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SYNTHESIS OF 5-ALKYL-8-QUINOLINOL

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ABSTRACT : Synthesis of new 5-alkyl-8-quinolinol was described in order to obtain substituted copper 8-hydroxyquinolinate more soluble in organic solvents than unsubstituted one. The synthesis of copper complex is described and their solubility investigated in different solvents.

8-Quinolinol reacts easily with metal ions to form 8-quinolinol stable chelates.[1] Among them, copper 8-hydroxyquinolinate, also known as oxine, has been described as an efficient fungicide used for agrochemical applications[2] and for wood preservation.[3] However, because of its poor solubility, cosolvents and surfactants must be used for its formulation in water or organic solvents.[4] In this work, we report tne synthesis of new 8-quinolinol substituted at the 5 position with an hydrophobic group **1** and of their copper chelates **7** in order to obtain new fungicides more soluble in organic solvents than unsubstituted 8-quinolinol (scheme 1). Moreover, such compounds could be valuable materials for the extraction, separation and pre-concentration of many metal ions in organic solvents.[5,6]

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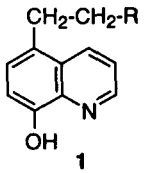
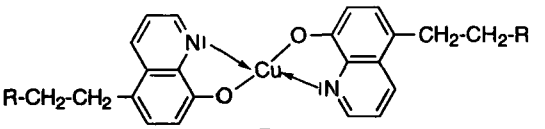
Scheme 1



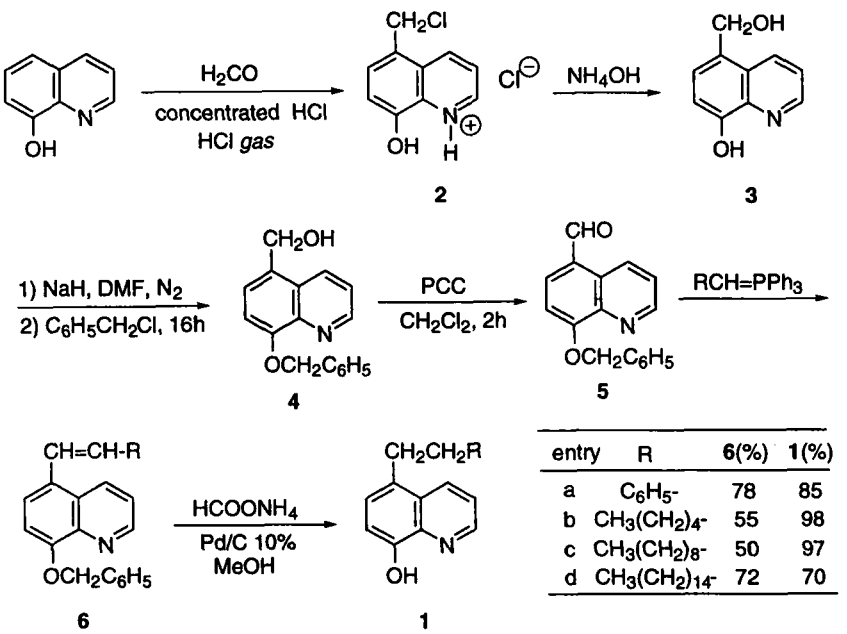
1



7

The synthetic route chosen to synthetize these products is shown in the following scheme.

Scheme 2



entry	R	6(%)	1(%)
a	C_6H_5-	78	85
b	$CH_3(CH_2)_4$-	55	98
c	$CH_3(CH_2)_8$-	50	97
d	$CH_3(CH_2)_{14}$-	72	70

The synthesis started by chloromethylation of 8-quinolinol followed by hydrolysis with dilute ammonia to give **3** which phenolic group was protected with a benzyl group to afford **4**. Both of these steps were previously described.[7,8] Oxidation of **4** with pyridinium chlorochromate (PCC) gave the aldehyde **5**, which was subject to Wittig reaction to give **6**. The reaction was performed under phase

transfer conditions with benzyltriphenylphosphonium chloride using NaOH as base, while aprotic conditions were used for *n*-alkyltriphenylphosphonium salts using BuLi as base. Purification of products **6** was effected by chromatography on silica gel. Separation of the (*E*) and (*Z*) isomers was possible only for **6a**. Catalytic hydrogenation of compounds **6** resulted in debenzylation and reduction of the double bond yielding the desired products **1**. Synthesis of copper chelates was performed in refluxing ethyl alcohol using 0.5 eq. of copper hydroxide. Their solubility was investigated in different solvents and compared to that of oxine. For this purpose, 10 mg of chelate were weighed at ± 0.2 mg and solubilized in 3 ml of solvent at 25°C. The solubility was estimated visually and the results given in table 1.

Table 1. Solubility of copper 8-hydroxyquinolinate

Product	Solubility in [a]						
	Toluene	Hexane	White spirit	Dichloro-methane	Acetone	Ethanol	Water
Oxine	- +	- -	- -	- +	- +	- +	- -
1a	+ -	- +	- +	+ +	- +	- +	- -
1b	+ -	- +	- +	+ +	- +	- +	- -
1c	+ -	- +	- +	+ +	- +	- +	- -
1d	+ -	+ -	+ -	+ +	- +	- +	- -

[a] - - : insoluble, - + : slightly soluble, + - : nearly soluble, + + : soluble.

As expected the grafting of an alkyl chain allows to obtain substituted copper 8-hydroxyquinolinate more soluble than unsubstituted one in organic solvents especially for heptadecyl chain.

In conclusion, we have elaborated an efficient synthesis of new 5-alkyl-8-quinolinol. Evaluation of biological activities of their copper chelates are currently under investigation in our laboratory. Moreover, we believe these new compounds will be interesting surfactants or extractants for different applications.

Experimental section

Commercially available reagents were purchased from Aldrich or Lancaster. NMR spectra were recorded in $CDCl_3$ solutions using TMS as internal standard on a Bruker AM 400 or AC 250 instrument. IR spectra were recorded as thin film between sodium chloride plates or KBr disks on a Mattson Genesis Series FT IR. Column chromatographic separations were performed on Kieselgel 60 (70-230 mesh ASTM) purchased from Macherey Nagel. Thin layer chromatographies were performed using precoated Macherey Nagel plates, silica gel 60 SIL G/UV_{254}. All organic solvents were appropriately dried and purified before use. Melting points were determined with a Büchi Tottoli apparatus and are reported uncorrected. MS were taken on a FISON MD 800 at ionizing potential of 70 eV and a source temperature of 200°C.

8-Benzyloxy-5-formylquinoleine (5). 8-Benzyloxy-5-hydroxymethylquinoleine (**4**) (10 g, 37.59 mmol) was added to a solution of pyridinium chlorochromate (8.83 g, 40.97 mmol) in dichloromethane (20 ml) and the solution stirred at room temperature until disappearance of the starting material (TLC). The solution was then washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography using dichloromethane methanol (100:3) mixture. Evaporation gave a green solid. Yield = 65%. mp = 114°C. ^1H NMR (400 MHz, $CDCl_3$) : 10.12 (s, 1H), 9.68 (dd, J = 1.5 Hz, J = 8.5 Hz, 1H), 9.06 (dd, J = 1.5 Hz, J = 4.5 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 7.64 (dd, J = 8.5 Hz, J = 4.5 Hz, 1H), 7.53 (d, J = 7.5 Hz, 2H), 7.42-7.34 (m, 3H), 7.14 (d, J = 7.5 Hz, 2H), 5.54 (s, 2H). IR : 2720, 1680, 1559, 1497 and 1450 cm^{-1}. EI.MS (70 eV) : m/z (% rel. intensity) = 263 (M^+, 95), 186 (30), 157 (50), 91 (100), 65 (33). Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.14; H, 4.82; N, 5.37.

General procedure for the synthesis of 5-alkenyl-8-benzyloxyquinoleine (6).

Method A. Benzyltriphenylphosphonium chloride (1.9 mmol, 740 mg) was mixed in 5 ml of dichloromethane with 8-benzyloxy-5-formylquinoleine (1.9 mmol, 500 mg) in a 10 ml flask. The mixture is stirred as vigorously as possible and 1.5 ml of 50 per cent aqueous sodium hydroxide are added by the means of a syringe. After disappearing of the starting material (TLC) the mixture is transferred to a small separating funnel containing dichloromethane (20 ml) and water (20 ml). The organic layer is separated, dried over $MgSO_4$ and concentrated. The resulting solid is purified by chromatography on silica gel using AcOEt/hexane (50/50) as eluent.

8-Benzyloxy-5-(2-phenylethenyl)quinoleine (6a). *E/Z* = 70/30. ^{1}H NMR (400 MHz, $CDCl_3$) : *E* (δ) : 9.03 (dd, J = 4 Hz, J = 1.4 Hz, 1H), 8.51 (dd, J = 8.5 Hz, J = 1.4 Hz, 1H), 7.72-7.30 (m, 12H), 7.29 (d, J = 9.5 Hz, 1H), 7.08 (m, 1H), 7.05 (d, J = 9.5 Hz, 1H), 5.50 (s, 2H). *Z* (δ) : 9.00 (dd, J = 4 Hz, J = 1.5 Hz, 1H), 8.34 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H), 7.56-7.04 (m, 12H), 6.95 (d, J = 8 Hz, 1H), 6.94 (d, J = 12 Hz, 1H), 6.82 (d, J = 12 Hz, 1H), 5.45 (s, 2H). IR : 3028, 2924, 2857, 1596, 1570, 1498 and 1450 cm^{-1}. EI.MS (70 eV) : m/z (% rel. intensity) = 337 (M^+, 80), 260 (22), 246 (55), 91 (100). Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.35; H, 5.72; N, 4.38.

Method B. The phosphonium salt (2.85 mmol), previously dried under vacuum at 50°C during one night, was dissolved in 5 ml of a mixture of DMSO/THF (1/1) and butyllithium (1.6 M in hexane, 2.9 mmol) was added to the reaction mixture, followed by stirring for 1 hour under N_2. 8-Benzyloxy-5-formylquinoleine (1.9 mmol, 500 mg) was then added dropwise and the stirring continued for 6 hours at room temperature. Water was added to the reaction mixture and the product extracted with CH_2Cl_2. Purification of the crude reaction mixture was

effected by chromatography on silica gel using AcOEt/hexane (20/80) as eluent to give the desired product as a mixture of *E* and *Z* isomers.

8-Benzyloxy-5-heptenylquinoleine (6b). *E*/*Z* = 46/54. ^{1}H NMR (400 MHz, $CDCl_3$) : *E* (δ) : 8.9 (d, J = 1.5 Hz, 1H), 8.42 (dd, J = 9 Hz, J = 1.5 Hz, 1H), 7.58-7.20 (m, 6H), 7.0 (d, J = 6 Hz, 1H), 6.98 (d, J = 6 Hz, 1H), 6.91 (d, J = 16 Hz, 1H), 6.12 (td, J = 16 Hz, J = 7 Hz, 1H), 5.45 (s, 2H), 2.30 (m, 2H), 1.26-1.16 (m, 6H), 0.91 (t, J = 7 Hz, 3H). *Z* (δ) : 8.9 (d, J = 1.5 Hz, 1H), 8.29 (dd, J = 9 Hz, J = 1.5 Hz, 1H), 7.58-7.20 (m, 6H), 7.0 (d, J = 6 Hz, 1H), 6.98 (d, J = 6 Hz, 1H), 6.70 (d, J = 11 Hz, 1H), 5.89 (td, J = 11 Hz, J = 7 Hz, 1H), 5.45 (s, 2H), 2.11 (m, 2H), 1.40-1.30 (m, 6H), 0.82 (t, J = 7 Hz, 3H). IR : 3032, 2925, 2856, 1620, 1600, 1570 and 1500 cm^{-1}. EI.MS (70 eV) : m/z (% rel. intensity) = 331 (M^+, 52), 254 (26), 226 (24), 91 (100). Anal. Calcd for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 82.89; H, 7.81; N, 4.25.

8-Benzyloxy-5-undecenylquinoleine (6c). *E*/*Z* = 30/70. ^{1}H NMR (400 MHz, $CDCl_3$) : *E* (δ) : 8.97 (d, J = 1 Hz, 1H), 8.43 (dd, J = 8.5 Hz, J = 1 Hz, 1H), 7.56-7.19 (m, 6H), 7.0 (d, J = 7 Hz, 1H), 6.98 (d, J = 7 Hz, 1H), 6.91 (d, J = 16 Hz, 1H), 6.12 (td, J = 16 Hz, J = 7 Hz, 1H), 5.45 (s, 2H), 2.31 (m, 2H), 1.50-1.09 (m, 14H), 0.98 (t, J = 7 Hz, 3H). *Z* (δ) : 8.97 (d, J = 1 Hz, 1H), 8.28 (dd, J = 8.5 Hz, J = 1 Hz, 1H), 7.56-7.19 (m, 6H), 7.0 (d, J = 7 Hz, 1H), 6.98 (d, J = 7 Hz, 1H), 6.71 (d, J = 11 Hz, 1H), 5.89 (td, J = 11 Hz, J = 7 Hz, 1H), 5.45 (s, 2H), 2.09 (m, 2H), 1.50-1.09 (m, 14H), 0.86 (t, J = 7 Hz, 3H). IR : 3031, 2922, 1596, 1571, 1501 and 1450 cm^{-1}. EI.MS (70 eV) : m/z (% rel. intensity) = 387 (M^+, 58), 310 (20), 282 (23), 91 (100). Anal. Calcd for $C_{27}H_{33}NO$: C, 83.68; H, 8.58; N, 3.61. Found: C, 83.58; H, 8.50; N, 3.58.

8-Benzyloxy-5-heptadecenylquinoleine (6d). *E*/*Z* = 39/61. ^{1}H NMR (400 MHz, $CDCl_3$) : *E* (δ) : 8.97 (d, J = 1 Hz, 1H), 8.43 (dd, J = 8.5 Hz, J = 1 Hz, 1H), 7.56-7.20 (m, 6H), 7.0 (d, J = 6 Hz, 1H), 6.99 (d, J = 6 Hz, 1H),

6.91 (d, J = 16 Hz, 1H), 6.12 (td, J = 16 Hz, J = 7 Hz, 1H), 5.45 (s, 2H), 2.30 (m, 2H), 1.55-1.18 (m, 26H), 0.88 (t, J = 7 Hz, 3H). *Z* (δ) : 8.97 (d, J = 1 Hz, 1H), 8.28 (dd, J = 8.5 Hz, J = 1 Hz, 1H), 7.56-7.20 (m, 6H), 7.0 (d, J = 6 Hz, 1H), 6.99 (d, J = 6 Hz, 1H), 6.70 (d, J = 11 Hz, 1H), 5.88 (td, J = 11 Hz, J = 7 Hz, 1H), 5.45 (s, 2H), 2.07 (m, 2H), 1.55-1.18 (m, 26H), 0.88 (t, J = 7 Hz, 3H). IR : 2916, 2847, 1600, 1571, 1502 and 1465 cm^{-1}. Anal. Calcd for $C_{33}H_{45}NO$: C, 84.02; H, 9.62; N, 2.97. Found: C, 83.87; H, 9.91; N, 2.81.

General procedure for the synthesis of 5-alkyl-8-hydroxyquinoleine (1). 5-Alkenyl-8-benzyloxyquinoleine (1 mmol) was dissolved in methanol (3 ml) and ammonium formate (6 mmol) was added. After 5 minutes of stirring, palladium on carbon (10%, 25 mg) was added. The mixture was stirred 15 minutes at room temperature and then heated at 50°C. Completion of the reaction was monitored by TLC. The reaction mixture was filtered on celite, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under vacuum to give the desired product.

5-(2-Phenylethyl)-8-quinolinol (1a). ^1H NMR (250 MHz, acetone D_6) : (δ) 8.82 (dd, J = 4 Hz, J = 1.5 Hz, 1H), 8.55 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H), 7.58 (dd, J = 8.5 Hz, J = 4 Hz, 1H), 7.32 (d, J = 8 Hz, 1H), 7.29-7.17 (m, 5H), 7.04 (d, J = 8 Hz, 1H), 3.30 (t, J = 8 Hz, 2H), 3.00 (t, J = 8 Hz, 2H), 2.81 (br s, 1H). IR : 3267, 2923, 2860, 1578, 1503 and 1450 cm^{-1}. EI.MS (70 eV) : m/z (% rel. intensity) = 249 (M^+, 45), 159 (43), 158 (100), 130 (28), 103 (25), 91 (18), 77 (30). mp = 116.9°C. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 82.01; H, 6.09; N, 5.51.

5-Heptyl-8-quinolinol (1b). ^1H NMR (400 MHz, $CDCl_3$) : (δ) 8.77 (d, J = 1 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.20 (br s, 1H), 7.45 (dd, J = 8.5 Hz, J =

4 Hz, 1H), 7.28 (d, J = 7 Hz, 1H), 7.09 (d, J = 7 Hz, 1H), 2.94 (t, J = 7 Hz, 2H), 1.69 (m, 2H), 1.36-1.20 (m, 8H), 0.90 (t, 7 Hz, 3H). IR : 3328, 2923, 2857, 1506, 1466 and 1410 cm^{-1}. EI.MS (70 eV) : m/z (% rel. intensity) = 243 (M^+, 80); 159 (54), 158 (100), 130 (35), 103 (6), 77 (23). mp = 54°C. Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.01; H, 9.32; N, 5.86.

5-Undecyl-8-quinolinol (1c). ^1H NMR (400 MHz, $CDCl_3$) : (δ) 8.78 (d, J = 1.5 Hz, 1H), 8.34 (dd, J = 8.5 Hz, J = 1.5 Hz, 1H), 8.20 (br s, 1H), 7.45 (dd, J = 8.5 Hz, J = 4.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.10 (d, J = 7.5 Hz, 1H), 2.94 (t, J = 7 Hz, 2H), 1.69 (m, 2H), 1.38-1.20 (m, 16H), 0.90 (t, 7 Hz, 3H). IR : 3310, 2920, 2847, 1578, 1506, 1464 and 1417 cm^{-1}. EI.MS (70 eV) : m/z (% rel. intensity) = 299 (M^+, 93), 159 (65), 158 (100), 130 (35), 103 (13), 77 (14). mp = 62°C. Anal. Calcd for $C_{20}H_{29}NO$: C, 80.22; H, 9.76; N, 4.68. Found: C, 80.17; H, 10.15; N, 4.79.

5-Heptadecyl-8-quinolinol (1d). ^1H NMR (400 MHz, $CDCl_3$) : (δ) 8.76 (d, J = 3 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 7.45 (dd, J = 8.5 Hz, J = 3 Hz, 1H), 7.27 (d, J = 8 Hz, 1H), 7.08 (d, J = 8 Hz, 1H), 2.95 (t, J = 7 Hz, 2H), 1.67 (m, 2H), 1.42-1.05 (m, 28H), 0.88 (t, 7 Hz, 3H). IR : 3330, 2922, 2848, 1507, 1468 and 1413 cm^{-1}. EI.MS (70 eV) : m/z (% rel. intensity) = 383 (M^+, 20), 172 (15), 159 (25), 158 (100), 130 (5). mp = 72°C. Anal. Calcd for $C_{26}H_{41}NO$: C, 81.41; H, 10.77; N, 3.65. Found: C, 81.53; H, 10.87; N, 3.67.

General procedure for the synthesis of copper chelates. 5-alkyl-8-hydroxyquinoleine (1 mmol) was mixed with copper hydroxide (0.5 mmol) in 10 ml of EtOH (95%) and heated at reflux during 6 hours. The solvent was then evaporated and the resulting copper complex dried under vacuum over KOH. The yields are nearly quantitative.

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