivocally assigned. The employment of benzene as the solvent for B resolved the ambiguities. In the aromatic solvent the two N-Me groups are easily identified. One is a singlet at δ = 2·65 ppm and the other a doublet at δ = 2·41 ppm (J = 5·3 Hz). With this information, the N-Me doublet can be located at δ = 2·92 ppm (J = 5·3 Hz) in $CDCl_3$ solution. In both solvents, the N-Me doublet collapsed to a singlet upon shaking with D_2O.

Two structures can be advanced for this compound:



5a

or



5b

There is no concrete evidence presently available by which one may be distinguished from the other. However, in 5a one ring is fully aromatic and would appear to be energetically more favorable than the cross conjugated system in 5b. This assignment is in agreement with the structure proposed earlier for *leuco*-naphthazarin.[5]

As would be expected, the UV spectra of these compounds reflect the increase in conjugation as the compounds are oxidized, 4→5→7 (Fig. 2). The maximum for 4 being at 368 mμ, shifting to 519 mμ in 5, and finally to 648 mμ in the fully oxidized 7.

Compound C, assigned structure 6 likewise presents certain ambiguities as the methylene groups overlap with the N-Me signals when examined in $CDCl_3$ solution. When benzene is used as the solvent, however, the spectrum is readily interpreted. The NH-Me coupling of 5·5 Hz is clearly observed at δ = 2·94 ppm. When the chloroform solution of 6 is shaken with a few drops of D_2O, the amine hydrogens exchange and the N-Me doublet collapses to a singlet. The methylene groups contiguous to the oxygen are preferred to the alternative 6b where the methylenes adjacent to the methylamino groups lead to a less stabilized aromatic system.[*]

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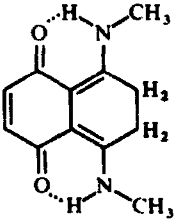
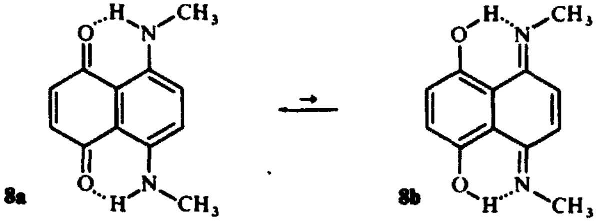
[*] The chemical shift of the vinyl hydrogen (δ = 7·10 ppm) is in better agreement with 6a. In the case of 6b, the vinyl resonance should be nearer to δ = 6·90 ppm.[8]

The visible spectrum of **6** has maxima at 507 and 528 mμ, upon oxidation to **8**, the maxima shift markedly and increase in intensity (Fig. 3) due to the increase in conjugation of the system. The more symmetrical 1,4-compounds appear to have longer wavelength UV maxima than the 1,5-series, but the extinction coefficients are appreciably smaller.



6b

As stated previously, **7** is obtained on oxidation of **5**. The PMR spectrum of **7** is weak in intensity due to the limited solubility of the compound, but the spectrum is unexceptional. The two N-Me groups are split by the NH into a doublet ($J = 5{\cdot}2$ Hz), and the vinyl hydrogens are seen as equivalent AB quartets ($J = 10{\cdot}0$ Hz). In **8** an NH-Me spin coupling of 5·5 Hz is observed, placing the proton on the nitrogen.



The equilibrium thus is on the side of **8a** and the compound is accordingly 1,4-*bis*-(methylamino)-5,8-naphthoquinone and not the imine **8b**.

Two singlets at $\delta = 6{\cdot}88$ ppm and $7{\cdot}25$ ppm (each 2 protons) are clearly assignable

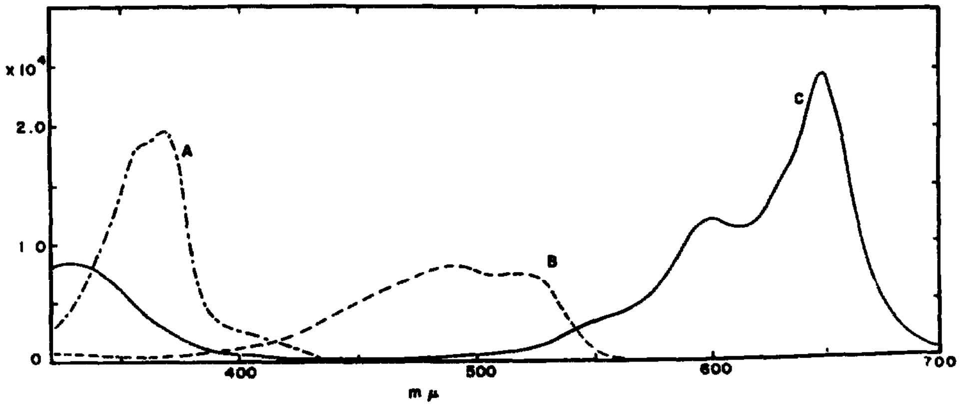


Fig. 2 UV spectra (ethanol solution) of: (A) Tetrahydro-1,5-bis(methylamino)-4,8-naphthoquinone, **4**. (B) Dihydro-1,5-bis(methylamino)-4,8-naphthoquinone, **5**. (C) 1,5-bis(methylamino)-4,8-naphthoquinone, **7**.

to the two vinyl groups, the first quinoid and the other aromatic.[6] PMR spectroscopy clearly distinguishes **7** and **8** *via* the vinyl hydrogens.

Since the synthesis of **4**–**6** produced both the 1,5- and 1,4-isomers, we investigated further to determine the step at which the isomerization occurred. The starting materials for these reduced aminonaphthoquinones are the "naphthazarin intermediate product" **2** and the "leuco compound" **3** derived from it. Since PMR spectroscopy is a very sensitive probe, we checked the structural integrity of **2**. The PMR spectrum, obtained in DMSO-d_6, exhibited an AB quartet with $J = 9{\cdot}4$ Hz (Table 1) for the aromatic proton resonances. To assess the presence of isomeric starting materials, the PMR spectrum of the commercial grade,[7] zinc chloride salt of **2** was obtained, again using DMSO-d_6 as solvent. An AB quartet was observed and if any 1,4-isomer was present in the 1,5-diamino-4,8-naphthoquinone, the amount was probably less than 5%.

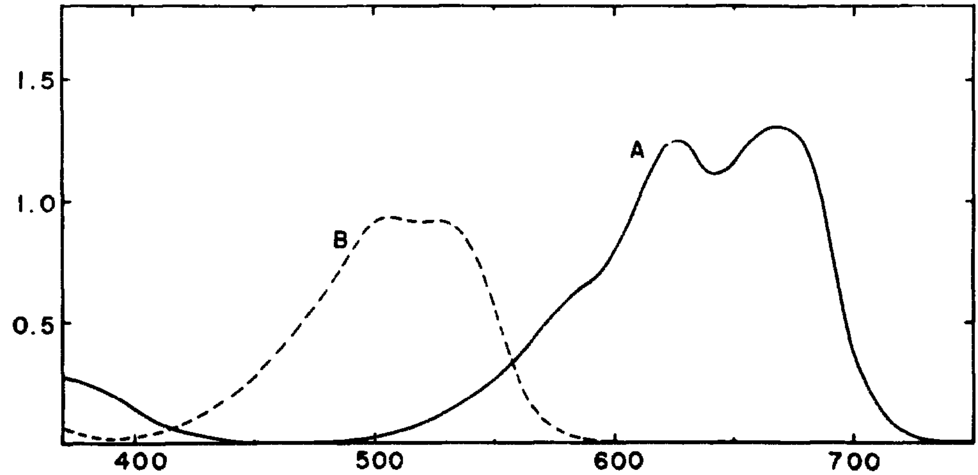


FIG. 3 UV spectra (ethanol solution) of: (A) 1,4-bis(methylamino)-5,8-naphthoquinone, **8**. (B) Dihydro-1,4-bis(methylamino)-5,8-naphthoquinone, **6**.

The "naphthazarin-intermediate product" **2** on reduction with stannous chloride in aqueous hydrochloric acid affords a crystalline, colorless dihydrochloride (*leuco* form) **3**, whose UV spectrum is in accord with that expected of a tetra-substituted naphthalene derivative (Table 2). The material fortunately is soluble enough in DMSO-d_6 that the PMR spectrum may be obtained. An AB quartet with $J = 8{\cdot}2$ Hz is observed with a decrease in the spin coupling in **3** as compared to **2**. Thus the isomerization process which produces both 1,4 and 1,5 materials from the 1,5-diamine occurs during the reaction of the *leuco* compound with the amine.

If methylamine is reacted with the *leuco* "naphthazarin intermediate product" **3** (as with the synthesis of **4**–**6**) and is followed by oxidation, there results a material m.p. about 200° giving two blue spots on a TLC plate. PMR analysis demonstrated unequivocally the presence of both the 1,4- and 1,5-isomers (m.p. 235° and 210° respectively) with the 1,4 isomer predominating. This is in accord with our results on compounds **4**–**6**.

In the patent of Klein,[8] it is reported that 1,4-*bis*-(alkylamino)-5,8-naphthoquinones are derived from the reaction of two moles of alkylamine with *leuco*-naphthazarin,

TABLE 1. PMR SPECTRAL DATA (IN PPM)[a]

Compound	Solvent	Acidic proton	R	Other protons	Aromatic protons
2	DMSO	10·9	8·20		6·83 7·24 (9·9)[b]
7[c]	$CDCl_3$	12·80	3·24 (5·3)		7·04 7·27 (10·0)
8	$CDCl_3$	10·8	3·09 (5·5)		6·88 7·24
9	$CDCl_3$	13·03 (6)			7·02 7·25 (9·9)
4	$CDCl_3$	11·27	2·87 (5·2)	2·51	
5	$CDCl_3$	9·02 16·1	3·33 2·92 (5·3)	2·9	6·90 7·13 (9·4)
	C_6H_6		2·65 2·41 (5·3)	2·2	
6	$CDCl_3$	8·99	2·94 (5·5)	2·89	7·10
	C_6H_6	9·18	2·42 (5·5)	2·51	6·67
10	$CDCl_3$	12·88			7·74

[a] From TMS as Reference.

[b] In Hz.

[c] Accuracy slightly less due to low solubility of compound.

TABLE 2. UV SPECTRAL DATA[a]

Compound	Solvent	$\lambda_{m\mu}$	$\varepsilon \times 10^4$	$\lambda_{m\mu}$	$\varepsilon \times 10^4$
2	EtOH	562	0·96	608	1·83
	MeSOMe	568	1·09	614	2·05
	C_5H_5N	571	1·15	617	2·12
7	EtOH	600	1·19	648	2·42
	$CHCl_3$	606	1·07	657	2·19
	C_5H_5N	609	1·10	660	2·28
8	EtOH	626	1·26	667	1·32
	$CHCl_3$	628	1·14	686	1·32
	CCl_4	636	1·15	692	1·31
9	EtOH	597	1·24	648	2·58
	CCl_4	608	1·20	658	2·54
4[b]	EtOH	358 (S)	1·79	368	1·92
	MeSOMe			370	1·82
5[b]	EtOH	488	0·79	519	0·73
6[b]	EtOH	507	0·94	528	0·91
	CCl_4	508	0·87	526	0·86
10	$CHCl_3$	622	1·27	674	2·48
	CCl_4	622	1·26	674	2·34
3	0·1N HCl	304	0·78	340	0·70

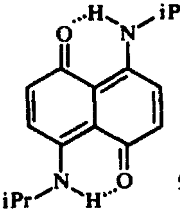
[a] The two most intense bands are given.

[b] Corrected for a small amount of the other compound present (by oxidation).

(S) Shoulder.

(see Fig. 1). He reported a m.p. of 200° for his compound, but below the 235° for the 1,4- and 210° for the 1,5-compounds. His reported m.p. is indentical to our m.p. for the mixture. Both synthetic procedures, therefore, give rise to a mixture of products.

We found that the reaction of isopropyl amine with *leuco*-naphthazarin, followed by air oxidation, produced only one isolable compound, m.p. 171–2°. This is presumably the same compound reported by Klein (m.p. 172°). The compound must be assigned the structure, **9**, 1,5-bis-(isopropylamino)-4,8-naphthoquinone on the basis of both the PMR and UV spectral studies.



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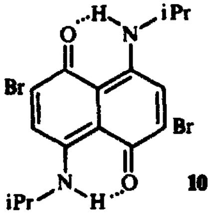

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In $CDCl_3$, the PMR spectrum clearly showed the AB quartet ($J = 9{\cdot}9$ Hz) typical of the 1,5-*bis*(alkylamino)-4,8-naphthoquinone system **2**. Furthermore, the electronic spectra of **9** are similar to that of the 1,5-*bis*(methylamino) compound **7**, and not to the 1,4-*bis*(methylamino) compound **8**. Upon bromination of **9**, the dibromide **10** results.

EXPERIMENTAL

UV spectra were taken on a Cary Model 14 Spectrometer. Cells of path lengths 1 mm to 5 cm were used as appropriate. The soln temp was ~25°. Soln for compounds **4**, **5** and **6** were made up in deaerated solvents under nitrogen atmosphere using 1 mm cells.

PMR spectra were taken on a Varian A-60 Spectrometer operating at 60·00 MHz, using internal TMS as the reference. Band positions were measured by sidebands generated by an audio oscillator monitored by a frequency counter. The probe temp was determined by measuring the separation between the resonances of a sample of MeOH.

The reaction of 1,5-dihydroxy-4,8-diaminonaphthalene dihydrochloride with methylamine. The double zinc chloride salt of the "naphthazarin intermediate product" (commercial sample)[9] was reduced by the procedure of Neudecker.[3] The reduction product, 1,5-dihydroxy-4,8-diaminonaphthalene dihydrochloride, 5·4 g, 0·02 moles, and sodium dithionate, 8 g were placed in a steel bomb, purged with N_2, 40% $MeNH_2$aq (40 ml) and 20% Na_2CO_3aq (20 ml) were added. The sealed bomb was kept at 100° for 3 hr, then cooled and opened. The contents were filtered off rapidly and washed with water, 3·5 g of dry crude product being obtained. The solid was Soxhlet extracted, employing about 150 ml of ethyl ether, until the extract changed from a reddish color to yellow. On cooling, 1·35 g of a "reddish" crystalline material was isolated from the ethyl ether which on analysis by TLC (E K silica), with hexane as solvent, showed two spots. The "yellow" solid in the extractor weighed 1·45 g.

Compounds A (**4**) *and* B (**5**). The "yellow" solid was crystallized from boiling acetone from which two compounds could be isolated. Compound A, m.p. 200°, (brownish needles) was quite soluble in hot acetone. A second compound b is obtained on concentration of the acetone soln. After a second crystallization from acetone, B melts at 172–3°, (greenish reflex). (Combustion analysis given in Table 4.)

Compound C (**6**). The "reddish" solid is most readily purified by column chromatography on Florisil. All traces of A or B are left on the column (TLC analysis) when compound C is eluted with ethyl ether. The desired compound travels as a reddish band. The compound was crystallized from 1 part of hot EtOAc by the addition of 10 parts of hot hexane, m.p. 163–4°.

Compound (**7**). A 200 mg sample of **5** was dissolved in 50 ml AcOH to which an excess of mercuric acetate was added, and warmed on the steam cone for 1 hr (TLC analysis used to determine the course of the oxidation) during which the color of the soln became blue. The solvent was removed and the residue dissolved in boiling benzene, filtered and concentrated. Platelets of **7** were obtained which were contaminated with mercuric acetate. The compound was treated with boiling water and filtered while hot. Crystallization from EtOAc–benzene yielded 100 mg of **7**, m.p. 210° (dec).

Compound (**8**). An excess of mercuric acetate in 100 ml AcOH was used to oxidize 450 mg of **6**. The soln was heated on the steam cone until **6** was no longer present in soln (TLC analysis). The solvent was removed and the residue dissolved in $CHCl_3$, filtered and added to the top of a Florisil column. Ethyl ether was used to elute any non-polar impurities, and a mixture of 10% EtOAc–90% ethyl ether was used to elute the blue **8**. After removal of the solvents, the dye from the column was crystallized from EtOAc-ethyl ether. Crystallization from benzene gave an analytical sample, 85 mg., m.p. 235–6° (needles with a reddish reflex).

TABLE 4. ANALYTICAL DATA

Compound	Formula	Found C	Found H	Found N	Calculated C	Calculated H	Calculated N	Molecular ion
4	$C_{12}H_{16}O_2N_2$	65·65	7·27	12·71	65·43	7·3	12·72	220
5	$C_{12}H_{14}O_2N_2$	66·03	6·47	12·84	66·20	6·0	12·71	218
6	$C_{12}H_{14}O_2N_2$	66·03	6·47	12·84	66·20	6·5	12·70	218
7	$C_{12}H_{12}O_2N_2$	66·65	5·59	12·96	66·72	5·5	12·80	216
8	$C_{16}H_{12}O_2N_2$	66·68	5·70	12·80	66·65	5·59	12·96	216
9	$C_{16}H_{20}O_2N_2$	70·56	7·40	10·29	70·56	7·38	10·37	272
10	$C_{16}H_{18}O_2N_2Br_2$[a]	44·69	4·45		44·67	4·22	6·51	428

[a] Br Calc. 37·15, Found 37·18.

Compound **9**. *Leuco*-naphthazarin, 0·8 g (2·7 mM) was added to a deaerated mixture of 2 ml isopropylamine and 5 ml pyridine. The soln was heated under N_2 for 2 hr. The solvents were removed with a stream of N_2, water added, and the solid filtered and dried. The solid was dissolved in EtOH and one drop of 10% NaOH aq added. Air was bubbled through the soln which turned blue. The addition of 1:1 EtOH-water caused precipitation of a solid which was filtered off, washed with water and dried. Crystallization from 95% EtOH yielded 130 mg of blue plates (red reflex) m.p. 171–2°. The compound was recrystallized from EtOH and dried under high vacuum at 60° for analysis (Table 4).

Compound **10**. In 5 ml AcOH, 0·50 g (1·8 mM) of **9** and 0·13 g (1·6 mM) of anhyd NaOAc were dissolved. The soln was heated to 60–70°, 2 ml (3·9 mM) Br_2 added, and then the soln was kept at ~65° for 1 hr. The ppt was filtered from the cooled soln, washed well with water and dried, 0·3 g resulted. The material was crystallized from EtOH and then from benzene, yielding bluish-red needles (m.p. > 330°).

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