Synthesis of 2-Heptyl-1-hydroxy-4(1*H*)-quinolone – Unexpected Rearrangement of 4-(Alkoxycarbonyloxy)quinoline *N*-Oxides to 1-(Alkoxycarbonyloxy)-4(1*H*)-quinolones

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Abstract: 2-Heptyl-4(1*H*)-quinolone was converted in two steps into the 4-ethoxycarbonyloxy-, 4-(*tert*-butoxycarbonyloxy)-, and 4-(dimethylaminocarbonyloxy)quinoline *N*-oxides. While the former two rearranged to the corresponding 1-(alkoxycarbonyloxy)-4(1*H*)-quinolones at room temperature, the latter was stable, even at 140 °C in refluxing xylenes. Basic hydrolysis of these compounds furnished 2-heptyl-1-hydroxy-4(1*H*)-quinolone.

Key words: acylations, heterocycles, quinolines, rearrangements, oxidations

Lightbown isolated from culture filtrates of *Pseudomonas aeruginosa* a product, which antagonized the antibacterial action of streptomycin and dihydrostreptomycin.[1,2] Cornforth and James proved the product to be a mixture and synthesized its principal constituents **1a–c** (Figure 1).[3] The major component was **1a**, the *n*-heptyl derivative of 1-hydroxy-4(1*H*)-quinolone [acronym: HQNO = 2-heptyl-4-hydroxyquinolone *N*-oxide, IUPAC: 2-heptyl-1-hydroxy-4(1*H*)-quinolone], and the most active one was found to be **1b**, the *n*-nonyl derivative. In the same year Lightbown and Jackson disclosed their finding that HQNO inhibits the cytochrome system of heart muscle and *Staphylococcus aureus*.[4] HQNO and other 4-hydroxyquinoline *N*-oxides and the underlying quinolones are inhibitors of respiratory[5,6] and photosynthetic electron[7] transport chains. Furthermore, HQNO was found to selectively block one (quinol oxidase) of the three respiratory terminal oxidases in the cyanobacterium *Synechocystis sp.* strain PCC6803.[8] Aurachin C[9] (**2**, Figure 1), isolated from the biomass of *Stigmatella aurantiaca,* shows a close chemical and inhibitory relationship[10] to HQNO.

The first syntheses of 1-hydroxy-4(1*H*)-quinolones **1** were performed by Cornforth and James.[3] They started from *o*-nitrobenzoyl chloride and the respective methyl 3-oxoalkanoate, which were condensed. The acylated ester was hydrolyzed and decarboxylated to give the 1,3-diketone. Its nitro group was reduced with $SnCl_2 \cdot 2H_2O$ and the nitroso compound cyclized to the desired compound. Alternatively for HQNO, they acylated 4(1*H*)-quinolone[11] **3** and oxidized it at nitrogen using MCPBA. The crude *N*-oxide **5** was hydrolyzed to yield HQNO (**1a**) (Scheme 1). Ames et al. transformed **3** into benzyl ether **6**, oxidized (MCPBA) it and deblocked ($Pd/SrCO_3/H_2$) the protected *N*-oxide **7** to get **1a**.[12] The former method was used later by others to prepare a variety of analogues with other *n*-alkyl groups in place of the heptyl group.[5]

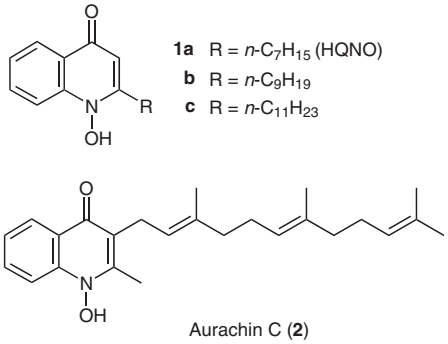
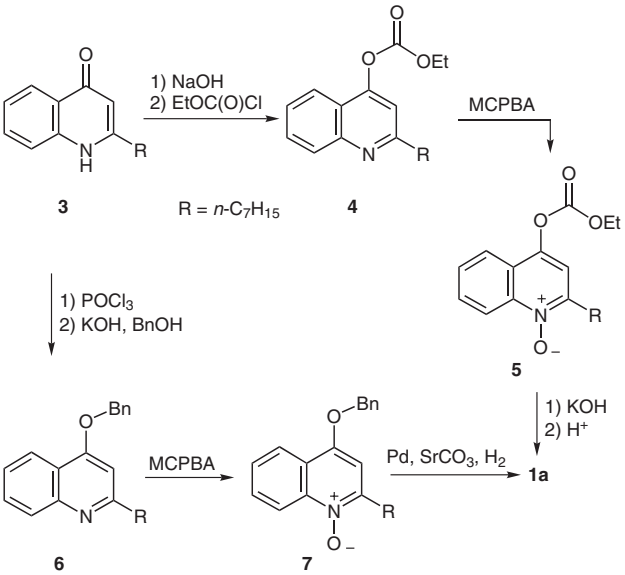


Figure 1 Naturally occurring 1-hydroxy-4(1*H*)-quinolones **1** and **2**

Needing for biological experiments HQNO, which was no longer commercially available, we decided to synthesize it. The method starting with the acylation of the 4-(1*H*)-quinolone seemed to be more attractive than any other



Scheme 1

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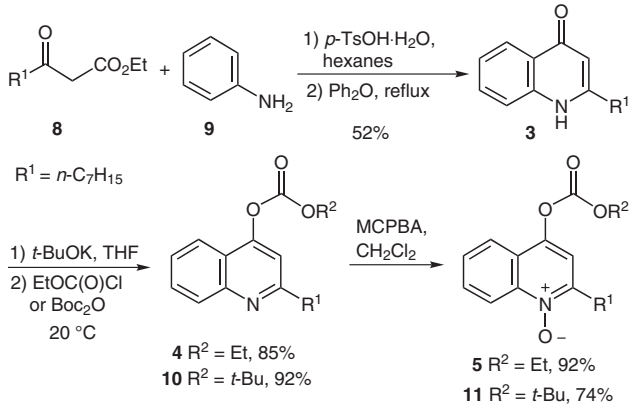
method. We were surprised to find that *N*-oxide **5** isomerized easily. This unknown rearrangement forms the basis of this work. Additionally, we optimized the inadequately described steps with in part missing yields and characterized the products spectroscopically, which has not been done previously.

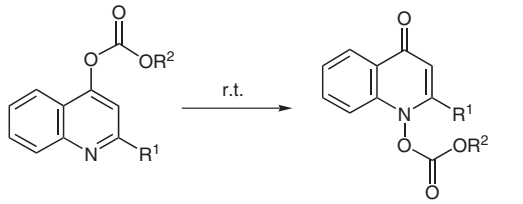
At first, we prepared 4(1*H*)-quinolone **3** by condensing aniline with ethyl 3-oxodecanoate using a catalytic amount of *p*-toluenesulfonic acid in hexanes and azeotropic removal of the water according to a literature procedure[13] (Scheme 2). Then, the crude enamine was cyclized in refluxing diphenyl ether (bp 259 °C) to give crystalline 4(1*H*)-quinolone **3** in 52% yield. Treatment of **3** with *t*-BuOK in anhydrous THF furnished the potassium salt which was esterified without prior isolation as in the case of the sodium salt with ethyl chloroformate to give 4-(ethoxycarbonyloxy)quinoline **4** in 85% yield. Oxidation with MCPBA furnished *N*-oxide **5** as a viscous oil (92%) resisting crystallization.



Scheme 2

Once, when a neat sample of *N*-oxide **5** was left for three days at room temperature, it had solidified. Surprisingly, the ^{1}H NMR spectrum of this material was completely different from that of the oil. The same was true for its ^{13}C NMR and the IR spectra. The product was crystallized from diisopropyl ether (30 to 4 °C) to yield colorless crystals with a low melting point (64–65 °C). As the microanalytical data of the crystals and the oil agreed within experimental error, the two compounds had to be isomers. The oil showed in the IR spectrum one characteristic absorption at 1769 cm^{-1} (OCO_2Et), similar to the one in **4** (1770 cm^{-1}), but different from that of the crystalline product having three (1803, 1634 and 1604 cm^{-1}). The ^{1}H NMR spectrum of the oily product revealed a significant singlet at 7.32 ppm (7.29 ppm in **4**), but shifted to 6.09 ppm in the crystalline product. Finally, the ^{13}C NMR spectrum of the crystalline product showed a significant resonance at 177.3 ppm, which was not present in the other compounds, but characteristic for a C=O [in addition to the C=O of the OC(O)OEt at 153.1 ppm]. The ^{13}C NMR spectrum of the oil has the lowest resonance at 152.4 ppm. On the basis of these spectroscopic data, structure **12** was tentatively assigned to the crystalline isomer (Scheme 3). It is an O-acylated vinylogous hydroxamic acid ester and slightly less polar than *N*-oxide **5**. This structure was secured by a single crystal X-ray structure analysis (Figure 2). With spectroscopic data of **12** in hands, we were able to detect trace amounts of it already in oily **5**. This rearrangement proceeds quantitatively and very smoothly in neat samples already at room temperature (3 days for **5**). When an NMR sample was kept at room temperature and a ^{1}H NMR spectrum was recorded at intervals of two days, the isomerization seemed to be extremely slow. To study the effect of replacing R^2 = Et by R^2 = *t*-Bu, *N*-oxide **11** was prepared similarly to **5** (Scheme 2). The potassium salt of quinolone **3** was acylated with Boc_2O to give **10** in 92% yield. Oxidation with MCPBA produced **11** (74%) as a viscous oil, which rearranged more slowly than **5**. Its chemical and physical properties and spectroscopic data are similar to those of **5**. A neat sample, when left at room temperature for 16 days, was a mixture of *N*-oxide **11** (20%), its isomer **13** (60%) and HQNO formed by hydrolysis of **13**.

To the best of our knowledge, this rearrangement has not yet been described in the literature, although 2-alkyl-1-hydroxy-4(1*H*)-quinolones have been prepared via the corresponding 4-(ethoxycabonyloxy)quinoline *N*-oxides.[3,7,14] Usually, the *N*-oxides were not isolated and



Scheme 3

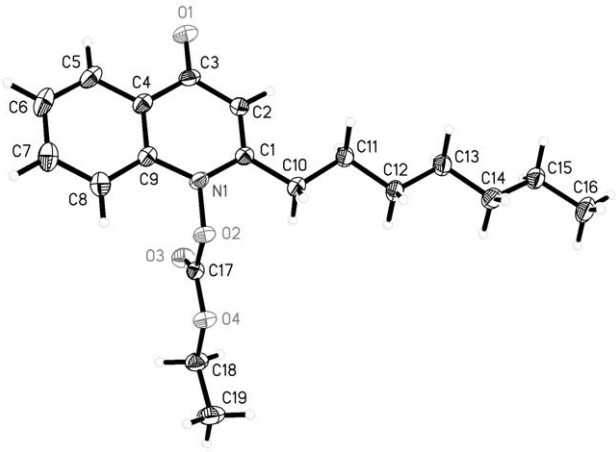
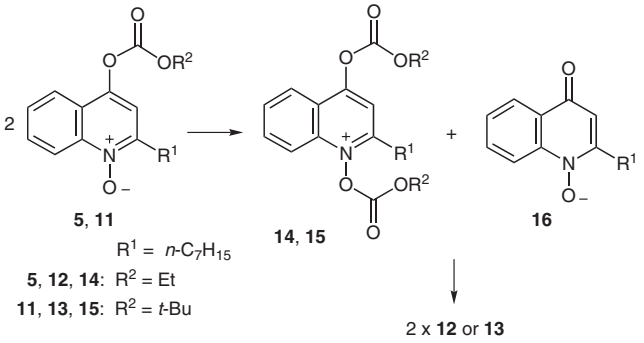
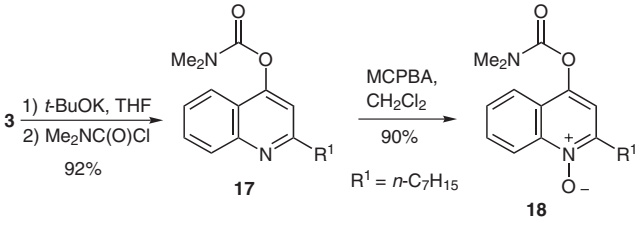


Figure 2 Molecular structure of quinolone **12** in the solid state. Only the first one of the four independent molecules is shown. Selected bond lengths (Å): N1–O2 1.398(1), N1–C1 1.365(2), N1–C9 1.380(2), C1–C2 1.360(2), C9–C4 1.405(2), C2–C3 1.439(2), C4–C3 1.476(2), C3–O1 1.241(2).

characterized, but immediately deprotected. The mechanism of the rearrangement is unclear. We favor an intermolecular transfer of the alkoxycarbonyl group from the oxygen at C-4 to that at N via possible intermediates **14** and **15**, respectively, and **16** (Scheme 4). It is noteworthy that the energy gain of the rearrangement outweighs the dearomatization of the heterocyclic ring. If the proposed mechanism applies, it should be a general reaction of 4-alkoxycarbonyloxy-, possibly also of 4-acyloxy-, but not of (dialkylaminocarbonyloxy)pyridine *N*-oxides, described in a patent[15] for the preparation of insecticidal compounds. To prove that, the 4-(dimethylaminocarbonyloxy)quinoline **17** was prepared similarly to the carbonates **4** and **10** in 92% yield (Scheme 5). Oxidation of **17** with MCPBA proceeded more rapidly than with **4** or **10** to give crystalline *N*-oxide **18**. It could not be induced to rearrange to the isomeric *N*-(dimethylaminocarbonyloxy)-4(1*H*)-quinolone, neither by refluxing for three hours in acetonitrile nor in xylenes.

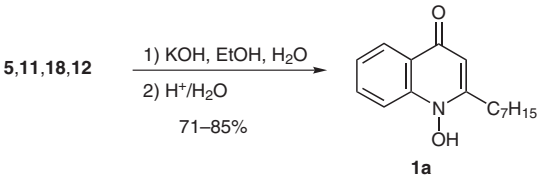


Scheme 4



Scheme 5

Finally, the *N*-oxides **5**, **11** and **18** and *N*-(ethoxycarbonyloxy)-4(1*H*)-quinolone **12** were hydrolyzed smoothly by potassium hydroxide in aqueous ethanol in one hour. Acidification and crystallization gave HQNO (**1a**) in yields of 71–85% (Scheme 6). The sequence via **3**, **4**, and **5** represents an optimized synthesis of HQNO. On the basis of the spectroscopic data (^{1}H and ^{13}C NMR) recorded in MeOH-d_4, **1a** is a quinolone and not the tautomeric 4-hydroxyquinoline *N*-oxide (see unpublished results in ref. 10).



Scheme 6

In summary, we have shown that 4-alkoxycarbonyloxy-2-heptylquinoline *N*-oxides isomerize by a novel rearrangement to *N*-alkoxycarbonyloxy-2-heptyl-4(1*H*)-quinolones at room temperature. The 4-dimethylaminocarbonyloxy analogue is stable even in refluxing xylenes.

^{1}H NMR and ^{13}C NMR (*J* modulated) spectra were measured in $CDCl_3$ or MeOH-d_4 at 300 K on a Bruker Avance DRX 400 spectrometer at 400.13 and 100.61 MHz, respectively. Chemical shifts were referenced to residual $CHCl_3$ ($\delta_H = 7.24$) or MeOH-d_4 ($\delta_H = 3.31$) and $CDCl_3$ ($\delta_C = 77.00$) or MeOH-d_4 ($\delta_C = 49.00$). IR spectra were run on a PerkinElmer 1600 FT-IR spectrometer; samples were measured as films [normally, a solution in $CDCl_3$ (from the NMR sample) was applied and the solvent was allowed to evaporate] on a silicon disc;[16] the IR of HQNO was recorded with a diamond ATR equipment. TLC was carried on 0.25 mm thick Merck plates, silica gel 60 F_{254}. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh). Spots were visualized by UV and/or I_2 or dipping the plate into a solution of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (23.0 g) and of $Ce(SO_4)_2\cdot 4H_2O$ (1.0 g) in 10% aq H_2SO_4 (500 mL), followed by heating with a hot gun. Melting points were determined on a Reichert Thermovar instrument and were uncorrected.

X-ray crystal structure data of **12** were measured on a Bruker Smart CCD area detector diffractometer using graphite-monochromated MoKα radiation (λ = 0.71073 Å) and 0.3° ω-scan frames covering a complete sphere of the reciprocal space.[17] The structure was solved by direct methods and refined on F^2 with the program system SHELX97.[18] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted in idealized positions and were refined riding with the atoms to which they were bonded.

2-Heptyl-4(1*H*)-quinolone (3)

A solution of ethyl 3-oxodecanoate (5.06 g, 23.6 mmol, prepared according to literature[19] or by alkylation of the dianion derived from ethyl acetoacetate with n-$C_6H_{13}I$ in analogy to the procedure for the preparation of ethyl 3-oxononanoate[20]), aniline (2.20 g, 2.15 mL, 23.6 mmol), and PTSA (0.070 g, 0.37 mmol) in hexanes (24 mL) was heated at reflux using a Dean–Stark water separator for 5 h.[13] The solution was concentrated under reduced pressure and the residue was added dropwise to refluxing diphenyl ether (5.9 mL). Refluxing was continued for 30 min and the formed EtOH was removed by distillation. After cooling, Et_2O (15 mL) and 2 M HCl (20 mL) were added and the mixture was left for 18 h at r.t. If a crystalline solid had formed, it was collected and washed with Et_2O. If no solid formed, ammonia was added to basify the mixture and then a solid formed. The crude product was crystallized from EtOAc by slowly cooling to 4 °C. A second crop was obtained by concentrating the mother liquor; combined yield of 4(1*H*)-quinolone **3**: 2.965 g (52%); mp 145 °C (Lit.[11] mp 146–147 °C).

IR (Si): 2927, 1635, 1594, 1552, 1509, 1472 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 13.39 (br s, 1 H, NH), 8.36 (dd, *J* = 8.3, 1.3 Hz, 1 H_{arom}), 8.08 (d, *J* = 8.3 Hz, 1 H_{arom}), 7.62 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1 H_{arom}), 7.39 (dd, *J* = 8.3, 7.1 Hz, 1 H_{arom}), 6.48 (s, 1 H, =CH), 2.84 (t, *J* = 7.8 Hz, 2 H, CH_2), 1.74 (quint, *J* = 7.8 Hz, 2 H, CH_2), 1.27 (m, 2 H, CH_2), 1.15 (m, 6 H, CH_2), 0.77 (t, *J* = 7.0 Hz, 3 H, CH_3).

^{1}H NMR (MeOH-d_4): δ = 8.20 (dd, *J* = 8.1 Hz, 1 H_{arom}), 7.65 (t, *J* = 8.1 Hz, 1 H_{arom}), 7.56 (d, *J* = 8.1 Hz, 1 H_{arom}), 7.36 (t, *J* = 8.1 Hz, 1 H_{arom}), 6.21 (s, 1 H, =CH), 2.68 (t, *J* = 7.7 Hz, 2 H, CH_2), 1.73

(quint, J = 7.7 Hz, 2 H, CH_2), 1.33 (m, 8 H, CH_2), 0.87 (t, J = 6.7 Hz, 3 H, CH_3).

^{13}C NMR (MeOH-d_4): δ = 180.6, 157.1, 141.6, 133.3, 126.0, 125.5, 125.0, 119.1, 108.8, 35.0, 32.8, 30.2, 30.1, 30.0, 23.6, 14.4.

4-Ethoxycarbonyloxy-2-heptylquinoline (4)

A mixture of *t*-BuOK (0.701 g, 6.25 mmol, 1.25 equiv) and 4(1*H*)-quinolone **3** (1.217 g, 5 mmol) in anhyd THF (36 mL) was stirred for 1 h at r.t. Ethyl chloroformate (0.597 g, 0.53 mL, 5.5 mmol) was added and stirring was continued for 30 min. The reaction was quenched with H_2O (10 mL) and the mixture was concentrated under reduced pressure after 5 min. H_2O (10 mL) was added to the residue and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to leave a residue, which was purified by flash chromatography (EtOAc, R_f = 0.92, starting material: R_f = 0.25) to give carbonate **4** (1.334 g, 85%) as an oil.

IR (Si): 2928, 2856, 1770, 1239 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.04 (dd, J = 8.6, 1.0 Hz, 1 H_{arom}), 7.97 (dd, J = 8.3, 1.5 Hz, 1 H_{arom}), 7.69 (ddd, J = 8.6, 7.1, 1.5 Hz, 1 H_{arom}), 7.49 (ddd, J = 8.3, 7.1, 1.0 Hz, 1 H_{arom}), 7.29 (s, 1 H, =CH), 4.38 (q, J = 7.1 Hz, 2 H, OCH_2), 2.95 (~t, J = 8.0 Hz, 2 H, CH_2), 1.80 (m, 2 H, CH_2), 1.42 (t, J = 7.1 Hz, 3 H, CH_3), 1.44–1.21 (m, 8 H, CH_2), 0.86 (t, J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 164.1, 154.3, 152.4, 149.6, 130.0, 128.9, 126.0, 120.9, 120.4, 111.8, 65.4, 39.6, 31.7, 29.8, 29.5, 29.1, 22.6, 14.2, 14.0.

4-Ethoxycarbonyloxy-2-heptylquinoline *N*-Oxide (5) and *N*-Ethoxycarbonyloxy-2-heptyl-4(1*H*)-quinolone (12)

A solution of quinoline **4** (0.995 g, 3.15 mmol) and MCPBA (0.760 g, 77%, 3.39 mmol) in anhyd CH_2Cl_2 (15 mL) was stirred for 3 h at r.t. (TLC: EtOAc). The solution was washed with aq 0.5 M Na_2CO_3 (2 × 5 mL) and H_2O (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc, R_f = 0.68) to give *N*-oxide **5** (0.964 g, 92%) as an oil. When the oil was left at room temperature for 3 days, a crystalline solid had formed and no *N*-oxide could be detected by ^{1}H NMR spectroscopy. Crystallization from *i*-Pr_2O (30 → 4 °C) furnished colorless crystals (mp 64–65 °C) of the N-substituted 4(1*H*)-quinolone **12**.

5

IR (Si): 2929, 1769, 1239 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.77 (dd, J = 8.5, 0.9 Hz, 1 H_{arom}), 7.97 (dd, J = 8.1, 1.1 Hz, 1 H_{arom}), 7.76 (ddd, J = 8.5, 7.0, 1.1 Hz, 1 H_{arom}), 7.60 (ddd, J = 8.1, 7.0, 0.9 Hz, 1 H_{arom}), 7.32 (s, 1 H, =CH), 4.38 (q, J = 7.1 Hz, 2 H, OCH_2), 3.10 (t, J = 7.8 Hz, 2 H, CH_2), 1.79 (quint, J = 7.5 Hz, 2 H, CH_2), 1.43 (t, J = 7.1 Hz, 3 H, CH_3), 1.43 (m, 2 H, CH_2), 1.35 (m, 2 H, CH_2), 1.26 (m, 4 H, CH_2), 0.85 (t, J = 7.1 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 152.4, 149.5, 143.6, 142.3, 130.9, 128.0, 122.6, 121.8, 120.1, 113.2, 65.7, 31.7, 29.5, 29.0, 26.0, 22.6, 14.1, 14.0.

12

IR (Si): 2930, 2857, 1803, 1634, 1604, 1487, 1466, 1230 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.33 (dd, J = 8.2, 1.4 Hz, 1 H_{arom}), 7.62 (ddd, J = 8.5, 7.1, 1.4 Hz, 1 H_{arom}), 7.34 (ddd, J = 8.2, 7.1, 1.0 Hz, 1 H_{arom}), 7.27 (dd, J = 8.5, 1.0 Hz, 1 H_{arom}), 6.09 (s, 1 H_{arom}), 4.44 (q, J = 7.1 Hz, 2 H, OCH_2), 2.55 (m, 2 H, CH_2), 1.68 (m, 2 H, CH_2), 1.42 (t, J = 7.1 Hz, 3 H, CH_3), 1.43–1.20 (m, 8 H, CH_2), 0.86 (t, J = 6.8 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 177.3, 153.1, 152.1, 139.2, 132.7, 126.7, 125.0, 124.1, 112.2, 108.5, 67.8, 31.6, 30.7, 29.0, 28.8, 27.3, 22.5, 14.1, 14.0.

Anal. Calcd for $C_{19}H_{25}NO_3$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.91; H, 7.41; N, 4.28.

X-ray Crystal Data of 4(1*H*)-quinolone 12[21]

Salient crystallographic data are: $C_{19}H_{25}NO_4$, M = 331.40, T = 100 K, triclinic, space group P–1 (no. 2), a = 8.9481(5), b = 17.9486(10), c = 22.3840(12) Å, α = 85.109(1)°, β = 84.633(1)°, γ = 80.510(1)°, V = 3521.3(3) Å^3, Z = 8, D_c = 1.250 g cm^{-3}, μ(Mo-Ka) = 0.087 mm^{-1}, 64928 reflections collected of which 20393 were independent and 14902 observed [$I > 2\sigma(I)$]. $R1$ = 0.0564, $wR2$ = 0.1424 [for I > 2s(I)]. The structure at T = 100 K was remarkable in that it contained four independent molecules which differ pairwise in the conformation of the heptyl chain (two molecules with anti-coplanar chains, two molecules with synclinal configurations for C(12)–C(13)–C(14)–C(15) (see Figure 2). At T = 173 K and above the structure is monoclinic, space group *C*2/*c*, a = 13.8037(7), b = 11.5567(6), c = 22.6319(11) Å, β = 97.729(1)°, V = 3577.6(3) Å^3, Z = 8, and has disordered heptyl chains.

4-(*tert*-Butoxycarbonyloxy)-2-heptylquinoline (10)

4(1*H*)-Quinolone **3** (0.487 g, 2 mmol) was converted into carbonate **10** in analogy to the preparation of carbonate **4**, using Boc_2O (0.480 g, 2.2 mmol) in anhyd THF (2 mL) and heating the mixture at 60 °C for 1 h. The crude product was purified by flash chromatography (hexanes–EtOAc, 7:1, R_f = 0.45) to yield carbonate **10** (0.635 g, 92%) as an oil.

IR (Si): 2929, 1766, 1605, 1247, 1145 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.03 (dd, J = 8.3, 1.3 Hz, 1 H_{arom}), 7.96 (dd, J = 8.3, 1.5 Hz, 1 H_{arom}), 7.67 (ddd, J = 8.3, 7.1, 1.5 Hz, 1 H_{arom}), 7.47 (ddd, J = 8.3, 7.1, 1.3 Hz, 1 H_{arom}), 7.25 (s, 1 H, =CH), 2.94 (t, J = 7.9 Hz, 2 H, CH_2), 1.79 (m, 2 H, CH_2), 1.58 (s, 9 H, *t*-C_4H_9), 1.43–1.20 (m, 8 H, CH_2), 0.85 (t, J = 6.9 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 164.0, 154.3, 150.5, 149.5, 129.8, 128.8, 125.9, 121.0, 120.7, 112.0, 84.4, 39.6, 31.7, 29.8, 29.5, 29.1, 27.6, 22.6, 14.0.

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.45; H, 8.66; N, 3.96.

4-(*tert*-Butoxycarbonyloxy)-2-heptylquinoline *N*-Oxide (11) and *N*-(*tert*-Butoxycarbonyloxy)-2-heptyl-4(1*H*)-quinolone (13)

4(1*H*)-Quinoline **10** (0.503 g, 1.46 mmol) was converted into *N*-oxide **11** in analogy to the preparation of *N*-oxide **5**, except that the mixture was stirred under argon for 4 h at 0 °C (TLC: EtOAc). The crude product was purified by flash chromatography (hexanes–EtOAc, 2:1, R_f = 0.25) to give *N*-oxide **11** (0.387 g, 74%) as a viscous oil. When the NMR sample was left at r.t., 0.6%, 1.1% and 3% had rearranged after 9, 16 and 29 days, respectively. When a sample of oily *N*-oxide was left at r.t. for 18 days, the rearrangement was virtually finished. *i*-Pr_2O (4 mL) was added to the mixture. Filtration gave a solution, which left an oil on concentration. Two crystallization from *i*-Pr_2O–hexanes (slow cooling from 20 to –27 °C) furnished an analytical sample of the rearranged product **13**; mp 70–72 °C.

11

IR (Si): 2928, 1766, 1371, 1248, 1143, 1112 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.77 (dd, J = 8.5, 1.0 Hz, 1 H_{arom}), 7.97 (dd, J = 8.2, 1.3 Hz, 1 H_{arom}), 7.76 (ddd, J = 8.5, 7.0, 1.3 Hz, 1 H_{arom}), 7.61 (ddd, J = 8.2, 7.0, 1.0 Hz, 1 H_{arom}), 7.29 (s, 1 H, =CH), 3.10 (t, J = 7.8 Hz, 2 H, CH_2), 1.80 (quint, J = 7.8 Hz, 2 H, CH_2), 1.58 (s, 9 H, *t*-C_4H_9), 1.44 (m, 2 H, CH_2), 1.36 (m, 2 H, CH_2), 1.28 (m, 4 H, CH_2), 0.86 (t, J = 7.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 150.4, 149.6, 143.8, 142.3, 130.7, 127.9, 122.8, 121.9, 120.1, 113.4, 85.0, 31.71, 31.68, 29.5, 29.0, 27.6, 26.0, 22.6, 14.0.

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.39; H, 8.16; N, 3.84.

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IR (Si): 2931, 1799, 1634, 1604, 1488, 1466, 1244, 1152, 1139, 1110 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.34 (dd, *J* = 8.1, 1.3 Hz, 1 H_{arom}), 7.62 (ddd, *J* = 8.1, 7.2, 1.3 Hz, 1 H_{arom}), 7.34 (br t, *J* = ~7.3 Hz, 1 H_{arom}), 7.28 (br t, *J* = ~8.5 Hz, 1 H_{arom}), 6.10 (s, 1 H, =CH), 2.55 (m, 2 H, CH_2), 1.69 (m, 2 H, CH_2), 1.56 (s, 9 H, *t*-C_4H_9), 1.32 (m, 8 H, CH_2), 0.86 (*J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 177.3, 152.3, 150.9, 139.4, 132.6, 126.6, 125.1, 124.0, 112.3, 108.4, 88.3, 31.6, 30.8, 29.1, 28.8, 27.5, 27.3, 22.6, 14.0.

Anal. Calcd for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90. Found: C, 70.37; H, 8.21; N, 3.81.

4-(Dimethylaminocarbonyloxy)-2-heptylquinoline (17)

4(1*H*)-Quinolone **3** (0.245 g, 1.01 mmol) was converted into carbamate **17** in analogy to the preparation of carbonate **4**, using *N,N*-dimethylcarbamoyl chloride (0.118 g, 0.10 mL, 1.1 mmol, 1.1 equiv) and stirring the mixture for 2 h (TLC: EtOAc). The crude product was purified by flash chromatography (hexanes–EtOAc, 1:5, TLC: EtOAc, R_f = 0.79) to yield carbamate **17** (0.292 g, 92%) as an oil.

IR (Si): 2927, 2856, 1733, 1622, 1604, 1505, 1390, 1373, 1350, 1150 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.02 (br d, *J* = 8.4 Hz, 1 H_{arom}), 7.92 (dd, *J* = 8.2, 1.3 Hz, 1 H_{arom}), 7.65 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1 H_{arom}), 7.45 (ddd, *J* = 8.2, 6.8, 1.0 Hz, 1 H_{arom}), 7.25 (s, 1 H, =CH), 3.22 (s, 3 H, NCH_3), 3.06 (s, 3 H, NCH_3), 2.93 (m, 2 H, CH_2), 1.79 (m, 2 H, CH_2), 1.43–1.20 (m, 8 H, CH_2), 0.85 (t, *J* = 6.8 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 164.1, 154.8, 153.3, 149.6, 129.6, 128.8, 125.6, 121.2, 121.0, 112.3, 39.6, 36.9, 36.6, 31.7, 29.9, 29.5, 29.1, 22.6, 14.0.

Anal. Calcd for $C_{19}H_{26}N_2O_2$: C, 72.58; H, 8.33; 8.91. Found: C, 72.49; H, 8.25; N, 8.80.

4-(Dimethylaminocarbonyloxy)-2-heptylquinoline *N*-Oxide (18)

A solution of carbamate **17** (0.265 g, 0.843 mmol) and MCPBA (0.200 g, 77%, 0.893 mmol) in anhyd CH_2Cl_2 (4 mL) was stirred for 1 h at r.t. (TLC: Et_2O). The mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (EtOAc, R_f = 0.39) to give *N*-oxide **18** (0.250 g, 90%) as colorless needles; mp 71–72 °C (1,2-$C_2H_4Cl_2$–*i*-Pr_2O, 30 °C → –17 °C).

IR (Si): 2928, 2856, 1733, 1362, 1212, 1154, 1083 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.77 (br d, *J* = 8.6 Hz, 1 H_{arom}), 7.92 (dd, *J* = 8.3, 1.4 Hz, 1 H_{arom}), 7.74 (ddd, *J* = 8.6, 6.8, 1.4 Hz, 1 H_{arom}), 7.58 (ddd, *J* = 8.3, 6.8, 1.1 Hz, 1 H_{arom}), 7.27 (s, 1 H, =CH), 3.24 (s, 3 H, NCH_3), 3.09 (m, 2 H, CH_2), 3.07 (s, 3 H, NCH_3), 1.79 (m, 2 H, CH_2), 1.44 (m, 2 H, CH_2), 1.35 (m, 2 H, CH_2), 1.28 (m, 4 H, CH_2), 0.85 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 153.3, 149.7, 144.5, 142.2, 130.6, 127.7, 123.3, 121.9, 120.2, 113.8, 37.0, 36.7, 31.74, 31.7, 29.6, 29.0, 26.1, 22.6, 14.0.

Anal. Calcd for $C_{19}H_{26}N_2O_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 69.02; H, 7.89; N, 8.52.

2-Heptyl-1-hydroxy-4(1*H*)-quinolone (1a); Deblocking of Protected 4(1*H*)-Quinoline-*N*-oxides 5, 11, 18, and *N*-(Ethoxycarbonyloxy)-2-heptyl-4(1*H*)-quinolone (12); General Procedure

Aq 5 M KOH (2.5 mL) was added to a solution of the respective substrate (1 mmol) in EtOH (5 mL). After 1 h at r.t., H_2O (15 mL) was added and the pH was brought to 1–2 using concd HCl, whereupon a milky suspension formed which soon crystallized. The product was collected by suction, washed with H_2O and crystallized (EtOH–H_2O, 4:1) to yield **1a** as colorless leaflets; mp 158–159 °C (Lit.[3] mp 158–160 °C; Lit.[12] mp 153–155 °C).

N-Oxide **5** (0.621 g, 1.87 mmol) gave **1a** (0.390 g, 80%), *N*-oxide **11** (0.390 g, 1.08 mmol) gave **1a** (0.239 g, 85%), *N*-oxide **18** (0.210 g, 0.636 mmol) gave **1a** (0.117 g, 71%), and 4(1*H*)-quinolone **12** (0.400 g, 1.21 mmol) gave **1a** (0.250 g, 80%).

IR (ATR): 2926, 2853, 2400 (br), 1732 (br), 1590, 1548, 1451, 1404, 1342, 1266, 1177, 1151, 1120, 1022, 931 cm^{-1}.

^{1}H NMR (MeOH-d_4): δ = 8.26 (dd, *J* = 8.3, 1.5 Hz, 1 H_{arom}), 8.09 (br d, *J* = 8.6, 1 H_{arom}), 7.84 (ddd, *J* = 8.2, 7.1, 1.5 Hz, 1 H_{arom}), 7.50 (ddd, *J* = 8.3, 7.1, 1.0 Hz, 1 H_{arom}), 6.34 (s, 1 H, =CH), 2.92 (t, *J* = 7.7 Hz, 2 H, CH_2), 1.78 (quint, *J* = 7.7 Hz, 2 H, CH_2), 1.51–1.27 (m, 8 H, CH_2), 0.91 (t, *J* = 6.9 Hz, 3 H, CH_3).

^{13}C NMR (MeOH-d_4): δ = 174.0 (C=O, from HMBC), 156.5, 142.0, 133.7, 126.0, 125.9, 125.4, 116.8, 107.5, 32.9, 32.6, 30.4, 30.1, 28.9, 23.7, 14.4.

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(21) CCDC 616835-616836 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data.requecst/cif.