Alkylation of 2-Phenyl-4-quinolones: Synthetic and Structural Studies

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The alkylation of 2-phenyl-4-quinolones was investigated and showed that the *N*-alkylation *versus O*-alkylation is highly dependent on whether C-5 is hydroxylated or not. *N*-Alkylation is favoured by the presence of a 5-hydroxyl group. The synthetic and the NMR structural studies are reported.

Key words 2-phenyl-4-quinolone; *N*-alkylation; regioselectivity

2-Phenyl-4-quinolones are a class of molecules used as aza analogues of flavones (Fig. 1). Over the last ten years, the interest in 2-phenyl-4-quinolones and related compounds has been the subject of extensive study as potent cytotoxic antimitotic agents,[1] antibacterial agents,[2] anti-platelet agents[3] and as cardiovascular protectors.[4] Replacement of the O_1 by a nitrogen would allow the attachment of groups that may give rise to beneficial interactions with the biological active site. Also, the presence of a nitrogen would allow ammonium salts to enhance the solubility of the synthesized compound.

In an ongoing program aimed at the synthesis and the biological activities of flavone analogs, we investigated the synthesis of *N*-alkyl-2-phenyl-4-quinolones bearing a 5-hydroxy group (**III** in Fig. 1). The 5-OH group and C_2–C_3 double bond in concert with a 4-oxo functionality at the C-ring are often required for the activity of flavonoids.[5] *N*-alkyl-4-quinolones can be prepared by two main methods: starting from *N*-alkylaniline derivatives and elaboration of the latter to *N*-alkyl-quinolones[6,7]; by direct alkylation of 2-phenyl-4-quinolones.[8,9] The first method is less convenient, especially if a large series of *N*-alkylquinolones is needed. Regarding the second method, it has been reported that alkylation of 2-phenyl-4-quinolones leads predominantly to 4-alkoxyquinolines. Among *N*-alkyl-quinolones studied, only *N*-methyl-2-phenyl-4-quinolone was obtained.[8,9] This has prompted us to reinvestigate the *N*-alkylation of 2-phenyl-4-quinolones and we have found that the presence of a 5-hydroxyl group is essential for the *N*-alkylation.

Results and Discussion

While the alkylation of 2-phenyl-4-quinolones was being studied, we observed that the alkylation regioselectivity (*O* or *N*-alkylation) depends on whether C-5 is hydroxylated or not. We decided to test and compare the reactivity behavior of 2-phenyl-4-quinolones where position 5 is either hydroxylated or methoxylated (masked OH).

5,7-Dimethoxy-2-phenyl-4-quinolone **3** and 5-hydroxy-7-methoxy-2-phenyl-4-quinolone **4** (Chart 1) were used as models for this study. They were synthesized starting from 3,5-dimethoxyaniline as shown in Chart 1. Reaction of the latter with benzoyl chloride in the presence of Et_3N gave *N*-(3,5-dimethoxyphenyl)benzamide **1** in 96% yield. Friedel–Crafts acylation with acetyl chloride in 1,2-dichloroethane and in the presence of $SnCl_4$ gave *N*-(2-acetyl-3,5-dimethoxyphenyl)benzamide **2** in 58% yield together with its regioisomer, *N*-(4-acetyl-3,5-dimethoxyphenyl)benzamide **2a** (isolated in less than 5% yield). Cyclization of **2** in the presence of *t*-BuOK in THF gave quinolone **3** in 83% yield. Treatment of **3** with BBr_3 (1.5 eq) in CH_2Cl_2 for 24 h afforded 5-hydroxy-7-methoxy-2-phenyl-4-quinolone **4** in 80% yield. Under these conditions the 7-methoxy group remained intact.[10]

Quinolones **3** and **4** were treated with an alkyl halide in the presence of NaH or K_2CO_3. The alkylation was conducted under several conditions (NaH/THF, NaH/DMF, K_2CO_3/acetone, K_2CO_3/DMF) at different temperatures. The K_2CO_3/DMF system and temperature elevation led to the highest yields but there was no significant influence on the regioselectivity compared to the other systems used.

In the case of **3** bearing a methoxy group on C-5, treatment with K_2CO_3 in DMF followed with alkyl halide led to the formation of 4-alkoxy-2-phenylquinoline **5** as the only product (Chart 2, Table 1). It can be postulated that the amino group is deprotonated and equilibrated to give the more reactive intermediate **3a** which can be alkylated to af-

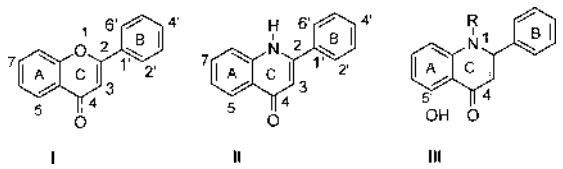
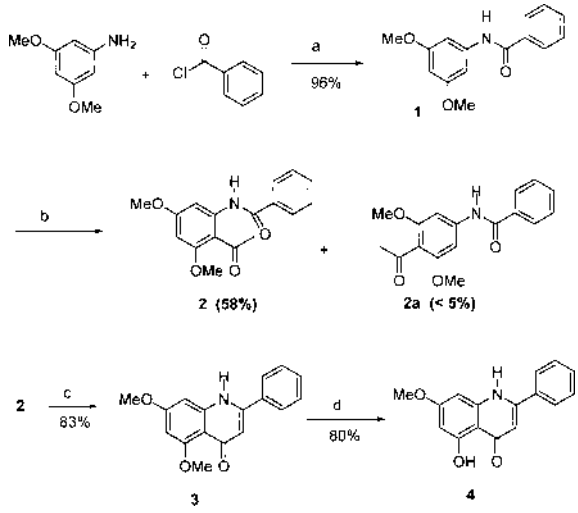


Fig. 1



a) THF/Et_3N; b) CH_3COCl, $SnCl_4$, 1,2-dichloroethane; c) *t*-BuOK, THF, 80 °C; d) BBr_3, CH_2Cl_2.

Chart 1

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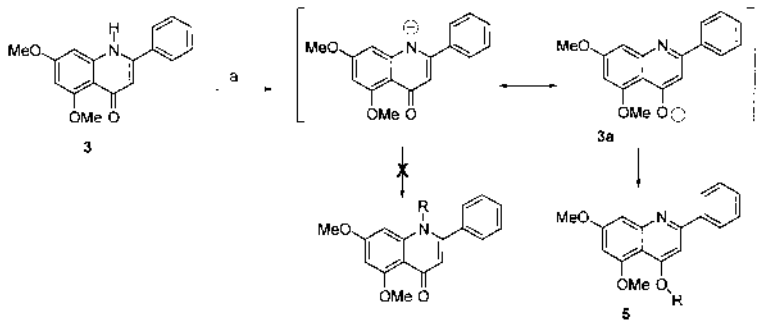
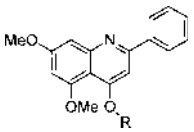


a) Alkyl halide, K_2CO_3, DMF.

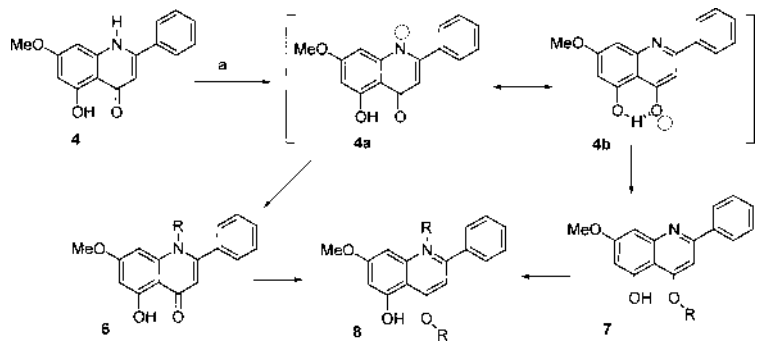
Chart 2. Alkylation of 5,7-Dimethoxy-2-phenyl-4-quinolone

Table 1. Physicochemical Data of Quinolines **5**



5a—d

Compd.	Yield (%)	mp (°C)	MS *m/z*	^{1}H-NMR ($CDCl_3$) δ:
5a R=Me (Me–I)	89	116 (AcOEt)	295 (M^+)	8.05 (m, 2H), 7.50 (m, 3H), 7.11 (d, *J*=2.3 Hz, 1H), 7.05 (s, 1H), 6.50 (d, *J*=2.3 Hz, 1H), 4.07 (s, 3H), 3. 95 (s, 3H), 3.94 (s, 3H). *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.14; H, 5.73; N, 4.70.
5b R=Et (Et–Br)	94	106 (AcOEt)	309 (M^+)	8.04 (m, 2H), 7.48 (m, 3H), 7.10 (d, *J*=2.3 Hz, 1H), 7.02 (s, 1H), 6.48 (d, *J*=2.3 Hz, 1H), 4.29 (q, *J*=7 Hz, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 1.58 (t, *J*=7 Hz, 3H). *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.70; H, 6.11; N, 4.49.
5c R=*n*-Bu (*n*Bu–Br)	86	107 (AcOEt)	337 (M^+)	8.06 (m, 2H), 7.47 (m, 3H), 7.08 (d, *J*=2.3 Hz, 1H), 7.02 (s, 1H), 6.47 (d, *J*=2.3 Hz, 1H), 4.22 (t, *J*=6.2 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 1.93 (m, 2H), 1.65 (m, 2H), 1.04 (t, *J*=7.3 Hz, 3H). *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.69; H, 6.82; N, 4.12.
5d R=Bz (Bz–Cl)	76	amorph.	371 (M^+)	8.03 (m, 2H), 7.60—7.23 (m, 8H), 7.11 (d, *J*=2.3 Hz, 1H), 7.07 (s, 1H), 6.47 (d, *J*=2.3 Hz, 1H), 5.25 (s, 2H), 3.96 (s, 3H), 3.94 (s, 3H). *Anal.* Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.55; H, 5.66; N, 3.75.



a) Alkyl Halide, K_2CO_3, DMF.

Chart 3. Alkylation of 5-Hydroxy-7-methoxy-2-phenyl-4-quinolone

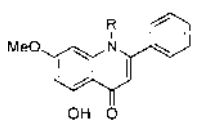
ford **5**. This observation is in accordance with the reported results regarding the alkylation of 5-unsubstituted-2-phenyl-4-quinolones.[8,9]

When **4** was treated under the same conditions as **3**, compounds **6** and **7** were produced (Chart 3). In this case, the amino group was deprotonated to give the intermediate **4**. Due to the chelation of the formed enol by the OH-5, components (**4a**, **b**) were able to co-exist and to be alkylated to give quinolone **6** and quinoline **7**, respectively (Table 2). In this case, it is worthy to note that the dialkylation products, namely *N*-alkyl-4-alkoxyquinolines **8** (Table 3), were detected when the reaction was carried out at 80 °C for 3 h and no similar observation was noticed with **3**.

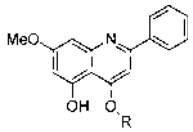
As can be seen in Table 2, only the methyl iodide gives exclusively the *N*-methylquinolone. Higher alkyl halide led to the formation of *N*-alkylquinolone **6** and 4-alkoxyquinolines **7**.

The structures of **5**—**8** were confirmed by mass spectrometry, ^{1}H- and ^{13}C-NMR (Tables 1—3). *N*-Alkyl-4-quinolones **6** can be easily identified by comparing their ^{1}H-NMR spec-

Table 2. Physicochemical Data of Quinolones **6** and Quinolines **7**



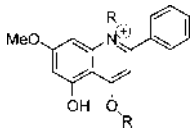
6a—d



7b—d

Compd.	Yield (%)	mp (°C)	MS *m/z*	^{1}H-NMR ($CDCl_3$) δ:
R=Me (Me–I)				
6a	46	188 (CH_2Cl_2)	281 (M^+)	7.6—7.30 (m, 5H), 6.35 (d, *J*=2 Hz, 1H), 6.25 (d, *J*=2 Hz, 1H), 6.06 (s, 1H), 3.85 (s, 3H), 3.45 (s, 3H). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.54; H, 5.30; N, 4.96.
R=Et (Et–Br)				
6b	26	160 (AcOEt)	295 (M^+)	7.50 (m, 2H), 7.4 (m, 3H), 6.41 (d, *J*=2.1 Hz, 1H), 6.35 (d, *J*=2.1 Hz, 1H), 6.0 (s, 1H), 3.94 (q, *J*=7.1 Hz, 2H), 3.89 (s, 3H), 1.26 (t, *J*=7 Hz, 3H). *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.14; H, 5.73; N, 4.70.
7b	30	amorph.	295 (M^+)	8.03 (m, 2H), 7.45 (m, 3H), 7.04 (d, *J*=2.1 Hz, 1H), 7.00 (s, 1H), 6.42 (d, *J*=2.1, 1H), 4.22 (t, *J*=6.6 Hz, 2H), 3.95 (s, 3H), 1.64 (t, *J*=6.6 Hz, 3H). *Anal.* Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.16; H, 5.75; N, 4.72.
R=*n*-Bu (*n*Bu–Br)				
6c	30	amorph.	323 (M^+)	7.50—7.35 (m, 5H), 6.41 (d, *J*=2.1 Hz, 1H), 6.33 (d, *J*=2.1 Hz, 1H), 6.07 (s, 1H), 3.90 (t, *J*=6.5 Hz, 2H), 3.89 (s, 3H), 1.65 (m, 2H), 1.26 (m, 2H), 0.76 (t, *J*=7.2 Hz, 3H). *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.24; H, 6.53; N, 4.30.
7c	17	amorph.	323 (M^+)	8.06 (m, 2H), 7.47 (m, 3H), 7.08 (d, *J*=2.2 Hz, 1H), 7.01 (s, 1H), 6.45 (d, *J*=2.2 Hz, 1H), 4.22 (t, *J*=6.4 Hz, 2H), 3.93 (s, 3H), 1.94 (m, 2H), 1.54 (m, 2H), 1.03 (t, *J*=7.2 Hz, 3H). *Anal.* Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.22; H, 6.50; N, 4.29.
R=Bz (Ph–CH_2–Br)				
6d	28	amorph.	358 $(M+1)^+$	7.40—7.27 (m, 10H), 6.35 (d, *J*=2.2 Hz, 1H), 6.18 (s, 1H), 6.13 (d, *J*=2.2 Hz, 1H), 5.15 (s, 2H), 3.70 (s, 3H). *Anal.* Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.24; H, 5.31; N, 3.90.
7d	19	96 (AcOEt)		8.06 (m, 2H), 7.63—7.26 (m, 8H), 7.09 (d, *J*=2.2 Hz, 1H), 7.03 (s, 1H), 6.44 (d, *J*=2.2 Hz, 1H), 5.28 (s, 2H), 3.95 (s, 3H). *Anal.* Calcd for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.25; H, 5.33; N, 3.88.

Table 3



8b—d

Compd.	Yield (%)	mp (°C)	MS *m/z*	^{1}H-NMR ($CDCl_3$) δ:
8b R=Et (Et–Br)	94	138 (CH_2Cl_2)	324 (M^+)	8.06 (dd, J_1=1.8 Hz, J_2=8.1 Hz, 2H), 7.47 (m, 3H), 7.09 (d, *J*=2.3 Hz, 1H), 7.01 (s, 1H), 6.46 (d, *J*=2.3 Hz, 1H), 4.27 (q, *J*=7 Hz, 2H), 4.11 (q, *J*=7 Hz, 2H), 3.93 (s, 3H), 1.59 (t, *J*=7 Hz, 3H), 1.54 (t, *J*=7 Hz, 3H).
8c R=*n*-Bu (*n*Bu–Br)	86	54 (CH_2Cl_2)	379 $(M-1)^+$	8.07 (dd, J_1=1.8 Hz, J_2=8 Hz, 2H), 7.46 (m, 3H), 7.08 (d, *J*=2.3 Hz, 1H), 7.01 (s, 1H), 6.46 (d, *J*=2.3 Hz, 1H), 4.23 (t, *J*=6.3 Hz, 2H), 4.04 (t, *J*=6.3 Hz, 2H), 3.93 (s, 3H), 1.93 (m, 4H), 1.65 (m, 4H), 1.04 (m, 6H).
8d R=Bz (Bz–Cl)	76	amorph.	448 (M^+)	8.06 (dd, J_1=1.8 Hz, J_2=8 Hz, 2H), 7.50—7.21 (m, 13H), 7.15 (s, 1H), 7.12 (d, *J*=2.2 Hz, 1H), 6.60 (d, *J*=2.2 Hz, 1H), 5.33 (s, 2H), 5.25 (s, 2H), 3.94 (s, 3H).

tra with the starting quinolone **4**. The structure of quinolines **5** and **7** was based on the NMR spectral evidence which included the appearance of H-3 at 7.00—7.20 ppm instead of 6.0—6.2 ppm (in quinolones). Interestingly, the upfield shift of H-2′ and H-6′ (8.10—8.00 ppm) instead of (7.60—7.50 ppm) indicated the presence of an electron withdrawing group (imino group) in *ortho* position. Further, ^{13}C-NMR confirmed the absence of the C-4 (186—180 ppm).

In summary, 2-phenyl-4-quinolones are being studied as potential therapeutic agents. Compared to the naturally occurring flavonoids, 2-phenyl-4-quinolones have available nitrogen for further extension. In this study, we have shown that *N*-alkyl-2-phenyl-4-quinolones cannot be obtained by applying the standard alkylation conditions. The presence of 5-OH group is essential for obtaining *N*-alkylquinolones. Thus it is recommended that if *N*-alkyl-2-phenyl-4-quinolones are targeted with the aim of extension at the nitrogen, the presence of a 5-hydroxy group in the starting quinolone should be considered.

Experimental

Melting points were determined on a Buchi 510 melting points apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AC200 spectrometer. Chemical shifts are reported in ppm from tetramethylsilane as internal standard. *J* values are given in Hz. Electron impact (EI) mass spectra and high resolution (HR)-MS were obtained at 70 eV using a Fisons Trio 1000 instrument. Thin-layer chromatography (TLC) was carried out using E. Merck silica gel F-254 plates (thickness 0.25 mm) and flash chromatography was accomplished using Merck silica gel 60, 200—400 mesh. All solvents were distilled prior to use. All chemicals and reagents

used were obtained from either Aldrich or ACROS and used as received.

***N*-(3,5-Dimethoxyphenyl)benzamide (1)** To a solution of 3,5-dimethoxyaniline (3 g, 19.6 mmol) in dry THF (50 ml) was added Et_3N (4.1 ml, 29.4 mmol). The solution was stirred at 0 °C (ice bath) for 10 min and treated by dropwise addition of benzoyl chloride (3.4 ml, 29.4 mmol). The reaction mixture was stirred at room temperature for 1 h then hydrolyzed by adding H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography eluted with cyclohexane : AcOEt (9 : 1) to yield 4.84 g of pure **1** as a white solid. Yield 96%. mp 143—145 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 7.86 (2H, m), 7.51 (3H, m), 6.91 (2H, d, J=2 Hz), 6.30 (1H, t, J=2 Hz), 3.81 (6H, s). HR-MS *m*/*z*: 256.9907 (Calcd for $C_{15}H_{15}NO_3$: 256.9909). EI-MS *m*/*z*: 257 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.98; H, 5.83; N, 5.36.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)benzamide (2)** To an ice cold solution of **1** (4.7 g, 18.3 mmol) in freshly distilled 1,2-dichloroethane (60 ml) under N_2 was added dropwise $SnCl_4$ (4.3 ml, 36.6 mmol). Freshly distilled acetyl chloride (1.41 ml, 20 mmol) as a solution in 1,2-dichloroethane (5 ml) was also added dropwise. After stirring at room temperature for 1.5 h, the solution was poured into crushed ice, extracted with AcOEt, washed with brine, dried over Na_2SO_4 and concentrated. Purification by column chromatography eluted with AcOEt : cyclohexane (1 : 1) afforded 3.18 g of **2** as white crystals. Yield 58%. mp 119—121 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 12.7 (1H, bs), 8.3 (1H, d, J=2.1 Hz), 8.15 (2H, m), 7.50 (3H, m), 6.25 (1H, d, J=2.1 Hz), 3.96 (3H, s), 3.93 (3H, s), 2.64 (3H, s). HR-MS *m*/*z*: 298.9280 (Calcd for $C_{17}H_{17}NO_4$: 298.9284). EI-MS *m*/*z*: 299 (M^+). *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.15; H, 5.63; N, 4.66.

***N*-(2-Acetyl-3,5-dimethoxyphenyl)benzamide (2a)** This regioisomer (more polar than **2**) was obtained with less than 5% yield as white crystals. mp 137—139 °C (EtOAc). ^{1}H-NMR ($CDCl_3$) δ: 8.94 (s, 1H), 7.89 (d, J=7 Hz, 2H), 7.37 (m, 3H), 7.01 (s, 2H), 3.60 (s, 6H), 2.43 (s, 3H). EI-MS *m*/*z*: 299 (M^+). *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.18; H, 5.66; N, 4.63.

5,7-Dimethoxy-2-phenyl-4-quinolone (3) To a stirred solution of **2** (3.1 g, 10.3 mmol) in anhydrous THF (30 ml) under N_2 atmosphere was added *t*-BuOK (5.7 g, 51.5 mmol). The reaction mixture was then refluxed for 20 h. After cooling, the resultant mixture was added to a saturated aqueous solution of NH_4Cl and the whole was extracted with AcOEt (3×50 ml), dried over anhydrous Na_2SO_4 and evaporated. The crude material was purified by column chromatography eluted with cyclohexane : AcOEt (3 : 7) to give 2.41 g of **3** as a yellow solid. Yield 83%. mp 144—145 °C (CH_2Cl_2). ^{1}H-NMR ($CDCl_3$) δ: 7.72 (m, 2H), 7.50 (m, 3H), 6.52 (d, J=2.1 Hz, 1H), 6.29 (s, 1H), 6.21 (d, J=2.1 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 3H). HR-MS *m*/*z*: 281.0129 (Calcd for $C_{17}H_{15}NO_3$: 281.0131). EI-MS *m*/*z*: 281 (M^+). *Anal.* Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.52; H, 5.30; N, 4.97.

5-Hydroxy-7-methoxy-2-phenyl-4-quinolone (4) To a stirred solution of **3** (0.54 g, 1.92 mmol) in anhydrous CH_2Cl_2 (20 ml) at 0 °C under N_2 atmosphere was added BBr_3 (0.49 ml, 2.88 mmol). The solution was stirred at room temperature for 24 h, then it was cooled again to 0 °C, and a mixture of ice and water was added. Extraction with CH_2Cl_2, drying and concentration afforded a crude **4** which was purified by column chromatography eluted with cyclohexane : AcOEt (7 : 3) to give 0.41 g of **4** as a yellow solid. Yield 80%; mp 257—259 °C (MeOH). ^{1}H-NMR (acetone-d_6) δ: 13.45 (1H, s), 7.82 (2H, m), 7.56 (3H, m), 6.61 (1H, d, J=2.2 Hz), 6.27 (1H, s), 6.18 (1H, d, J=2.2 Hz), 3.84 (3H, s). HR-MS *m*/*z*: 266.9856 (Calcd for $C_{16}H_{13}NO_3$: 266.9861). EI-MS *m*/*z*: 267 (M^+). *Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.84; H, 4.83; N, 5.19.

5-Methoxy-4-alkoxyquinolines 5, *N*-Alkyl-4-quinolones 6 and 5-Hydroxy-4- alkoxyquinolines 7: Standard Procedure Quinolone **3** or **4** and the alkyl halide (1.5 eq) were dissolved in anhydrous DMF (5 ml/mmol) and K_2CO_3 (3 eq) was added. The reaction mixture was stirred at room temperature for 2 h then heated at 80 °C for 3 h, after heating, the reaction mixture was poured into water, extracted with EtOAc and concentrated. Products were purified either by chromatography column eluted with hexane : AcOEt (9 : 1) or by preparative TLC using hexane : AcOEt (7 : 3) as eluant.

References and Notes

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