Synthesis of Some Novel Polyoxygenated Quinolines

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Polyfunctional quinolines were obtained *via* thermal cyclization of phenylaminocrotonates and malonanilides and characterized by uv, ir, and ^1H and ^{13}C nmr spectra. Dehydration of a derivative of 5-hydroxymethyl-4(1*H*)-quinolone yielded a derivative of 5*H*-furo[2,3,4-*de*]quinoline, representing a novel tricyclic system.

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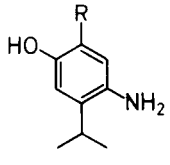
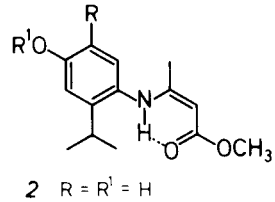
Quinolines bearing oxygen substituents at C2 or C4 are accessible *via* the classical Conrad-Limpach-Knorr approach; 2,4-dioxygenated quinolines can be obtained by cyclization of malonanilides [1,2]. Oxygenated quinolines constitute the nucleus of an abundant group of alkaloids of rutaceous plants [3], and are of considerable pharmaceutical interest, particularly as antibacterials [4,5]. This paper describes some novel quinolines of this type.

Condensation [6] of the aminophenol **1** [7] with methyl acetoacetate smoothly afforded the phenylaminocrotonate **2**, which upon heating to 250-260° yielded **3**. By the same route the aminophenol **4** [8] was converted to **6**. Acylation of the intermediate phenylaminocrotonates **2** and **5** gave **7** and **9**, cyclized to **8** and **10**, respectively.

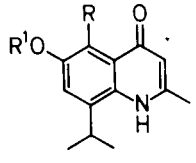
Scheme 1



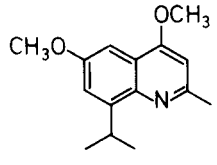
1 R = H
4 R = CH_3



2 R = R^1 = H
5 R = CH_3, R^1 = H
7 R = H, R^1 = $COCH_3$
9 R = CH_3, R^1 = $COCH_3$



3 R = R^1 = H
6 R = CH_3, R^1 = H
8 R = H, R^1 = $COCH_3$
10 R = CH_3, R^1 = $COCH_3$



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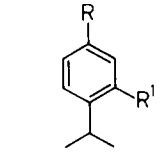
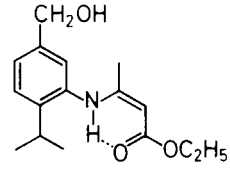
4-Hydroxyquinolines generally exist in the form of tautomeric 4(1*H*)-quinolones [9,10], as corroborated by the spectroscopic data for **3**, **6**, **8** and **10**. However, methylation of **3** with sodium hydride and methyl iodide gave the *O*-methylated product **11**. Although the ^1H chemical shifts of the heteroatom-bonded methyl groups (δ 3.91 and 4.00) do not clearly exclude *N*-methylation [11-13], their ^{13}C chemical shifts (δ 55.3 and 55.4) are only compatible with *O*-methyl ethers [13,14]. This conclusion is supported by the blue shift of the uv spectrum as compared to **3** [15], the absence of ir absorption above 1600 cm^{-1} [16,17], and the lack of *peri*-deshielding of H5 [18].

Similarly, the amine **14** gave **15**. The ^1H nmr spectrum of the latter (deuteriochloroform) showed the presence of a single isomer (olefinic proton at δ 4.70). The previously mentioned analogs **2**, **5**, **7** and **9** (Scheme 1) were likewise obtained as single isomers (olefinic proton at δ 4.47-4.65). Aminocrotonates generally exist as the hydrogen-bonded *Z* forms, at least in non-polar media [12,19-21], and the *Z* configuration of **15** was confirmed by nOe measurements. Thus irradiation of the olefinic methyl resonance caused 10% enhancement of the intensity of the olefinic signal; weaker nOe's were observed between the methyl group and the aromatic H6, the methylene group and the latter, and the amino proton and the isopropyl proton.

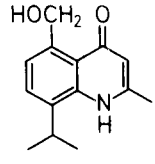
Scheme 2



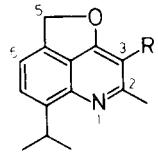
12 R = CHO, R^1 = NO_2
13 R = CH_2OH, R^1 = NO_2
14 R = CH_2OH, R^1 = NH_2



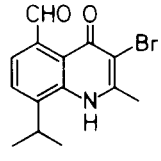
15



16



17 R = H
18 R = Br



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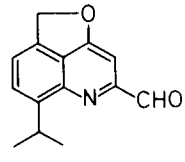

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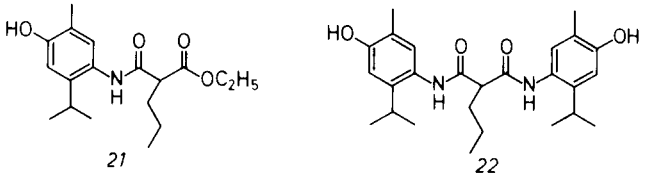
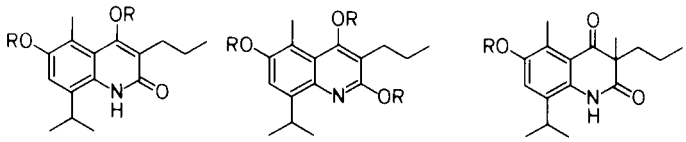
Thermal cyclization of **15** gave only a low yield of the expected 4(1*H*)-quinolone **16**, a large proportion of the product being dehydrated to **17**. The 5*H*-furo[2,3,4-*de*]quinoline **17** constitutes a novel tricyclic combination [22,23]. Formation of **17** was also observed on attempted vacuum distillation of **15**. Bromination of **17** with *N*-bromosuccinimide afforded **18** [24]. Treatment of the latter with an ad-

ditional equivalent of the reagent and chromatography on silica gel converted **18** into **19**. Selenium dioxide oxidation of **17** gave the aldehyde **20**. A characteristic feature of the ^{1}H nmr spectra of **17**, **18** and **20** is the presence of a four-bond coupling between the methylene group and H6 (J = 1.5 Hz); no such splitting is observed with **16**. Another characteristic property of these quinolines, also shared by **11**, is deshielding of the isopropyl methine proton to δ 4.05-4.20; in the 4(1*H*)-quinolones (Scheme 1 and 2) this signal appears at considerably higher field (δ 3.24-3.64).

Scheme 3



21 *22*



23 R = H
24 R = $COCH_3$

25 R = $COCH_3$

26 R = H
27 R = CH_3

Heating of the aminophenol **4** with a large excess of diethyl propylmalonate gave the monoanilide **21** along with a small amount of **22**. Cyclization of **21** in refluxing diphenyl ether gave the trioxygenated quinoline **23**. The expected [9,10] 2(1*H*)-quinolone structure is confirmed by spectral data, particularly by the uv and ^{13}C nmr spectra. Thus while the 4(1*H*)-quinolones shown in Schemes 1 and 2 give the C4 carbonyl resonances close to δ 180, the C2 carbonyl resonances of 2(1*H*)-quinolones appear around δ 165 (14,25,26). The uv absorption of 2(1*H*)-quinolones is equally characteristic [15,27]. Brief acetylation of **23** with acetic anhydride in pyridine yielded **24**, which on prolonged treatment with the reagent was converted to **25** [28]. The spectral properties of **24** are similar to those of **23**, whereas the quinoline structure of **25** is emphasized by the absence of strong ir absorption around 1600 cm^{-1}, diminished uv absorption, absence of ^{13}C resonances above δ 156 (other than three closely spaced acetyl carbonyl signals at δ 168-169), and the downfield shift of the isopropyl methine resonance, as pointed out above. Methylation of **23** with sodium hydride and methyl iodide gave the products of *C*-methylation, **26** and **27** [29].

EXPERIMENTAL

The nmr spectra were recorded on a Varian EM360L, Bruker AM250 or Bruker AM500 spectrometer. The ir and uv spectra were obtained on a Perkin Elmer model 781 and a Shimadzu model 265 spectrophotometer, respectively. Mass spectra were measured with a Finnigan model 4515B gc/ms system.

Column-chromatographic separations were carried out using Merck silica gel 60, 0.066-0.2 mm. The hplc separations were performed on a 1.6 × 25 cm column of Lichrosorb Si60 (7 μm) with solvent flow of 15 ml/minute (Waters model 590 pump) and absorbance detection at 330-350 nm, using an 80-μl flow cell with 2 mm light path (Waters Lambda-max spectrophotometer). Melting points were determined in capillaries and are corrected. Microanalyses were performed by Mr. P. Hansen, Chemical Laboratory II, University of Copenhagen.

3-(1-Methylethyl)-4-aminophenol **1**.

3-(1-Methylethyl)phenol was converted to the 4-nitroso derivative as described by Gilman *et al.* [7]. The crude product (20 g) was dissolved in a mixture of 130 ml of concentrated aqueous ammonia and 200 ml of water, and hydrogen sulfide was passed through the solution until an orange liquid and bulky, greyish precipitate was obtained, and then for an additional 15 minutes (total of 1 hour). The solution was filtered and the precipitate washed thoroughly with water and air-dried, yield 16 g (87%). The product was used for subsequent reactions without purification; a small sample recrystallized from ether melted at 170-172° (lit mp 175-176° [7]); ir (potassium bromide): 3100-2500 (m), 1655 (s), 1600 (m) cm^{-1}; ^{1}H nmr (DMSO-d_6): 60 MHz, δ 1.10 (d, J = 7 Hz, CH_3), 2.91 (h, J = 7 Hz, CH), 4.12 (br s, NH_2), 6.40 (m, aromatic), 8.27 (br s, OH).

2-Methyl-6-hydroxy-8-(1-methylethyl)-4(1*H*)-quinolone **3**.

A solution containing **1** (6 g), methyl acetoacetate (6 g) and 5 drops of glacial acetic acid in 12 ml of absolute methanol was boiled under reflux with 12 g of anhydrous calcium sulfate for 3.5 hours. Filtration and evaporation gave crude ester **2**, which was used for subsequent cyclization without purification; ^{1}H nmr (deuteriochloroform): δ 1.08 (d, J = 7 Hz, CH_3), 1.73 (s, CH_3), 3.0 (h, J = 7 Hz, CH), 3.65 (s, OCH_3), 4.62 (s, olefinic), 7.01 (m, aromatic), 6.30 and 9.73 (each br s, NH and OH).

The ester (3.6 g) was mixed with liquid paraffin (20 g) and the mixture heated for 10 minutes at 250-260° in a flask flushed with nitrogen. The mixture was chilled, an excess of petroleum ether added, and the product that precipitated overnight at 5° was collected by filtration, yield 3.1 g (99%) of brown crystals. Repeated recrystallization from methanol (charcoal) gave a colorless product that did not melt upon heating to 260°; ir (potassium bromide): 3500-2500 (m), 3270 (m), 3190 (m), 1605 (s), 1595 (s) cm^{-1}; uv (methanol): 347 (ε 9000), 337 (9700), 297 (3700), 286 (3800), 243 (34100), 215 (20100) nm; ^{1}H nmr (DMSO-d_6): 500 MHz, δ 1.25 (d, J = 6.7 Hz, CH_3), 2.39 (s, CH_3), 3.63 (h, J = 6.7 Hz, CH), 5.83 (br s, H3), 7.05 and 7.32 (each d, H = 2.6 Hz, H5 and H7), 9.40 and 10.25 (each br s, NH and OH); ^{13}C nmr (DMSO-d_6): 62.9 MHz, δ 19.6, 23.1, 25.7, 105.7, 107.0, 117.5, 126.6, 130.9, 138.1, 148.7, 153.1, 176.4.

Anal. Calcd. for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.72; H, 7.10; N, 6.26.

2-Methyl-4-amino-5-(1-methylethyl)phenol **4**.

The aminophenol was obtained in about 80% yield from 2-methyl-5-(1-methylethyl)phenol (carvacrol) as described by Kremers *et al.* [30] for 2-(1-methylethyl)-5-methylphenol, and was used without purification; a small sample recrystallized from acetone melted at 129-131° (lit mp 134° [8]); ir (potassium bromide): 3500-2350 (m), 3390 (s), 3320 (s), 1590 (m) cm^{-1}; ^{1}H nmr (DMSO-d_6): 60 MHz, δ 1.16 (d, J = 7 Hz, CH_3), 3.07 (h, J = 7 Hz, CH),

3.67 (br s, NH_2 and OH), 6.90 and 7.17 (each s, aromatic).

5-Methyl-6-hydroxy-8-(1-methylethyl)-4(1*H*)-quinolone **6**.

The reaction between **4** and methyl acetoacetate was carried out as described for **1**; the ester **5** was used for subsequent cyclization without purification; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.12 (d, J = 7 Hz, CH_3), 1.73 (s, CH_3), 2.10 (s, CH_3), 2.96 (h, J = 7 Hz, CH), 3.60 (s, OCH_3), 3.60 (br s, OH), 4.65 (s, olefinic), 6.80 and 6.88 (each s, aromatic), 9.97 (br s, NH).

Cyclization of **5** was carried out as described for **2**, yield about 80% (recrystallized from methanol), mp 270° dec; ir (potassium bromide): 3500-2500 (m), 3440 (s), 1620 (s), 1605 (s) cm^{-1}; uv (methanol): 335 (shoulder, ε 8600), 345 (9400), 299 (3700), 291 (3650), 245 (32800), 217 (18300) nm; ^{1}H nmr (DMSO-d_6): 500 MHz, δ 1.21 (d, J = 6.6 Hz, CH_3), 2.33 (s, CH_3), 2.65 (s, CH_3), 3.58 (h, J = 6.6 Hz, CH), 5.75 (br s, H3), 7.12 (s, H7), 9.14 and 9.91 (each s, NH and OH); ^{13}C nmr (DMSO-d_6): 125.6 MHz, δ 13.2, 19.2, 23.1, 25.5, 109.1, 116.5, 119.4, 124.5, 132.4, 133.7, 147.1, 150.3, 180.0.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.65; H, 7.60; N, 5.90.

2-Methyl-6-acetyloxy-8-(1-methylethyl)-4(1*H*)-quinolone **8**.

The ester **2** was acetylated by treatment with an excess of pyridine and acetic anhydride (1:1) overnight; evaporation of the solution gave the crude ester **7** which was used for subsequent cyclization without purification; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.15 (d, J = 7 Hz, CH_3), 1.77 (s, CH_3), 2.20 (s, $COCH_3$), 2.97 (h, J = 7 Hz, CH), 3.60 (s, OCH_3), 4.59 (s, olefinic), 6.83 (m, aromatic), 9.83 (br s, NH). The cyclization of **7** (7 g) was carried out as described for **2** and the product (6.2 g or 99%) recrystallized from acetone; mp 249-251°; ir (potassium bromide): 3200-2900 (br, s), 1765 (s), 1755 (s) cm^{-1}; uv (methanol): 332 (ε 10800), 320 (11800), 310 (shoulder, 8000), 291 (4450), 280 (shoulder, 3280), 238 (32100), 215 (23500) nm; ^{1}H nmr (DMSO-d_6): 250 MHz, δ 1.25 (d, J = 6.7 Hz, CH_3), 2.28 and 2.42 (each s, CH_3 and $COCH_3$), 3.67 (h, J = 6.7 Hz, CH), 5.93 (s, H3), 7.31 and 7.64 (each d, J = 2.7 Hz, H5 and H7), 10.50 (br s, NH); ^{13}C nmr (DMSO-d_6): 62.9 MHz, δ 19.3, 20.3, 22.5, 25.5, 107.6, 113.9, 121.6, 125.2, 134.6, 138.1, 145.5, 149.8, 168.9, 175.8.

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.36; H, 6.66; N, 5.34.

5-Methyl-6-acetyloxy-8-(1-methylethyl)-4(1*H*)-quinolone **10**.

The ester **5** was quantitatively converted to **9** as described for **2**; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.12 (d, J = 7 Hz, CH_3), 2.08 (s, CH_3), 2.17 (s, $COCH_3$), 2.93 (h, J = 7 Hz, CH), 3.60 (s, OCH_3), 4.47 (s, olefinic), 6.16 (br s, OH), 6.57 (s, aromatic), 9.58 (br s, NH). Cyclization of **9** as above gave **10** in about 90% yield, recrystallized from acetone/ethyl acetate; mp 212-213°, ir (potassium bromide): 3500-2300 (m), 1760 (s), 1640 (s), 1610 (s) cm^{-1}; uv (methanol): 337 (ε 9700), 324 (10900), 313 (shoulder, 7640), 293 (5300), 283 (shoulder, 4000), 239 (30600), 218 (22600) nm; ^{1}H nmr (deuteriochloroform): 500 MHz, δ 1.31 (d, J = 6.7 Hz, CH_3), 2.36 (s, CH_3 and $COCH_3$), 2.73 (s, CH_3), 3.24 (h, J = 6.7 Hz, CH), 6.01 (br s, H3), 7.11 (s, H7), 8.58 (br s, NH); ^{13}C nmr (deuteriochloroform): 125.7 MHz, δ 14.3, 20.1, 20.8, 22.7, 27.1, 111.2, 122.3, 124.4, 129.3, 133.3, 136.9, 144.7, 146.7, 169.7, 181.5.

Anal. Calcd. for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.42; H, 6.80; N, 5.10.

2-Methyl-4,6-dimethoxy-8-(1-methylethyl)quinoline **11**.

The quinolone **3** (17 g) was heated at 100° in 200 ml of DMF with 2.5 g of sodium hydride (80% suspension in mineral oil) for 30 minutes. After addition of 20 ml of methyl iodide the solution was evaporated and the residue chromatographed on silica gel with ethyl acetate/toluene (2:1) to give 6 g (76%) of the product, recrystallized from petroleum ether, mp 102.5-103°; ir (potassium bromide): 1620 (m), 1600 (s) cm^{-1}; uv (methanol): 330 (ε 3600), 317 (3200), 285 (shoulder, 5150), 276 (5900), 265 (shoulder, 5150), 235 (52000) nm; ^{1}H nmr (deuteriochloroform): 500 MHz, δ 1.32 (d, J = 6.7 Hz, CH_3), 2.66 (s, CH_3), 3.91 and 4.00 (each s, OCH_3), 4.20 (h, J = 6.7 Hz, CH), 6.60 (s, H3), 7.21 and 7.27 (each d, J = 2.0 Hz, aromatic); ^{13}C nmr (deuteriochloroform): 125.7 MHz, δ 23.5, 26.0, 27.2, 55.3, 55.4, 97.0, 100.5, 117.8, 120.4, 142.8, 148.5, 155.8, 156.6, 161.5.

Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.58; H, 8.06; N, 5.58.

3-Amino-4-(1-methylethyl)benzenemethanol **14**.

3-Nitro-4-(1-methylethyl)benzaldehyde **12** [31] was reduced with sodium borohydride in THF to give a practically quantitative yield of **13**, distilled under reduced pressure, bp about 130° at 0.5 mm Hg; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.27 (d, J = 6.8 Hz, CH_3), 2.50 (br s, OH), 3.37 (h, J = 6.8 Hz, CH), 4.70 (s, CH_2), 7.48 (m, H5 and H6), 7.68 (s, H2). The product was hydrogenated in THF at 2-3 atmospheres using 5% Pd/C and the resulting **14** used for subsequent reaction without purification; a sample recrystallized from ether melted at 68-69°; ir (potasssium bromide): 3420 (m), 3340 (m), 1635 (m), 1580 (s) cm^{-1}; ^{1}H nmr (deuteriochloroform): 60 MHz, δ 1.23 (d, J = 7 Hz, CH_3), 2.87 (h, J = 7 Hz, CH), 3.60 (br s, NH_2), 4.03 (s, CH_2), 5.72 (s, OH), 6.97 (s, H2), 6.87 and 7.13 (each d, J = 8 Hz, H5 and H6).

Ethyl (*Z*)-3-[2-(1-Methylethyl)-5-(hydroxymethyl)phenylamino]-butenoate **15**.

The ester was obtained from **14** and ethyl acetoacetate as described for **2**, and the product used for subsequent cyclization without purification; when left at 0°, the melt deposited large, yellowish crystals, mp 48.5-51°; ir (film): 3400 (br, m), 3260 (br, m), 1650 (s), 1620 (s), 1600 (s) cm^{-1}; ^{1}H nmr (deuteriochloroform): 250 MHz, δ 1.20 (d, J = 6.9 Hz CH_3), 1.28 (t, J = 7.1 Hz, CH_3), 1.82 (s, CH_3), 2.09 (br s, OH), 3.17 (h, J = 6.9 Hz, CH), 4.15 (q, J = 7.1 Hz, CH_2), 4.63 (s, CH_2), 4.70 (s, olefinic), 7.06 (d, J = 1.7 Hz, H6), 7.20 (dd, J = 1.7 Hz, and 8.0 Hz, H4), 7.28 (d, J = 8.0 Hz, H3), 10.11 (br s, NH); ^{13}C nmr (deuteriochloroform): 62.9 MHz, δ 14.6, 20.1, 23.2, 28.1, 58.7, 64.7, 85.1, 125.3, 126.0, 126.3, 136.7, 139.0, 144.0, 160.2, 170.7.

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.50; H, 8.44; N, 4.82.

2-Methyl-5-(hydroxymethyl)-8-(1-methylethyl)-4(1*H*)-quinolone **16** and 2-Methyl-8-(1-methylethyl)-5*H*-furo[2,3,4-*de*]quinoline **17**.

The phenylaminocrotonate **15** (3 g) in five times as much liquid paraffin was heated under nitrogen at 250-260° for 10 minutes, chilled, the mixture diluted with petroleum ether, and the precipitate chromatographed on silica gel using ethyl acetate/methanol (9:1) to give two fractions.

The fraction eluted first contained 0.5 g (22%) of **17**, recrystallized from ether, mp 136-137°; ir (potassium bromide): 1630 (s), 1620 (m), 1590 (m) cm^{-1}; uv (methanol): 294 (ε 8200), 231 (48800)

nm; ^{1}H nmr (deuteriochloroform): 250 MHz, δ 1.38 (d, J = 7.0 Hz, CH_3), 2.70 (s, CH_3), 4.10 (h, J = 7.0 Hz, CH), 5.73 (d, J = 1.5 Hz, CH_2), 6.56 (s, H3), 7.19 (dt, J = 7.2 Hz and 1.5 Hz, H6), 7.53 (d, J = 7.2 Hz, H7); ^{13}C nmr (deuteriochloroform): 62.9 MHz, δ 23.6, 26.7, 26.8, 78.0, 98.6, 115.3, 123.3, 127.3, 135.3, 143.5, 144.5, 163.0, 169.2; ms: (70 eV) m/z 213 (48%, M), 212 (45%, M-1), 198 (91%, M-15), 185 (100%, M-28), 171 (36%, M-42).

Anal. Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.58; H, 7.20; N, 6.51.

The second fraction contained 0.8 g (32%) of **16**, recrystallized from ethyl acetate, mp 184-185°; ir (potassium bromide): 3400-2750 (m), 3290 (m), 1630 (s), 1605 (s) cm^{-1}; uv (methanol): 334 (ε 10300), 321 (11600), 310 (shoulder, 8000), 295 (shoulder, 4600), 285 (shoulder, 2800), 255 (shoulder, 4200), 238 (27900), 220 (22300) nm; ^{1}H nmr (DMSO-d_6): 250 MHz, δ 1.25 (d, J = 6.7 Hz, CH_3), 2.42 (s, CH_3), 3.65 (h, J = 6.7 Hz, CH), 4.84 (s, CH_2), 5.75 (br s, OH), 6.00 (s, H3), 7.31 and 7.51 (each d, J = 7.7 Hz, H6 and H7), 10.37 (br s, NH); ^{13}C nmr (DMSO-d_6): 62.9 MHz, δ 19.5, 23.2, 25.9, 64.1, 110.5, 122.4, 122.9, 127.5, 135.5, 139.0, 140.3, 149.6, 180.0.

Anal. Calcd. for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.90; H, 7.58; N, 6.23.

2-Methyl-3-bromo-8-(1-methylethyl)-5*H*-furo[2,3,4-*de*]quinoline **18**.

A solution of **17** (1.35 g) in 25 ml of tetrachloromethane was refluxed with 1.2 g of NBS for 1 hour or until tlc showed complete conversion. Filtration and evaporation gave practically pure **18**, recrystallized from ether/petroleum ether, mp 137-138°; ir (potassium bromide): 1625 (s), 1610 (s), 1590 (s) cm^{-1}; uv (methanol): 321 (ε 4000), 307 (5800), 297 (6700), 237 (51000) nm; ^{1}H nmr (deuteriochloroform): 250 MHz, δ 1.37 (d, J = 7.0 Hz, CH_3), 2.83 (s, CH_3), 4.05 (h, J = 7.0 Hz, CH), 5.83 (d, J = 1.5 Hz, CH_2), 7.22 (dt, J = 7.2 Hz and 1.5 Hz, H6), 7.54 (d, J = 7.2 Hz, H7); ^{13}C nmr (deuteriochloroform): 62.9 MHz, δ 23.4, 26.1, 27.0, 79.0, 93.5, 116.5, 124.1, 127.5, 135.2, 142.5, 143.8, 160.6, 165.7; ms: (70 eV) m/z 291/293 (29%, M), 290/292 (23%, M-1), 276/278 (49%, M-15), 263/265 (100%, M-28), 249/251 (24%, M-42).

Anal. Calcd. for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79. Found: C, 57.41; H, 4.86; N, 4.70.

2-Methyl-3-bromo-4(1*H*)-oxo-8-(1-methylethyl)quinoline-5-carboxaldehyde **19**.

Treatment of **18** with NBS was carried out as described for **17**; filtration and evaporation followed by chromatography (silica gel, ethyl acetate/toluene, 2:1) gave **19** in 30-40% yield, recrystallized from ether, mp 217-220° dec; ir (potassium bromide): 3300 (s), 1665 (s), 1605 (s) cm^{-1}; uv (methanol): 338 (ε 8900), 253 (21300), 222 (23700) nm; ^{1}H nmr (DMSO-d_6): 250 MHz, δ 1.30 (d, J = 6.7 Hz, CH_3), 2.72 (s, CH_3), 3.78 (h, J = 6.7 Hz, CH), 7.43 and 7.72 (each d, J = 7.7 Hz, H6 and H7), 10.77 (s, CHO), 10.96 (br s, NH); ^{13}C nmr (DMSO-d_6): 62.9 MHz, δ 21.2, 22.9, 26.1, 107.0, 121.8, 123.0, 127.9, 136.2, 141.3, 149.8, 172.2, 193.8.

Anal. Calcd. for $C_{14}H_{14}BrNO_2$: C, 54.56; H, 4.58; N, 4.55. Found: C, 54.28; H, 4.81; N, 4.32.

8-(1-Methylethyl)-5*H*-furo[2,3,4-*de*]quinoline-2-carboxaldehyde **20**.

A solution of 0.45 g selenium dioxide in 16 ml of dioxane and 4 ml of water was added 0.8 g of **17**, and boiled for 2 hours. Filtration, evaporation and chromatography of the residue on silica gel with ethyl acetate/toluene (1:4) afforded 0.3 g (35%) of **20**, further purified by hplc using heptane/THF (10:1) and recrystallized from ether/pentane, mp 138-139.5°; ir (potassium bromide): 1710 (s), 1620 (m), 1610 (m), 1595 (m) cm^{-1}; uv (methanol): 355 (ε 1300), 317 (shoulder, 4200), 303 (6800), 296 (7200), 257 (12800), 250 (shoulder, 11600), 231 (47300) nm; ^{1}H nmr (deuteriochloroform): 250 MHz, δ 1.44 (d, J = 6.9 Hz, CH_3), 4.16 (h, J = 6.9 Hz, CH), 5.84 (d, J = 1.5 Hz, CH_2), 7.28 (s, H3), 7.40 (dt, J = 7.2 Hz and 1.5 Hz, H6), 7.67 (d, J = 7.2 Hz, H7), 10.18 (s, CHO); ^{13}C nmr (deuteriochloroform): 62.9 MHz, δ 23.4, 27.5, 78.7; 94.9, 118.8, 126.6, 128.4, 135.7, 144.7, 145.6, 156.9, 170.1, 194.3; ms: (70 eV) m/z 226 (46%, M-1), 212 (100%, M-15), 199 (91%, M-28), 185 (39%, M-42).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.76; N, 6.16. Found: C, 73.92; H, 5.70; N, 6.41.

Ethyl 2-[2-(1-Methylethyl)-4-hydroxy-5-methylphenylcarbamoyl]-butanoate **21**.

A solution of **4** (3 g) in 6 ml of diethyl propylmalonate was heated to boiling (220°) in a flask flushed with nitrogen, chilled, evaporated *in vacuo*, and the residue chromatographed on silica gel (ethyl acetate/toluene 1:4), to give 3.8 g (65%) of pure product. When the reaction was repeated with 10 g of **4**, the residue after evaporation was diluted with ether and left for crystallization at 5° to give, in several steps, a total of 12 g (62%) of the product, recrystallized from acetone/ether, mp 143.5-145°; ir (potassium bromide): 3410 (br, m), 3260 (br, m), 1715 (s), 1645 (s) cm^{-1}; ^{1}H nmr (deuteriochloroform): 500 MHz, δ 0.96 (t, J = 7.3 Hz, CH_3), 1.16 and 1.17 (each d, J = 6.8 Hz, CH_3), 1.32 (t, J = 7.0 Hz, CH_3), 1.46 (m, CH_2), 1.99 (m, CH_2), 2.11 (s, CH_3), 2.93 (h, J = 6.8 Hz, CH), 3.40 (t, J = 7.4 Hz, CH), 4.25 (q, J = 7.0 Hz, OCH_2), 5.89 and 8.37 (each br s, NH and OH), 6.66 and 7.24 (each s, aromatic); ^{13}C nmr (deuteriochloroform): 125.7 MHz, δ 13.6, 14.0, 15.3, 20.5, 22.9, 27.8, 34.0, 53.1, 61.6, 112.3, 121.9, 125.7, 127.7, 140.7, 152.7, 167.6, 173.1.

Anal. Calcd. for $C_{18}H_{27}NO_4$: C, 67.27; H, 8.46: N, 4.36. Found: C, 66.99; H, 8.67; N, 4.28.

N,N'-Bis[2-(1-methylethyl)-4-hydroxy-5-methylphenyl]-2-propylpropanediamide **22**.

The residue obtained after crystallization of crude **21** described above was chromatographed (silica gel, ethyl acetate/toluene, 1:4), to give 1.5 g (11%) of the diamide **22**, recrystallized from acetone/ether, mp 117-118°; ir (potassium bromide): 3340 (br m), 1655 (s) cm^{-1}; ^{1}H nmr (DMSO-d_6): 250 MHz, δ 0.96 (t, J = 7.3 Hz, CH_3), 1.03 and 1.09 (each d, J = 6.8 Hz, CH_3), 1.40 (s, J = 7.5 Hz, CH_2), 1.88 (q, J = 7.5 Hz, CH_2), 2.06 (s, CH_3), 2.98 (h, J = 6.8 Hz, CH), 3.44 (t, J = 7.5 Hz, CH), 6.70 and 6.92 (each s, aromatic), 9.16 and 9.24 (each br s, NH and OH); ^{13}C nmr (DMSO-d_6): 62.9 MHz, δ 13.8, 15.6, 20.4, 23.2, 23.4, 27.3, 33.2, 53.5, 111.4, 121.3, 125.5, 128.9, 141.7, 153.9, 169.4.

Anal. Calcd. for $C_{26}H_{36}N_2O_4$: C, 70.88; H, 8.23; N, 6.36. Found: C, 70.96; H, 8.29; N, 6.19.

3-Propyl-4,6-dihydroxy-5-methyl-8-(1-methylethyl)-2(1*H*)-quinolone **23**.

The ester **21** (11 g) was dissolved in 45 g of diphenyl ether and the solution was refluxed for 3.5 hours under nitrogen. The solution was chilled, diluted with petroleum ether, and the yellow mass obtained filtered off and washed thoroughly with petroleum ether to give 9 g (96%) of **23**, recrystallized from acetone/ether,

mp 214-217° dec; ir (potassium bromide): 3500-2600 (s), 1615 (s), 1595 (s), 1560 (s) cm^{-1}; uv (methanol containing traces of hydrogen chloride): 346 (ε 4300), 301 (7400), 290 (shoulder, 6600), 254 (35500), 216 (29100) nm; ^1H nmr (DMSO-d_6): 500 MHz, δ 0.80 (t, J = 7.0 Hz, CH_3), 1.02 (d, J = 6.8 Hz, CH_3), 1.31 (s, J = 7.0 Hz, CH_2), 2.43 (s and t, CH_3 and CH_2), 3.46 (h, J = 6.8 Hz, CH), 6.86 (s, H7), 8.90, 9.40 and 10.30 (each br s, NH and OH); ^{13}C nmr (DMSO-d_6): 125.7 MHz, δ 14.1, 14.3, 21.5, 23.1, 25.0, 25.4, 111.1, 115.3, 115.9, 117.1, 129.1, 131.5, 149.8, 160.5, 163.0.

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.83; H, 7.77; N, 4.90.

3-Propyl-4,6-diacetyloxy-5-methyl-8-(1-methylethyl)-2(1*H*-quinolone **24**.

Treatment of **23** (0.5 g) with 30 ml of a mixture of pyridine and acetic anhydride (1:1) for 12 hours at room temperature, followed by evaporation and crystallization of the residue from ethyl acetate, gave 0.33 g (50%) of **24**, mp 228-229°; ir (potassium bromide): 1760 (s), 1650 (s) cm^{-1}; uv (methanol): 350 (shoulder, ε 4400), 336 (5800), 325 (shoulder, 4600), 291 (8900), 281 (10400), 270 (shoulder, 7600), 251 (18200), 234 (26400), 209 (29300) nm; ^1H nmr (DMSO-d_6): 250 MHz, δ 0.93 (t, J = 7.3 Hz, CH_3), 1.18 (d, J = 6.6 Hz, CH_3), 1.49 (q, J = 7.3 Hz, CH_2), 2.28, 2.32 and 2.43 (each s, CH_3 and $COCH_3$, overlap CH_2 at *ca* 2.36), 3.66 (h, J = 6.6 Hz, CH), 7.20 (s, H7), 10.96 (br s, NH); ^{13}C nmr (DMSO-d_6): 62.9 MHz, δ 13.1, 14.0, 20.5, 20.7, 20.8, 22.7, 25.4, 26.6, 115.2, 121.5, 122.2, 125.1, 133.2, 144.2, 153.3, 161.8, 168.5, 169.2.

Anal. Calcd. for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.62; H, 7.20; N, 3.75.

2,4,6-Triacetyloxy-3-propyl-5-methyl-8-(1-methylethyl)quinoline **25**.

Acetylation of **23** with an excess of pyridine/acetic anhydride (1:1) during two days at room temperature gave **25** in practically quantitative yield. The material could also be obtained by overnight acetylation of the diacetate **24** under the same conditions, and was recrystallized from ether/petroleum ether, mp 108-109°; ir (potassium bromide): 1760 (s), 1750 (s), 1605 (m), 1585 (w) cm^{-1}; uv (methanol): 323 (shoulder, ε 1830), 290 (5150), 240 (57500), 210 (35200) nm; ^1H nmr (deuteriochloroform): 500 MHz, δ 0.98 (t, J = 7.3 Hz, CH_3), 1.30 (d, J = 6.9 Hz, CH_3), 1.60 (s, J = 7.3 Hz, CH_2), 2.36, 2.39, 2.42 and 2.47 (each s, CH_3 and $COCH_3$, overlap CH_2 at *ca* 2.47), 4.07 (h, J = 6.9 Hz, CH), 7.20 (s, aromatic); ^{13}C nmr (deuteriochloroform): 125.7 MHz, δ 13.6, 14.5, 20.9, 21.2, 21.3, 22.1, 23.2, 27.7, 120.3, 121.2, 121.4, 122.8, 143.2, 146.7, 147.6, 154.5, 155.8, 168.3, 168.7, 169.2.

Anal. Calcd. for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.62; H, 6.91; N, 3.40.

3,5-Dimethyl-3-propyl-6-hydroxy-8-(1-methylethyl)-2,4(1*H*)-quinolinedione **26** and 3,5-Dimethyl-3-propyl-6-methoxy-8-(1-methylethyl)-2,4(1*H*)-quinolinedione **27**.

A solution of 3.4 g of **23** in 100 ml of DMF was methylated in a procedure similar to that described for **3**, the solution evaporated, and the residue fractionated on silica gel with ethyl acetate/toluene (1:1) to give 2.0 g (56%) of **27**, eluted before 1.5 g (40%) of **26**. The yellow ketones were finally purified by hplc with hexane/THF (4:1).

The ketone **26** was recrystallized from ether/petroleum ether, mp 151-153°; ir (potassium bromide): 3400 (br, m), 3240 (br, m), 1690 (s), 1660 (s) cm^{-1}; uv (methanol): 376 (ε 3100), 270 (shoulder, 4000), 244 (25900) nm; ^1H nmr (deuteriochloroform): 500 MHz, δ 0.84 (t, J = 7.3 Hz, CH_3), 1.25 and 1.27 (each d, J = 6.7 Hz, CH_3, overlap CH_2 multiplet), 1.45 (s, CH_3), 1.84 (m, CH_2), 2.47 (s, CH_3), 2.98 (h, J = 6.7 Hz, CH), 5.85 (br s, OH), 6.99 (s, H7), 8.00 (br s, NH); ^{13}C nmr (deuteriochloroform): 62.9 MHz, δ 12.6, 14.3, 18.2, 19.2, 22.5, 22.7, 26.9, 40.7, 57.8, 118.4, 120.0, 124.0, 130.9, 131.9, 150.5, 174.0, 199.8.

Anal. Calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.63; H, 8.28; N, 4.58.

The ketone **27** was recrystallized from pentane, mp 116-119°; ir (potassium bromide): 3240 (br, m), 1690 (s), 1665 (s) cm^{-1}; uv (methanol): 370 (ε 3300), 267 (shoulder, 5500), 243 (30300) nm; ^1H nmr (deuteriochloroform): 500 MHz, δ 0.84 (t, J = 7.3 Hz, CH_3), 1.25 (m, CH_2), 1.30 and 1.32 (each d, J = 6.7 Hz, CH_3), 1.44 (s, CH_3), 1.82 (m, CH_2), 2.44 (s, CH_3), 3.14 (h, J = 6.7 Hz, CH), 3.85 (s, OCH_3), 7.00 (s, H7), 8.40 (br s, NH); ^{13}C nmr (deuteriochloroform): 62.9 MHz, δ 12.6, 14.3, 18.2, 18.9, 22.7, 22.8, 27.1, 40.6, 56.6, 57.8, 114.1, 120.3, 127.6, 130.7, 131.5, 154.1, 173.9, 199.9.

Anal. Calcd. for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.30; N, 4.62. Found: C, 71.47; H, 8.52; N, 4.44.

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