Supporting Information

for

ALTERNATIVE APPROACH TO THE 2-OXO-PYRANO[3,2-C]QUINOLINE CORE

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Single crystals were coated with a trace of Fomblin oil and quickly transferred to the goniometer head of a Bruker Quest diffractometer with kappa geometry, an I-μ-S microsource X-ray tube, laterally graded multilayer (Goebel) mirror single crystal for monochromatization, a Photon-III C14 area detector and an Oxford Cryosystems low temperature device. Examination and data collection were performed with Cu Kα radiation (λ = 1.54178 Å) at 150 K. Data were collected, reflections were indexed and processed, and the files scaled and corrected for absorption using APEX.¹ The space groups were assigned and the structures were solved by direct methods using XPREP within the SHELXTL suite of programs² and refined by full matrix least squares against F² with all reflections using Shelx12018³ using the graphical interface Shelxle⁴ H atoms were positioned geometrically and constrained to ride on their parent atoms. C-H bond distances were constrained to 0.95 Å for aromatic and alkene C-H moieties, and to 0.98 Å for CH₃ moieties, respectively. Methyl CH₃ were allowed to rotate but not to tip to best fit the experimental electron density. Uiso(H) values were set to a multiple of Ueq(C) with 1.5 for CH₃ and 1.2 for C-H units, respectively.

Both symmetry independent molecules exhibit whole molecule disorder, with molecules being disordered by a pseudo-mirror operation perpendicular to the b-axis. Major and minor disordered moieties were each restrained to have similar geometries (SAME command of ShelxI). Uij components of ADPs for disordered atoms closer to each other than 2.0 Å were restrained to be similar (SIMU 0.01 command of ShelxI). For some atoms that overlap with their symmetry created counterparts Uii components of ADPs were restrained to be similar for these pairs of atoms (despite original atoms being further than 2 Å apart). Subject to these conditions the occupancy ratio refined to 0.854(5) to 0.146(5) for the A and C moieties, and to 0.869(5) to 0.131(5) for the B and D moieties.
2. Synthesis and deacylation of selected N-acylTHQs

In our group, it was observed that deacylation of 4-oxo-N-acylTHQs under mild conditions (K$_2$CO$_3$, MeOH) occurs more readily than their N-acylTHQ counterparts. As shown in Scheme 4, the deacylation of the 4-oxo-N-acylTHQs 23a, b and d using K$_2$CO$_3$ in MeOH occurred in a short time with good yield (70-95%).

Scheme 4. Deacylation of N-acylTHQs

In contrast, compounds 21a, 21b and 21e were unreactive under these conditions. It is believed that the presence of the 4-keto group weakens the N-acyl bond which makes the 4-oxo-N-acylTHQ more susceptible to hydrolysis.
2.1 General method for reducing and acetylating quinolines.

A solution of the quinoline (2.50 mmol) in glacial acetic acid was cooled to below 30 °C and sodium NaCNBH₃ (3.00 mmol) added in small portions. The mixture was then allowed to stir at room temperature for 3 h, neutralized with saturated aqueous sodium bicarbonate then extracted with diethyl ether (3 × 15 mL). The combined extract was dried over sodium sulfate then concentrated under reduced pressure. The crude product was treated with acetic anhydride (10 mL) and the resulting solution heated at 90 – 100 °C for 4 h. After allowing the mixture to cool to room temperature it was diluted with water (50 mL) and solid sodium hydrogen carbonate was then added until no further evolution of carbon dioxide was observed. The mixture was then extracted with diethyl ether, and the organic extract dried over sodium sulfate then evaporated under vacuum. The crude product was purified by flash column chromatography (hexane: EtOAc – 3:1) to give the product.

1-Acetyl-1,2,3,4-tetrahydroquinoline (21a).⁵ Yield: (82%); yellow oil. ¹H NMR δ 1.94 (2H, m, H-3), 2.22 (3H, s, Ac), 2.71 (2H, t, J = 6.5 Hz, H-4), 3.78 (2H, t, J = 6.5 Hz, H-2), 7.13 (4H, m, H-5,6,7,8). ¹³C NMR: δ 23.1, 24.0, 26.8, 124.6, 125.1, 126.0, 128.4, 139.2, 170.2.

1-Acetyl-2-methyl-1,2,3,4-tetrahydroquinoline (21b).⁶ Yield: (82%); yellow oil. ¹H NMR δ 1.35 (3H, m, CH₃), 1.94 (2H, m, H-3), 2.22 (3H, s, Ac), 2.71 (2H, t, J = 6.5 Hz, H-4), 3.78 (2H, t, J = 6.5 Hz, H-2), 7.13 (4H, m, H-5,6,7,8). ¹³C NMR δ 23.1, 24.0, 26.8, 124.6, 125.1, 126.0, 128.4, 170.2.

1-Acetyl-1,2,3,4-tetrahydroquinoline-2-carbonitrile (21c).⁷ Yield: (55%); brown oil. ¹H NMR δ 2.06 (1H, m, H-3a), 2.23 (3H, s, Ac), 2.45-2.71 (2H, m, H-4), 2.83 (1H, m, H-3b), 5.69 (1H, t, J = 7.4 Hz, 2-H), 7.24 (4H, m, 5,6,7,8-H). ¹³C NMR δ 22.6, 25.2, 29.2, 42.1, 118.4, 125.3, 126.8, 127.2, 128.3, 132.8, 136.2, 169.8.

2.2 Synthesis of 1-Acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (21d)⁸

Methyl 1-acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylate (0.60 g, 2.54 mmol) was dissolved in methanol (15 mL) and potassium carbonate (2 molar equivalents) added. The mixture was heated at reflux for 2 h, concentrated under reduced pressure and the residue diluted with water (20 mL). The resulting solution was acidified with dilute HCl (5% v/v) until effervescence ceased, and extracted with EtOAc (3 × 15 mL). The combined organic layer was concentrated under reduced pressure to yield 21d (0.55 g, 100%).

2.3 Synthesis of 1-acetyl-N-(2-bromophenyl)-1,2,3,4-tetrahydroquinoline-2-carboxamide (21e)⁹

1-Acetyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (21d) (0.25 g, 1.14 mmol) was dissolved in dichloromethane (20.0 mL), and DCC (0.21 g, 1.20 mmol), DMAP (0.01 g, 0.1 mmol) and 2-bromoaniline
(0.21 g, 1.20 mmol) added. The mixture was stirred at room temperature overnight. The mixture was concentrated and the crude product was purified using column chromatography (hexane: EtOAc, 3:1) to give 21e as a viscous orange oil (0.29 g, 0.75 mmol, 66%). IR ν\textsubscript{max} 1436, 1520, 1658, 1695 cm\textsuperscript{-1}. \textsuperscript{1}H NMR: δ 2.18 (4H, m, Ac-H-15\texttextsubscript{a}), 2.43 (2H, m, H-15\texttextsubscript{b}, H-14\texttextsubscript{a}), 2.77 (1H, m, H-14\texttextsubscript{b}), 5.40 (1H, t, J = 9.7 Hz, H-8), 6.92 (1H, t, J = 8.5 Hz, H-12) 7.20 (5H, m, H-2,3,4,11,13), 7.49 (1H, d, J = 7.2 Hz, H-1), 8.28 (1H, d, J = 8.5 Hz, H-10), 8.89 (1H, bs, NH). \textsuperscript{13}C NMR δ 22.8, 26.0, 27.0, 56.9, 113.7, 122.1, 125.2, 125.6, 126.9, 127.8, 128.2, 123.3, 135.7, 137.0, 169.2, 171.9. With EDC as coupling agent (instead of DCC), yield is 80%.

2.4 General Procedure for Oxidation of N-Acyltetrahydroquinolines using Chromium Hexacarbonyl.

N-acetyl-1,2,3,4-tetrahydroquinoline (0.540 mmol), chromium hexacarbonyl (0.6 mol. equiv.) and tert-butyl hydroperoxide (70 wt.% in water, 13 mL per g) were added to a round bottom flask containing MeCN (67 mL per g). The mixture was heated at reflux for 24 - 48 h, then cooled to room temperature, filtered and concentrated \textit{in vacuo}. The residue was purified by column chromatography (hexane, EtOAc; 2:1 or 3:1).

1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline (23a).\textsuperscript{10} Yield: 65%; brown viscous oil. \textsuperscript{1}H NMR δ 2.35 (3H, s, Ac), 2.78 (2H, t, J = 7.2 Hz, H-3), 4.24 (2H, t, J = 7.2 Hz, H-2), 7.27 (1H, t, J = 9.7 Hz, H-6), 7.52 (2H, m, H-5,7), 7.98 (1H, d, J = 9.7 Hz, H-8). \textsuperscript{13}C NMR δ 23.1, 39.4, 43.9, 124.1, 125.4, 126.0, 127.5, 134.0, 143.9, 169.3, 193.9.

1-Acetyl-4-oxo-1,2,3,4-tetrahydroquinoline-2-carbonitrile (23c). Yield: (50%), a white solid; mp 123-124 °C. [Found: C, 67.64; H, 4.80; N, 13.14. C\textsubscript{12}H\textsubscript{10}N\textsubscript{2}O\textsubscript{2} requires C, 67.28; H, 4.70; N, 13.07%]. IR ν\textsubscript{max} 1487, 1666 cm\textsuperscript{-1}; \textsuperscript{1}H NMR δ 2.36 (3H, s, Ac), 3.08 (2H, m, H-3), 6.44 (1H, m, H-2), 7.39 (2H, m, H-5,6), 7.68 (1H, m, H-7), 8.08 (1H, d, J = 9.7 Hz, H-8). \textsuperscript{13}C NMR δ 22.6, 42.2, 43.3, 116.9, 124.7, 125.4, 126.0, 127.5, 134.0, 143.9, 169.3, 193.9.

1-Acetyl-N-(2-bromophenyl)-4-oxo-1,2,3,4-tetrahydroquinoline-2-carboxamide (23d). Yield (50%); white solid, mp 181-182 °C. [Found: C, 55.88; H, 3.66; N, 7.20. C\textsubscript{18}H\textsubscript{15}N\textsubscript{2}O\textsubscript{3}Br requires C, 55.83; H, 3.90; N, 7.23%]. IR ν\textsubscript{max} 1477, 1598, 1666 cm\textsuperscript{-1}; \textsuperscript{1}H NMR δ 2.51 (3H, s, Ac), 2.99 (1H, dd, J = 16.9, 8.4 Hz, H-15\texttextsubscript{a}), 3.47 (1H, d, J = 16.9 Hz, H-15\texttextsubscript{b}), 6.03 (1H, d, J = 8.4 Hz, H-10), 6.92 (1H, t, J = 8.5 Hz, H-12) 7.28 (3H, m, H-2,3,13), 7.55 (2H, m, H-4,11), 8.04 (2H, m, H-1,8), 8.44 (1H, s, NH). \textsuperscript{13}C NMR δ 23.1, 39.0, 56.0, 121.7, 124.0, 125.5, 126.5, 128.2, 128.4, 132.3, 134.5, 135.0, 140.3, 167.1, 171.4, 191.3.
2.5 Synthesis of acetyl-2-methyl-4-oxo-1,2,3,4-tetrahydroquinoline (23b).
Acyltetrahydroquinoline 21b (0.10 g, 0.528 mmol) was dissolved in MeOH (5.0 mL) and K₂CO₃ (0.15 g, 1.09 mmol) added. The mixture was heated at reflux for 3.5 h, filtered and washed with hot MeOH. The filtrate was then concentrated under reduced pressure, the residue diluted with water (5 mL), extracted with EtOAc (3 × 10 mL), and dried over sodium sulfate. Removal of the solvent under reduced pressure and purification by column chromatography (hexane: EtOAc – 3:1) gave N-acetyl-1,2,3,4-tetrahydroquinoline 22b as an orange oil. The N-acetyl-1,2,3,4-tetrahydroquinoline (0.11 g, 0.540 mmol), chromium hexacarbonyl (0.13 g, 0.6 mmol) and tert-butyl hydroperoxide (70 wt.% in water, 1.3 mL) were added to a round bottom flask containing MeCN (6.7 mL). The mixture was heated at reflux for 24 h, then cooled to room temperature, filtered and concentrated in vacuo. The residue was purified by column chromatography (hexane, EtOAc; 2:1). Yield: 90%; white solid; mp 120–122 °C. [Found: C, 70.79; H, 6.63; N, 7.00. C₁₂H₁₃NO₂ requires C, 70.92; H, 6.45; N, 6.89%]. IR ν max 1483, 1600, 1652, 1677 cm⁻¹; ¹H NMR δ 1.25 (3H, d, J = 8.4 Hz, -CH₃), 2.34 (3H, s, Ac), 2.60 (1H, d, J = 15.7 Hz, H-3a), 3.02 (1H, dd, J = 15.7, 8.4 Hz, H-3b), 5.38 (1H, m, H-2), 7.29 (1H, t, J = 9.7 Hz, H-6), 7.38 (1H, m, H-5), 7.57 (1H, t, J = 9.7 Hz, H-7), 8.02 (1H, d, J = 9.7 Hz, H-8). ¹³C NMR δ 17.9, 23.5, 45.1, 48.5, 125.2, 125.4, 125.6, 127.3, 134.3, 141.3, 169.4, 193.5.

2.6 General Procedure for Deacylation Reaction. N-Acyltetrahydroquinoline (0.10 g) was dissolved in MeOH (5.0 mL) and K₂CO₃ (2 molar equivalents) added. The mixture was heated at reflux, filtered and washed with hot MeOH. The filtrate was then concentrated under reduced pressure, the residue diluted with water (5 mL), extracted with EtOAc (3 × 10 mL), and dried over sodium sulfate. Removal of the solvent under reduced pressure and purification by column chromatography (hexane: EtOAc – 3:1) gave the product.

1,2,3,4-tetrahydroquinoline-2-carbonitrile (22c).¹¹ Reaction time: 3 h; yield: (80%); viscous yellow oil. ¹H NMR δ 2.18 (2H, m, H-3a,4a), 2.76 (1H, m, H-4b), 3.08 (1H, m, H-3b), 4.12 (1H, dd, J = 15.7, 8.4 Hz, H-3b), 6.51 (1H, d, J = 8.3, H-5), 6.73 (1H, m, H-7), 7.00 (2H, m, H-6,8). ¹³C NMR δ 23.6, 25.2, 42.7, 115.1, 119.4, 120.0, 120.6, 127.3, 129.5, 140.7.

4-Oxo-1,2,3,4-tetrahydroquinoline (24a). Reaction time: 1 h; yield: (95%); yellow solid; mp 45 – 47°C, [lit¹² 42 - 44°C]. ¹H NMR δ 2.70 (2H, m, H-3), 3.58 (2H, m, H-2), 4.57 (1H, bs, NH), 6.69 (2H, m, H-6,8), 7.31 (1H, m, H-7), 7.84 (1H, d, J = 8.0 Hz, H-5). ¹³C NMR δ 38.1, 42.2, 115.8, 117.9, 119.3, 127.6, 135.2, 152.1, 193.9.

2-Methyl-4-oxo-1,2,3,4-tetrahydroquinoline (24b).⁶ Reaction time: 45 min; yield: (92%); brown oil. ¹H NMR δ 1.32 (3H, d, J = 6.3 Hz, CH₃), 2.45 (1H, m, H-3a), 2.63 (1H, m, H-3b), 3.77 (1H, m, H-2), 4.38 (1H,
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bs, NH), 6.70 (2H, m, H-6,8), 7.29 (1H, m, H-7), 7.82 (1H, dd, J = 7.9, 1.6 Hz, H-5). 13C NMR δ 21.3, 45.8, 49.1, 115.7, 117.9, 118.8, 127.4, 135.2, 151.7, 194.1.

N-(2-Bromophenyl)-4-oxo-1,2,3,4-tetrahydroquinoline-2-carboxamide (24d). Reaction time: 45 min; yield: (70%); yellow solid. [Found: C, 55.75; H, 3.70; N, 7.90. C16H13N2O2Br requires C, 55.67; H, 3.80; N, 8.11%]; 1H NMR δ 3.08 (2H, d, J = 7.7 Hz, H-15), 4.46 (1H, td, J = 7.7, 2.7 Hz, H-8), 4.94 (1H, bs, NH), 6.83 (2H, m, H-10,12), 7.03 (1H, td, J = 7.9, 1.6 Hz, H-3), 7.37 (3H, m, H-1,2,11), 7.88 (1H, dd, J = 8.2, 1.3 Hz, H-4), 8.33 (1H, dd, J = 8.2, 1.5 Hz, H-5), 8.65 (1H, bs, NH). 13C NMR δ 40.4, 57.1, 115.7, 116.5, 119.4, 119.6, 121.9, 125.9, 127.7, 128.5, 132.3, 134.7, 135.8, 149.0, 169.0, 190.9.

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