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Acid-catalyzed condensation of a series of 3-oxoalkanoic acid esters with aniline affords the corresponding 2-alkyl-4-quinolones in good yield. Treatment of these compounds with methyl iodide affords 2-alkyl-4-methoxyquinolines and 2-alkyl-*N*-methylquinolones. Three of the compounds are naturally-occurring alkaloids which are synthesized here for the first time.

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In recent years a number of 2-alkyl-4-quinolones (pseudans) have been isolated from microorganisms and from the family *Rutaceae* in the higher plants (1). The compounds have been isolated as NH and as *N*-Me derivatives with saturated (2-4) and unsaturated (5-7) alkyl groups at the 2-position. However, only a few 2-alkyl- and 2-aryl-4-methoxyquinolines are known to occur in nature (8). Cornforth and coworkers (9) isolated several 2-alkyl-4-hydroxyquinoline *N*-oxides from *Pseudomonas pyocyanea*, and these showed antagonist properties against dihydrostreptomycin. More recently, Tamura and coworkers (2) have reported that the fractions containing the quinolone alkaloids (10, 12, and 14; see Table) from *Evodia rutae-carpa* inhibit growth of the silkworm larva, *Brombyx mori* L. In this connection we have synthesized a series of 2-alkyl-4-methoxyquinolines and 2-alkyl-4-quinolones (Table 1) with unbranched side chains (5-13, 16). Of these, 7, 11, and 13 occur naturally, have been isolated from the aerial and root parts of *Ruta graveolens* (3,4) and are synthesized for the first time.

The synthetic route is shown in Scheme 1. Condensation of a long chain acid chloride with the carbanion derived from ethyl acetoacetate, followed by deacetylation using sodium ethoxide (10,11) gave the corresponding  $\beta$ -ketoester. These  $\beta$ -ketoesters were then condensed with aniline in the presence of *p*-toluene sulfonic acid and subsequently cyclized by boiling in diphenyl ether. Treatment with methyl iodide in DMF then gave a mixture of *N*-methylquinolone and 4-methoxyquinoline which were separated by preparative thick layer chromatography.

Scheme 1

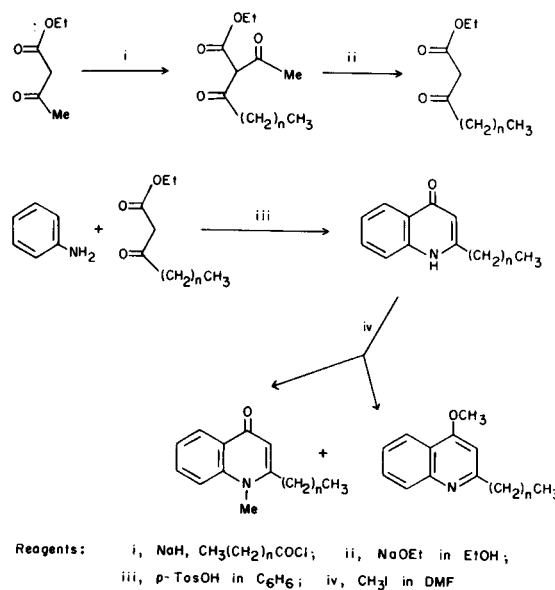


Table 1

Compound	R	n	Compound	n
(1)	H	5	(16)	5
(2)	Me	5	(17)	6
(3)	H	6	(18)	7
(4)	Me	6	(19)	8
(5)	H	7		
(6)	Me	7		
(7)	H	8		
(8)	Me	8		
(9)	H	9		
(10)	Me	10		
(11)	H	11		
(12)	Me	12		
(13)	H	13		
(14)	Me	14		
(15)	H	16		

The nature of the 2-alkyl side chains in the naturally occurring quinolones have been established mainly by interpretation of mass spectral fragmentation patterns (4-6,12). Mass spectra of our synthetic 4-quinolones showed the expected molecular ions and major peaks at *m/e* 159 and 172 due to  $\gamma$  and  $\alpha$ -hydrogen rearrangements, respectively. The *N*-methylquinolones similarly showed intense fragment peaks at *m/e* 173 and 186.

Table 2  
Proton NMR Spectra of Synthetic Quinolones and Methoxyquinolines

Compound	Solvent	NH	NMe	OMe	C <sub>5</sub> -H (d, J = 8 Hz)	C <sub>6,7</sub> -H (t, J = 8 Hz)	C <sub>8</sub> -H (d, J = 8 Hz)	3-H	Ar-CH <sub>2</sub> CH <sub>2</sub> (t, J = ca. 8 Hz, and m)	-(CH <sub>2</sub> ) <sub>n</sub> (m)	-CH <sub>3</sub> (t, J = 8 Hz)
2	CDCl <sub>3</sub>		3.67		8.30	7.60, 7.31	7.43	6.16	2.66, 1.60	1.26	0.87
3	DMSO-d <sub>6</sub>	11.50			8.04	7.60, 7.27	7.53	5.93	2.58, 1.66	1.29	0.85
4	CDCl <sub>3</sub>		3.68		8.30	7.60, 7.31	7.43	6.16	2.66, 1.60	1.26	0.86
5	DMSO-d <sub>6</sub>	11.51			8.05	7.61, 7.27	7.53	5.93	2.58, 1.66	1.29	0.84
6	CDCl <sub>3</sub>		3.71		8.42	7.61, 7.25	7.40	6.21	2.67, 1.66	1.26	0.87
7	DMSO-d <sub>6</sub>	11.40			8.04	7.60, 7.26	7.52	5.91	2.58, 1.68	1.24	0.84
8	DMSO-d <sub>6</sub>		3.71		8.43	7.61, 7.25	7.41	6.21	2.68, 1.66	1.26	0.87
9	DMSO-d <sub>6</sub>	11.46			8.03	7.60, 7.26	7.52	5.91	2.57, 1.66	1.23	0.84
11	DMSO-d <sub>6</sub>	11.47			8.02	7.58, 7.24	7.51	5.90	2.57, 1.66	1.22	0.84
13	DMSO-d <sub>6</sub>	11.47			8.03	7.59, 7.26	7.51	5.90	2.57, 1.64	1.22	0.95
15	DMSO-d <sub>6</sub>	11.46			8.03	7.58, 7.26	7.52	5.90	2.58, 1.63	1.21	0.94
16	CDCl <sub>3</sub>			3.99	8.11	7.93, 7.40	7.63	6.58	2.86, 1.79	1.35	0.86
17	CDCl <sub>3</sub>			3.99	8.11	7.96, 7.40	7.63	6.59	2.86, 1.79	1.36	0.86
18	CDCl <sub>3</sub>			4.00	8.12	7.95, 7.43	7.62	6.60	2.90, 1.79	1.26	0.86
19	CDCl <sub>3</sub>			4.00	8.12	7.95, 7.43	7.61	6.60	2.90, 1.79	1.25	0.87

## EXPERIMENTAL

Melting points were measured on a hot-stage apparatus, and are uncorrected. Proton nmr spectra were measured at 360 MHz on a Nicolet NT-360 spectrometer. Electronic absorption spectra were determined using a Cary 17 spectrophotometer, and infrared spectra were determined on a Beckmann IR 137. Mass spectra were measured at 70 eV (direct insertion probe) using a Finnegan 3200 spectrometer.

### General Method for Synthesis of $\beta$ -Ketoesters.

Ethyl acetoacetate (6.5 g, 0.05 mole) in dry ether (150 ml) was added dropwise to a mechanically stirred suspension of sodium hydride (2.4 g, 50% suspension in oil) in ether (300 ml). The mixture was stirred for 3 hours at room temperature, and to this was added decanoyl chloride (9.5 g, 0.05 mole) in dry ether (200 ml), dropwise, and the resulting mixture was stirred for 16 hours at room temperature. It was poured into water and the ether layer was dried over sodium sulfate. Evaporation of the solvent gave a yellowish brown oil (14 g), which was treated with sodium ethoxide (prepared from 1.2 g of metallic sodium in 200 ml of absolute ethanol) and stirred for 5 hours at room temperature. During this time the reaction was monitored by analytical thin layer chromatography (Merck silica gel G pre-coated sheets, 0.2 mm thickness). The mixture was poured into water and extracted with ethyl acetate which was then washed with dilute (2%) hydrochloric acid, dried over sodium sulfate, and evaporated to give a yellow oil, which was distilled under vacuum to give ethyl 3-oxononanoate as a colorless oil in 60% yield. Esters with  $n = 11, 13$  and  $16$  were purified by column chromatography on Merck silica. Using the above method,  $\beta$ -ketoesters with  $n = 5, 6, 7, 8, 9, 11, 13,$  and  $16$  were synthesized.

### General Method for Synthesis of 2-Alkyl-4-quinolones (2,5).

Freshly distilled aniline (320 mg, 0.003 mole), ethyl 3-oxononanoate (832 mg, 0.003 mole) and *p*-toluene sulfonic acid (50 mg) were heated together in benzene (50 ml) under reflux for 19 hours using a Dean-Stark apparatus. The solvent was removed by evaporation under vacuum to give a yellow oil which was then heated under reflux with diphenyl ether (15 ml) for 30 minutes. The final product was chromatographed on a silica column, eluting initially with petroleum ether (to remove diphenyl

ether) and then with methylene chloride containing 3% methanol, to give 2-nonyl-4-quinolone (515 mg, 55%). Proton nmr spectra of the quinolones synthesized are given in Table 2.

### General Method for Synthesis of *N*-Methyl-2-alkyl-4-quinolones.

2-Nonyl-4-quinolone **7** (1 g, 0.003 mole), potassium carbonate (0.97 g, 0.007 mole), and methyl iodide (1 g, 0.007 mole) in dry dimethylformamide (25 ml) were stirred together at room temperature for 2 days. The mixture was then poured into water and extracted into ethyl acetate, dried over sodium sulfate and finally evaporated to give a yellow oil. Separation on preparative thick layer plates (Merck GF 254 silica gel, 1.5 mm thickness; elution with methylene chloride/methanol, 8:1) gave a polar band containing *N*-methyl-2-nonyl-4-quinolone, **8**, (100 mg, 9.5%), and a mobile band containing 2-nonyl-4-methoxyquinoline, **19**, (516 mg, 49%). Proton nmr spectra of the quinolones and methoxyquinolines synthesized are given in Table 2.

### 2-Hexyl-4-quinolone (**1**) (13).

This compound had mp 140-141° [lit (13) 139°], yield 50%; ir (nujol): 1643, 1600, 1555, 1505, 1325 cm<sup>-1</sup>; uv (methanol): 315 nm ( $\epsilon$  10,600), 326 (10,000); ms: *m/e* (%), 229 (10), 172 (70), 159 (100).

Anal. Calcd. for C<sub>15</sub>H<sub>19</sub>NO: C, 78.60; H, 8.29; N, 6.11. Found: C, 79.04; H, 8.44; N, 6.14.

### *N*-Methyl-2-hexyl-4-quinolone (**2**).

This compound had mp 90-92°, yield 11%; ir (nujol): 1637, 1600, 1550 cm<sup>-1</sup>; uv (methanol): 335 nm ( $\epsilon$  15,600), 321 (15,300); ms: *m/e* (%) 243 (16), 186 (80), 173 (100).

Anal. Calcd. for C<sub>16</sub>H<sub>21</sub>NO: C, 79.01; H, 8.64; N, 5.76. Found: C, 78.76; H, 8.64; N, 5.64.

### 2-Hexyl-4-methoxyquinoline (**16**).

This compound was obtained as an oil in 46% yield, uv (methanol): 298 nm ( $\epsilon$  3,200), 310 (1,800).

Anal. Calcd. for C<sub>16</sub>H<sub>21</sub>NO: 243.1618. Found: C, 243.1620.

### 2-Heptyl-4-quinolone (**3**) (6).

This compound had 138-141° [lit (6) 142-143°], yield, 53%; ir (nujol): 1640, 1600 cm<sup>-1</sup>; uv (methanol): 315 nm ( $\epsilon$  10,100), 327 (10,000); ms: *m/e*

(%) 243 (10), 172 (70), 159 (100).

*Anal.* Calcd. for  $C_{16}H_{21}NO$ : C, 79.37; H, 8.94; N, 5.44. Found: C, 79.52; H, 8.81; N, 5.40.

*N*-Methyl-2-heptyl-4-quinolone (4).

This compound had mp 65-68°; yield 10%; ir (nujol): 1637, 1590, 1560, 1300, 1105  $cm^{-1}$ ; (methanol): 335 nm ( $\epsilon$  15,500), 323 (15,300); ms: *m/e* (%): 257 (18), 186 (80), 173 (100).

*Anal.* Calcd. for  $C_{17}H_{23}NO$ : C, 79.37; H, 8.94; N, 5.44. Found: C, 79.16; H, 9.05; N, 5.30.

2-Heptyl-4-methoxyquinoline (17).

This compound had mp 35-38°; yield 54%; uv (methanol): 298 nm ( $\epsilon$  3,400), 310 (1,900).

*Anal.* Calcd. for  $C_{17}H_{23}NO$ : C, 79.37; H, 8.94; N, 5.44. Found: C, 79.37; H, 9.00; N, 5.30.

2-Octyl-4-quinolone (5).

This compound had mp 128-130°, yield 50%; ir (nujol): 1640, 1600, 1550, 1500  $cm^{-1}$ ; uv (methanol): 315 nm ( $\epsilon$  10,700), 327 (10,100); ms: *m/e* (%): 257 (9), 172 (75), 159 (100).

*Anal.* Calcd. for  $C_{17}H_{23}NO$ : C, 79.38; H, 8.94; N, 5.44. Found: C, 79.38; H, 8.98; N, 5.44.

*N*-Methyl-2-octyl-4-quinolone (6).

This compound had 85-88°, yield, 9.7%; ir (nujol): 1637, 1580  $cm^{-1}$ ; ms: *m/e* (%): 271 (10), 186 (80), 173 (100).

*Anal.* Calcd. for  $C_{18}H_{25}NO$ : C, 79.70; H, 9.22; N, 5.16. Found: C, 79.97; H, 9.48; N, 4.88.

2-Octyl-4-methoxyquinoline (18).

This compound had mp 45-47°, yield, 47%; uv (methanol): 297 nm ( $\epsilon$  3,700), 310 (2,100).

*Anal.* Calcd. for  $C_{18}H_{25}NO$ : C, 79.70; H, 9.22; N, 5.16. Found: C, 79.51; H, 9.15; N, 5.04.

2-Nonyl-4-quinolone (7).

This compound had 129-132°, yield, 55%; ir (nujol): 1640, 1600, 1550, 1500  $cm^{-1}$ ; uv (methanol): 315 nm ( $\epsilon$  10,800), 326 (10,200); ms: *m/e* (%): 271 (10), 172 (76), 159 (100).

*Anal.* Calcd. for  $C_{18}H_{25}NO$ : C, 79.70; H, 9.22; N, 5.16. Found: C, 79.74; H, 9.28; N, 5.04.

*N*-Methyl-2-nonyl-4-quinolone (8) (4,7).

This compound had mp 74-76° [lit (4) 71-75°] yield 9.5%; ir (nujol): 1618, 1600, 1567, 1505, 1230, 1190, 1155, 1125, 1020, 980, 825  $cm^{-1}$ ; uv (methanol): 333 nm ( $\epsilon$  15,400), 321 (15,300); ms: *m/e* (%): 285 (6), 186 (80), 173 (100).

*Anal.* Calcd. for  $C_{19}H_{27}NO$ : C, 80.00; H, 9.47; N, 4.91. Found: C, 79.79; H, 9.45; N, 4.80.

2-Nonyl-4-methoxyquinoline (19).

This compound had mp 48-50°; uv (methanol): 297 nm ( $\epsilon$  4,500), 310 (2,500).

*Anal.* Calcd. for  $C_{19}H_{27}NO$ : C, 80.00; H, 9.47; N, 4.91. Found: C, 80.04; H, 9.55; N, 4.77.

2-Decyl-4-quinolone (9).

This compound had mp 134-135°, yield 52%; ir (nujol): 1640, 1600, 1555, 1505  $cm^{-1}$ ; uv (methanol): 315 nm ( $\epsilon$  10,800), 326 (10,200); ms: *m/e* (%): 285 (7), 172 (58), 159 (100).

*Anal.* Calcd. for  $C_{19}H_{27}NO$ : C, 80.00; H, 9.47; N, 4.91. Found: C, 80.01; H, 9.48; N, 4.73.

2-Dodecyl-4-quinolone (11).

This compound had mp 137°, yield 54%; ir (nujol): 1650, 1600, 1555, 1505  $cm^{-1}$ ; uv (methanol): 314 nm ( $\epsilon$  11,000), 327 (10,300); ms: *m/e* (%): 313 (10), 172 (76), 159 (100).

*Anal.* Calcd. for  $C_{21}H_{31}NO$ : C, 80.51; H, 9.90; N, 4.47. Found: C, 80.67; H, 9.97; N, 4.35.

2-Tetradecyl-4-quinolone (13).

This compound had mp 132-134°, yield 46%; ir (nujol): 1640, 1600, 1555, 1505  $cm^{-1}$ ; uv (methanol): 315 nm ( $\epsilon$  10,000), 327 (9,400); ms: *m/e* (%): 341 (9), 172 (68), 159 (100).

*Anal.* Calcd. for  $C_{23}H_{35}NO$ : C, 80.93; H, 10.26; N, 4.10. Found: C, 80.76; H, 10.42; N, 3.96.

2-Heptadecyl-4-quinolone (15).

This compound had mp 134-135°, yield 49%; ir (nujol): 1640, 1600, 1555, 1505  $cm^{-1}$ ; uv (methanol): 315 nm ( $\epsilon$  10,000), 327 (9,300); ms: *m/e* (%): 383 (6), 172 (70), 159 (100).

*Anal.* Calcd. for  $C_{26}H_{41}NO$ : C, 81.46; H, 10.70; N, 3.65. Found: C, 81.49; H, 10.75; N, 3.65.

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