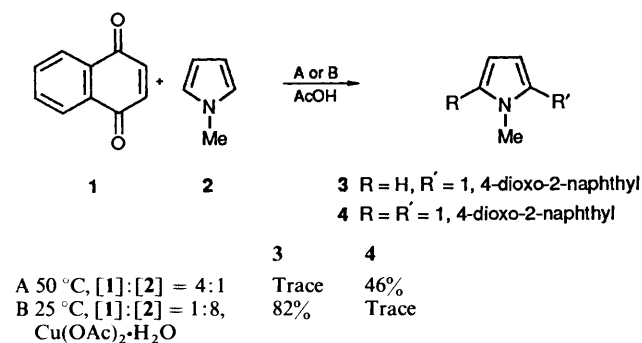


Selective Synthesis and Metallochromic Properties of Pyrrolylated Quinoline-5,8-diones

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Quinoline-5,8-dione **5** reacted with 1-methylpyrrole in acetic acid to give 6- and 7-(1-methylpyrrol-2-yl)quinoline-5,8-diones, one of which (6-isomer) showed remarkable metallochromic behaviour. Selective synthesis of the 6-isomer from **5** was achieved by addition of metal salts.

Quinoline-5,8-dione syntheses have attracted much interest because of their interesting physiological and colouring properties. Earlier,¹ we reported that various 6-substituted quinoline-5,8-diones had been conveniently synthesized by regioselective 6-amination and 6-arylation of quinoline-5,8-dione **5** promoted by metal ions. We also found that products with strong electron-donating 6-substituents are markedly metallochromic;² the first absorption bands are markedly shifted to longer wavelengths, with a concomitant large increase in the absorption intensity, upon metal chelation. The resulting chelates have an intense absorption band in the near-IR region. Also, we have recently found³ that the reaction of 1,4-naphthoquinone **1** and 1-methylpyrrole **2** in acetic acid allows the selective synthesis of either the mono- or bis-(1,4-dioxo-2-naphthyl)pyrroles, **3** or **4**, by addition of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, and changing the molar ratio of the starting materials.



Scheme 1

In continuation of these studies, the present work was aimed at synthesizing pyrrolylated quinoline-5,8-diones, the metallochromic properties of which are also investigated.

Results and Discussion

Synthesis of Pyrrolylated Quinoline-5,8-diones.—As in the reaction of 1,4-naphthoquinone **1** with 1-methylpyrrole **2**, it was found that the molar ratio of the starting materials significantly affected the distribution of the products³ (see Scheme 1). In this work, we treated quinoline-5,8-dione **5** with **2** in acetic acid in the molar ratio $[\text{5}]:[\text{2}] = 1:8$ in order to avoid the formation of bis(5,8-dioxoquinolyl)pyrroles: the results are summarized in Table 1. In the absence of metal salts, the reaction gave a mixture of isomeric pyrrolylquinoline-5,8-diones and 6- and 7-(1-methylpyrrol-2-yl)quinoline-5,8-dione, **6** and **7**, in low yields (Run 1), the subsequent oxidation of the initial hydroquinone products **6'** and **7'** to **6** and **7** being less than smooth in the presence of air (Scheme 2). Increased yields of **6** and **7** were

Table 1 The reaction of quinoline-5,8-dione **5** with 1-methylpyrrole **2** in acetic acid

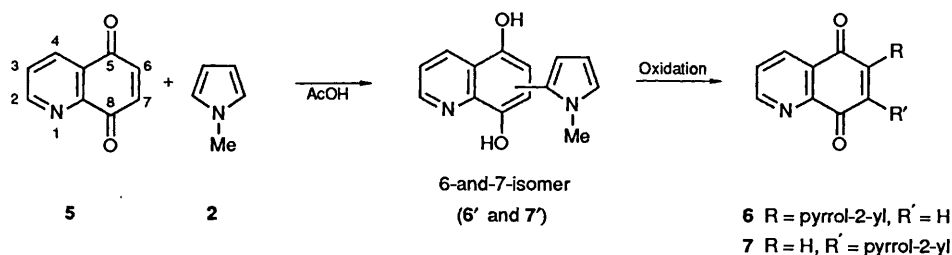
Run	Metal salt	PbO_2	Time (min)	Product (%) ^d	
				6	7
1 ^a	None	No	180	20	9
2 ^a	None	Yes ^c	180	33	20
3 ^a	$\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$	Yes ^c	60	47	0
4 ^b	$\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$	No	5	49	0
5 ^b	$\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	No	5	65	0

^a Reactant **5** (3.14 mmol) was stirred with **2** (25.12 mmol) in acetic acid (50 cm³) in the absence or in the presence of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (3.14 mmol) in an open flask at 30 °C. ^b The reaction was conducted in a separatory funnel at room temperature (see Experimental section). ^c After the starting material **5** had been consumed, PbO_2 (3.14 mmol) was added to the reaction mixture to oxidize the hydroquinone products **6'** and **7'** to the final quinone products **6** and **7**. ^d Isolated yield after column chromatography.

obtained when the reaction mixture was treated with PbO_2 (Run 2). However, in the presence of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, or $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$, the reaction gave exclusively the 6-isomer **6** in moderate yields (Runs 3–5). Similar, selective 6-substitution of **5** promoted by metal ions have previously been reported for the reaction of **5** with various amines.^{1,4} The formation of a metal chelate in which the 1-nitrogen atom and the 8-carbonyl group of **5** coordinate to the metal ion was considered to promote the 6-substitution. Although in the addition of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ subsequent oxidation with PbO_2 was required, with $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ or $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ the final product **6** was directly obtained in satisfactory yield for a reaction time of only 5 min at room temperature. In the last mentioned cases, the metal ions act both as chelating and oxidizing agents in the regioselective 6-pyrrolylation.

Physical and Metallochromic Properties of the Two Isomers 6 and 7.—The physical properties of, and the analytical data for, the two isomeric products **6** and **7** are summarized in Table 2. The ¹H NMR, IR and UV–VIS spectra of the two isomers are too closely similar for them to be distinguished from their spectral data. Fig. 1 shows the ¹H NMR chemical shift changes of 6-H (or 7-H), 3'-H, and the protons of the CH_3 group of **6** and **7** induced by addition of $\text{Eu}(\text{fod})_3$ as a chemical shift reagent, the europium ion being coordinated between the 1-nitrogen and 8-carbonyl group. The orders of magnitude of the chemical shifts are 7-H > 3'-H ~ CH_3 in **6**, 3'-H > CH_3 ~ 6-H in **7**, and 7-H > 6-H. These results are compatible with **6** and **7** being the 6- and 7-pyrrolylated isomers, respectively.

In an investigation of the metallochromic behaviour of the two isomers upon chelation, markedly different spectral changes were observed. For example, Fig. 2 shows the spectral



Scheme 2

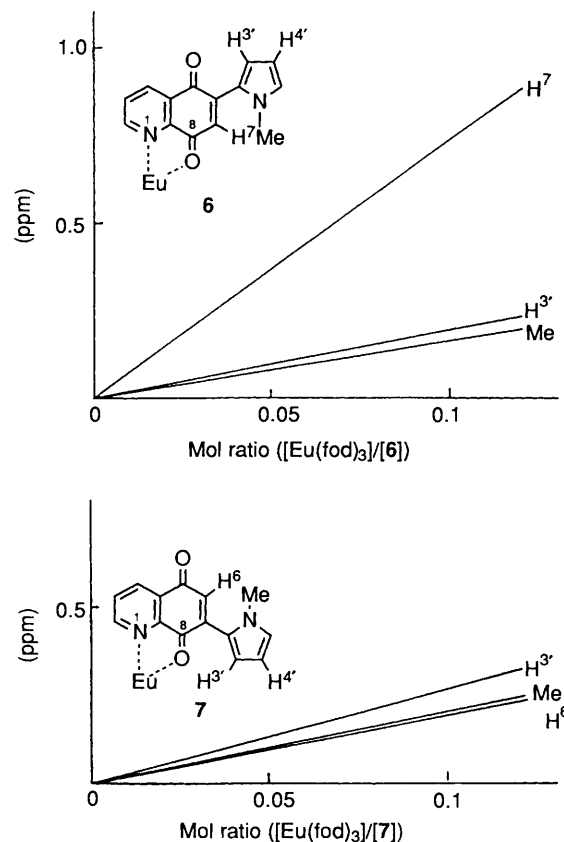
Table 2 The analytical and physical data of the two isomeric products **6** and **7** (see Fig. 1 for numbering scheme)

	6-Isomer 6	7-Isomer 7
M.p. (°C)	167–168	137–138
ν_{\max} (KBr)/ cm^{-1}	1671, 1645 (C=O)	1689, 1641 (C=O)
λ_{\max} (MeCN)/nm (ϵ_{\max})	484 (5300)	484 (5000)
δ_{H} (CDCl_3)	3.71 (3 H, s, CH_3), 6.27 (1 H, dd, J 2.6, 3.9, 4'-H), 6.75 (1 H, dd, J 1.8, 3.9, 3'-H), 6.91 (1 H, dd, J 1.8, 2.6, 5'-H), 7.02 (1 H, s, 7-H), 7.66 (1 H, dd, J 4.6, 8.0, 3-H), 8.47 (1 H, dd, J 1.8, 8.0, 4-H) and 9.03 (1 H, dd, J 1.8, 4.6, 2-H)	3.71 (3 H, s, CH_3), 6.27 (1 H, dd, J 2.6, 3.9, 4'-H), 6.73 (1 H, dd, J 1.8, 3.9, 3'-H), 6.90 (1 H, dd, J 1.8, 2.6, 5'-H), 6.94 (1 H, s, 6-H), 7.67 (1 H, dd, J 4.6, 8.0, 3-H), 8.42 (1 H, dd, J 1.8, 8.0, 4-H) and 9.01 (1 H, dd, J 1.8, 4.6, 2-H)
Found % (Calc. %)		
C, 70.2 (70.58)		C, 70.55 (70.58)
H, 4.4 (4.48)		H, 4.35 (4.48)
N, 11.9 (11.60)		N, 11.3 (11.60)
Mass (m/z)		
238 (M^+)		238 (M^+)

changes observed upon addition of $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ to MeCN solutions of **6** and **7**. In the former, an absorption band around 484 nm due to the free ligand decreased whilst a new and intense absorption band appeared around 598 nm. In the latter, complexation caused a bathochromic shift of the absorption band but a decrease in intensity [$R(\epsilon_{\max}) < 1$, see Table 3]. The two isomers are, therefore, easily distinguishable by a comparison of the spectral changes induced upon chelation. Similar results have previously been observed for 6- and 7-substituted quinoline-5,8-diones^{1,2,5} and related compounds.⁶ Isosbestic points were observed in both cases, which indicated the presence of a simple equilibrium in the solution. The continuous variation method indicated the formation of a 1:1 Cu^{II} -(**6** or **7**) complex in MeCN. Similar differences in the spectral changes between **6** and **7** were also observed in the formation of complexes with other metal salts. Table 3 summarizes the spectral data for the metal complexes with **6** and **7** in MeCN.

Experimental

Measurements.—M.p.s are uncorrected. UV and VIS spectra were measured with a JASCO Ubest-30 spectrophotometer equipped with a temperature controller (JASCO EHC-363). ^1H NMR spectra were recorded on a Hitachi Model R-90H spectrometer with TMS as the internal standard and IR spectra on a JASCO FT/IR 5000 spectrometer for KBr pellets. Mass spectra were run on a Shimadzu QP-1000 spectrometer and elemental analyses were measured on a Yanaco CHN recorder MT-3. Thin layer chromatography was performed on silica gel (Merck Kieselgel 60).

Fig. 1 Chemical shift changes by addition of $\text{Eu}(\text{fod})_3$

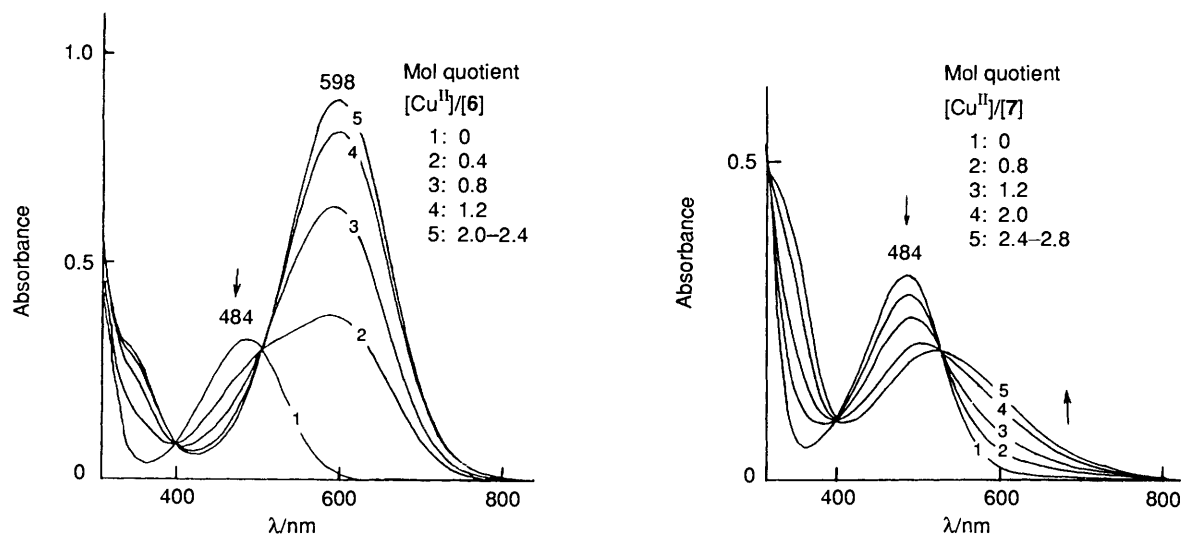
Materials.—Quinoline-5,8-dione **5** was prepared according to a literature procedure.⁷ $\text{Ni}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ ⁸ and $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ ⁹ were prepared by the literature methods. Other metal salts were reagent grade and were used without further purification.

Reaction of 5 with 2 in the Absence or in the Presence of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$.—A solution of **5** (0.5 g, 3.14 mmol) in acetic acid (40 cm^3) was added to a solution of **2** (25.12 mmol) in acetic acid (10 cm^3) with stirring in the absence or in the presence of $\text{Ni}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ (3.14 mmol) in an open flask at 30 °C. The reaction was monitored by TLC analysis. After the starting material **5** had been consumed, water (50 cm^3) and PbO_2 (3.14 mmol) were added to the reaction mixture and the whole repeatedly extracted with chloroform. The combined extracts were washed with aqueous sodium carbonate and water, dried (Na_2SO_4) and then concentrated under reduced pressure. The residue was separated by column chromatography (silica gel: Wakogel C-300) using 1,2-dichloroethane–ethyl acetate (10:1) as eluent. The yields are summarized in Table 1.

Table 3 Spectral data for complex formation between metal salts and substrates **6** and **7** in MeCN

Ligand		Mole quotient ^a		Complex (metal–ligand, 1:1)		
λ_{\max}/nm (ϵ_{\max})	Metal salt	[metal]	[ligand]	λ_{\max}/nm (ϵ_{\max})	$\Delta\lambda_{\max}^b/\text{nm}$	$R(\epsilon_{\max})^c$
6 484 (5300)	Cu(ClO ₄) ₂ ·6H ₂ O	2.0–2.4		598 (14 200)	114	2.68
	Ni(ClO ₄) ₂ ·6H ₂ O	2.0–2.4		576 (11 900)	92	2.25
	FeCl ₃ ·6H ₂ O	5.0–6.0		626 (13 000)	142	2.45
7 484 (5000)	Cu(ClO ₄) ₂ ·6H ₂ O	2.4–2.8		522 (3200)	38	0.64

^a Molar ratio range in which the maximum and constant absorbance were obtained (see Fig. 2). ^b $\Delta\lambda_{\max} = \lambda_{\max}(\text{complex}) - \lambda_{\max}(\text{free ligand})$.
^c $R(\epsilon_{\max}) = \epsilon_{\max}(\text{complex})/\epsilon_{\max}(\text{free ligand})$.

**Fig. 2** Spectral changes upon addition of Cu(ClO₄)₂·6H₂O to MeCN solutions of ligands **6** and **7**. [6] = [7] = 6.25 × 10⁻⁵ mol dm⁻³

Reaction of 5 with 2 in the Presence of Cu(OAc)₂·H₂O or FeCl₃·6H₂O.—The reaction was conducted in a separatory funnel at room temperature. To the metal salt (3.14 mmol) dissolved in 20% aqueous acetic acid (60 cm³) was quickly added **2** (25.12 mmol) and then **5** in chloroform (50 cm³). The mixture was vigorously shaken for 5 min after which the chloroform layer was quickly removed; the aqueous layer was then further extracted with chloroform (2 × 30 cm³). The combined extracts were washed with aqueous sodium carbonate and water, dried (Na₂SO₄) and then concentrated under reduced pressure. The crude products were separated by column chromatography (silica gel: Wakogel C-300) using 1,2-dichloroethane–ethyl acetate (10:1) as eluent. The yields are summarized in Table 1.

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