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A SPECTRAL STUDY OF TAUTOMERISM IN 4-ARYLAMINO-1,2-NAPHTHOQUINONES

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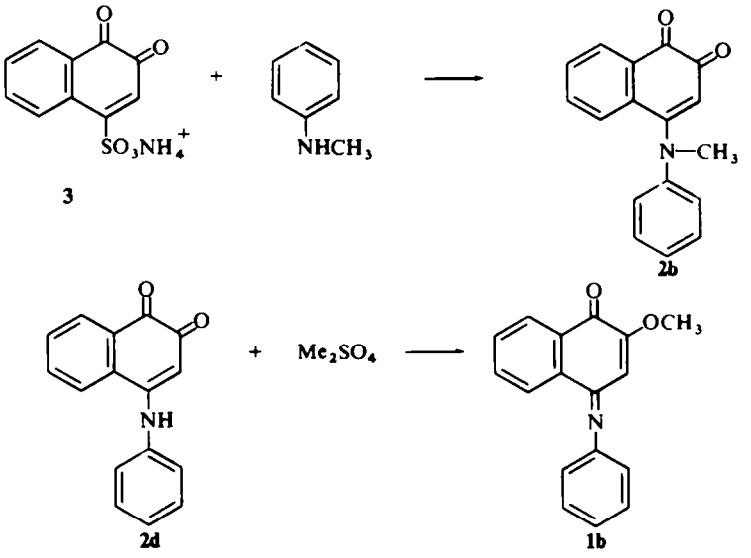
Abstract—The tautomerism of 4-arylamino-1,2-naphthoquinones in aqueous solutions has been investigated by UV-visible absorption spectroscopy. It has been demonstrated that in strongly acidic solutions (pH $\leqslant$ 0·8), protonation of the 2-keto group leads to 2-hydroxy-1,4-naphthoquinone-4-arylimine as the more stable tautomer. However, weakly acidic or alkaline solutions (pH 4–13) contain 4-arylamino-1,2-naphthoquinone as the more stable tautomer.

THE existence of tautomerism in the 4-aminonaphthoquinones was first reported by Fieser and Fieser in 1934.[2, 3] Since then very little work has been done to study this tautomerism, although there have been several reports on the investigation of the keto-enol tautomerism in general.[4–9] In our efforts to synthesize new potential antimalarial compounds, we investigated the chemistry of 4-(N-arylamino)-1,2-naphthoquinones. As a part of this program, we studied their tautomerism in aqueous solutions with the help of UV-visible absorption spectroscopy. Due to the high molar absorptivities of these compounds, the spectrophotometric method is much more sensitive than the potentiometric method used by Fieser and Fieser. Besides, it can be applied to compounds which are too insoluble in water to be determined potentiometrically. On the basis of potentiometric measurements, Fieser and Fieser had observed that between pH 10·4 and 11·5, the solutions contain equilibrium mixtures in which both the tautomers, 2-hydroxy-1,4-naphthoquinone-4-imine (**1a**) and 4-amino-1,2-naphthoquinone (**2a**) are present in appreciable amounts the α-form, **1a**, is the more stable tautomer at pH below 10·4, whereas the α-form, **2a** is the more stable tautomer at pH above 11·5. Contrary to these findings by Fieser and Fieser, we have obtained strong evidence that in strongly acidic solutions (pH 0·8), **1a** is the more stable form, whereas in weakly acidic or alkaline solutions (pH 4–13), **2a** is the more stable tautomer.

In order to determine the nature of the UV spectra characteristic of the tautomers **1a** and **2a**, representative examples of these two forms, which could not undergo tautomerism, were prepared and their spectra studied. 4-(N-Methylanilino)-1,2-naphthoquinone (**2b**) was prepared by the reaction of N-methylaniline with ammoniun 1,2-naphthoquinone-4-sulfonate (**3**) whereas 2-methoxy-1,4-naphthoquinone-4-anil (**1b**) was prepared by the reaction of 4-(anilino)-1,2-naphthoquinone (**2d**) with dimethylsulfate in the presence of sodium hydroxide.[10] The UV spectra of the compounds **1b** and **2b** are reproduced in Fig. 1. All the UV spectra were obtained in the presence of an optically transparent buffer (Table 3, Experimental) in order to eliminate the possible hydrolysis of the enol-ethers (**1a–1i**). The most significant difference between the two spectra is the presence of two sharp absorption maxima at 246 and 251 nm in the spectrum of **1b**. Subsequently, these two sharp maxima



centered around 248 nm were found to be characteristic of tautomers similar to **1a**. For instance, the UV spectrum of 2-methoxy-1,4-naphthoquinone, (**1c**), also had two sharp maxima at 240 and 248 nm, whereas the spectrum of 4-methoxy-1,2-naphthoquinone, (**2c**), did not. The compounds **1c** and **2c** were prepared by the method reported by Fieser.[11]

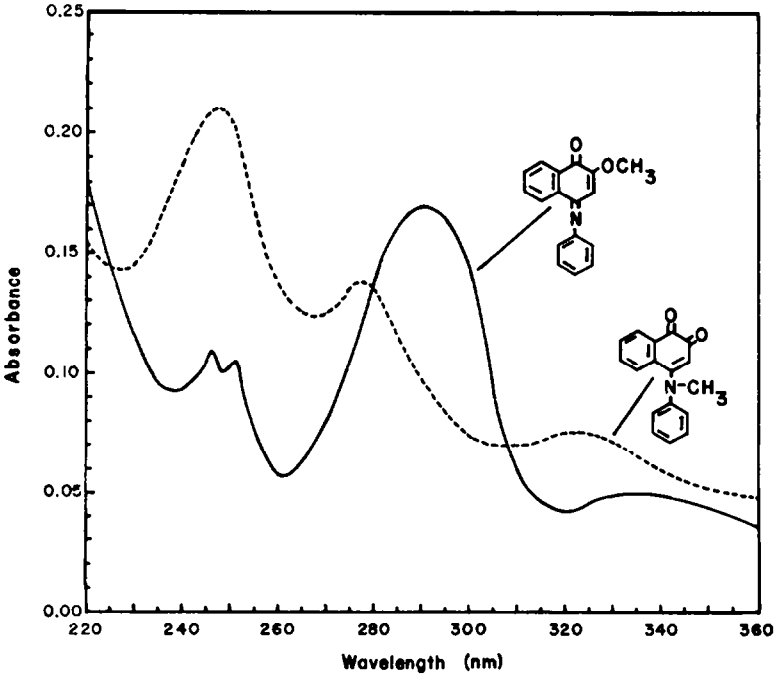


FIG. 1 UV spectra of 4-(N-methylanilino)-1,2-naphthoquinone (**2b**) and 2-methoxy-1,4-naphthoquinone-4-anil (**1b**).

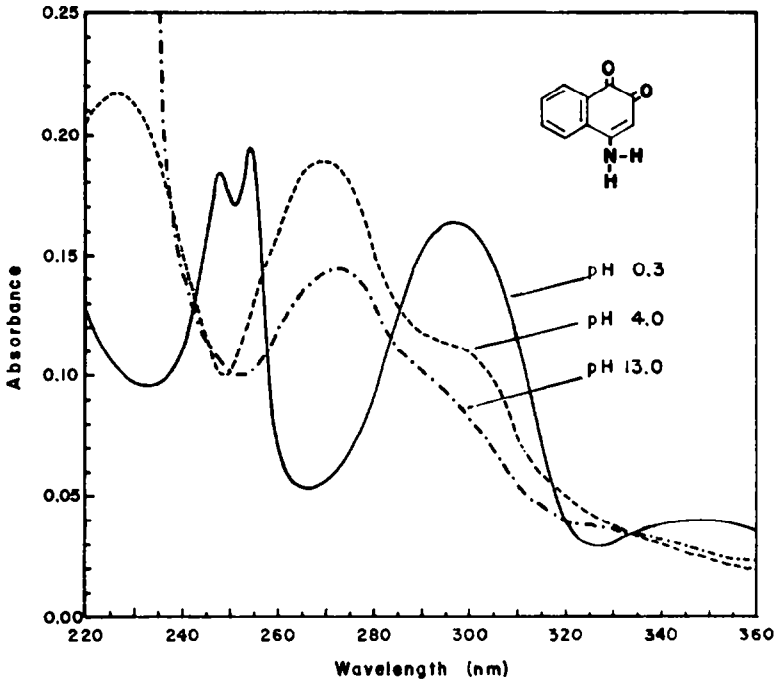
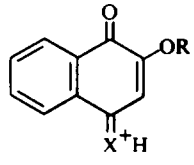
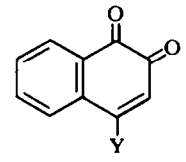


FIG. 2 UV Spectrum of 4-Amino-1,2-naphthoquinone (**1a**).

To study the tautomeric equilibrium of 4-amino-1,2-naphthoquinone, its UV spectra (reproduced in Fig. 2) at pH 0·3, 4·0, and 13·0 were obtained. The spectrum at pH 0·3 had two sharp absorption maxima at 248 and 255 nm, suggesting thereby that in solutions of 4-amino-1,2-naphthoquinone at pH 0·3, **1a** is the more stable

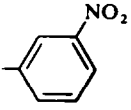




1a: R = H; X = NH

1b: R = CH_3; X = NC_6H_5

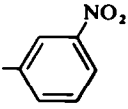
1c: R = CH_3; X = O
1d: R = H; X = NC_6H_5
1e: R = H; X = O

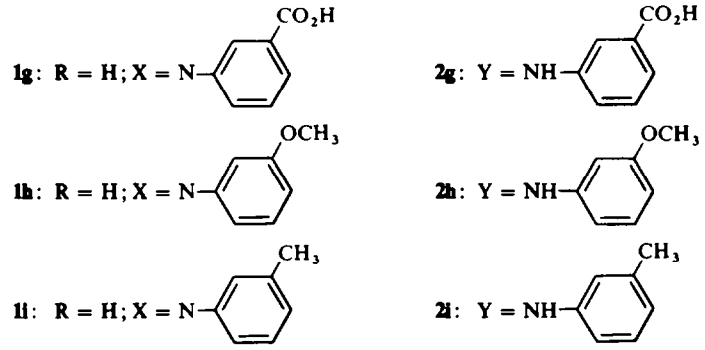
1f: R = H; X = 

2a: Y = NH_2

2b: Y = 

2c: Y = OCH_3
2d: Y = NHC_6H_5
2e: Y = OH

2f: Y = NH 



form. This is in accord with the observation that protonation of amides in strongly acidic solutions occurs on the O atom.[12] The spectra at pH 4·0 and 13·0 are devoid of this fine absorbance around 250 nm. They are identical except in the magnitude of the absorption in the 260–280 nm region. The UV spectrum of 4-amino-1,2-naphthoquinone at pH 4·0 and 13·0 and that of **2b** at pH 7·0 are very similar, the only difference being a bathochromic shift of about 25 nm. (There are many known examples of compounds which show bathochromic shifts of the order of 25 nm when deprotonated in alkaline solutions[13]). This indicates that in weakly acidic or alkaline solutions of the former, **2a** may be the predominant form.

To confirm and substantiate these experimental observations, a number of other 4-arylamino-1,2-naphthoquinones were prepared by the reaction of ammonium-1,2-naphthoquinone-4-sulfonate and arylamines containing electron withdrawing and electron donating substituents in the *meta*-position.[14] The UV spectral data of these 4-arylamino-1,2-naphthoquinones is summarized in Table 1.

It is clear from the UV data given in Table 1 that strongly acidic solutions (pH 0·0–0·8) of 4-arylamino-1,2-naphthoquinones contain 2-hydroxy-1,4-naphthoquinone-4-arylamines (**1b–1i**) as the more stable tautomers as evidenced by the presence of two sharp absorption maxima centred around 250 nm. On the other hand, the absence of these characteristic UV absorptions in weakly acidic or alkaline solutions (pH 4·0–13·0) indicates that in these solutions the 4-arylamino-1,2-naphthoquinones (**2b–2i**) might exist as the more stable tautomers.

The IR spectra (nujol) of the 4-arylamino-1,2-naphthoquinones had a sharp absorption band around 3200 cm^{-1} (NH) but no significant absorption around 3600 cm^{-1} (OH). This indicated that in the crystalline form these compounds might be devoid of any keto-enol tautomerism.

EXPERIMENTAL

The m.ps were taken on a Thomas-Hoover m.p apparatus and are corrected. The elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. The UV spectra were taken on a Cary 14 spectrophotometer. A Beckman IR-8 spectrophotometer was used to determine the IR spectra. The following general procedure was used to prepare the 4-arylamino-1,2-naphthoquinones.

General procedure for the preparation of 4-arylamino-1,2-naphthoquinones. To a soln of ammonium-1,2-naphthoquinone-4-sulfonate (0·05 mole) in 250 ml distilled water was added the aryl or the secondary amine (0·05 mole) with stirring (the liquid amines were used neat, while the solid amines were used as solns in 95% EtOH). The reaction mixture was stirred for 1 hr and cooled to 5°. Brightly colored crystals of the 4-arylamino-1,2-naphthoquinones, thus obtained, were filtered and dried.

TABLE 1. UV SPECTRAL DATA*

Compound	pH of the solution	Buffer (Table 3)	λ_{max} (nm)	ε_{max} (1 cm^{-1} $mole^{-1}$)
1a	0·3	A	248,255†	97,500
			296	82,500
2a	4·0	C	230	107,000
			270	94,500
			295 (sh)	57,500
1b	7·0	E	246,251†	55,000
			291	85,000
			335	25,000
2b	7·0	E	247	105,000
			278	67,500
			323	37,500
1c	7·0	E	240,248†	77,500
				58,800
2c	7·0	E	250	120,000
			275	51,300
1d	0·3	A	252,258†	105,000
			295	66,000
			350	51,500
2d	1·2	B	244	118,000
			276	67,000
	7·5	E	241	120,000
			272	69,500
	11·0	G	240	128,000
			278	70,600
1e	1·5	B	243,249†	108,000
			278	89,000
			337	16,000
2e	7·0	E	264	109,000
	13·0	H	265	122,000
1f	0·00	A	242,248†	148,000
			315	48,000
2f	9·0	F	237	161,000
			280	84,000
1g	0·00	A	245,250†	60,000
			280	40,000
2g	0·80	B	250,255†	167,000
			264	162,000
1h	0·30	A	250,256†	94,100
			286	80,000
2h	9·00	F	240	114,000
			281	65,000
1i	0·0	A	249,256†	111,000
			290	66,000
2i	4·0	C	240	107,000
			274	61,500
	11·0	I	238	127,000
			278	70,000

* Only significant UV absorptions are reported here.
† Characteristic sharp absorption maxima as shown in Figs 1 and 2.

The m.ps, elemental analyses, and the yields of all the new N-substituted-4-amino-1,2-naphthoquinones are summarized in Table 2. The analytical samples were prepared by recrystallization from 2-methoxyethanol.

2-Methoxy-1,4-naphthoquinone-4-anil (**1b**). To a stirred soln of **2d** (18·0 g, 0·072 mole) in NaOH (10%, 500 ml) was added Me_2SO_4 (13·6 g, 0·108 mole) dropwise over a period of 4 hr. The reaction mixture was stirred at room temp overnight. The resulting orange ppt was filtered and the solid was washed with water until neutral. Crystallization from MeOH or 2-propanol afforded 15·2 g (80%) of **1b**, m.p. 149·5–151° (lit,[10] m.p. 150–151°). The IR and NMR spectra were consistent with the structure.

TABLE 2. ANALYTICAL DATA

Compd	M.p. (°C)	Yield (%)	Empirical formulae	Anal. Calc. C	H	N	Found C	H	N
2f(1f)	335–337(d)	66	$C_{16}H_{10}N_2O_4$	65·31	3·43	9·52	65·15	3·64	9·27
2g(1g)*	345–347(d)	77	$C_{17}H_{11}NO_4$	69·45	3·78	4·78	69·37	3·81	5·04
2h	267–268(d)	71	$C_{17}H_{13}NO_3$	73·11	4·69	5·02	73·01	4·87	4·85
2i(1i)	293–294(d)	78	$C_{17}H_{13}NO_2$	77·54	4·97	5·32	77·30	4·92	5·09
2b†	173–174(d)	44	$C_{17}H_{13}NO_2$	77·54	4·97	5·32	77·49	5·02	5·36

* Recrystallized from DMF.
† Recrystallized from EtOH.

Determination of the UV spectra. The UV spectra were determined using 0·5–1·0 × 10^{-4} M solns of the 4-arylamino-1,2-naphthoquinones in 95% EtOH. To eliminate possible hydrolysis, the spectra were run in the presence of a buffer as quickly as possible (ca. 8 min. found by hydrolysis experiments to be the optimum time). The following UV transparent buffers were prepared by adding component **2** (in the solid form) to a 0·05 M soln of component **1** with stirring until the desired pH was obtained.

TABLE 3. UV TRANSPARENT BUFFER SYSTEMS

Buffer No.	pH range	Component 1	Component 2
A	0·0–0·5	H_2SO_4	$KHSO_4$
B	1·0–2·0	$KHSO_4$	Na_2SO_4
C	2·0–4·0	H_3PO_4	KH_2PO_4
D	4·8	sat'd KH_2PO_4	—
E	6·5–7·5	KH_2PO_4	Na_2HPO_4
F	8·0–9·5	$NaHCO_3$	Na_2CO_3
G	10·0–12·0	Na_2HPO_4	
H	12·0–13·0	Na_3PO_4	NaOH
I	14.0	NaOH	

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