Novel heterocyclic derivatives of pyrano[3,2-c]quinolinone from 3-[(1-ethyl-1,4-hydroxy-2-oxo-2H]-quinolin-3-yl)-3-oxopropanoic acid

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1. Introduction

4-Hydroxyquinolin-2(1H)-ones represents one of the most important class of heterocycles possessing wide spectrum of biological activities [1-8]. Heating N-ethylaniline with two equivalent diethylmalonate gave 4-hydroxy[3,2-c]quinolin-2(1H)-one (1) in one-pot double cyclocondensation process [9,10]. The pyranquinolinone 1 is a valuable intermediate for the synthesis of a variety of quinolin-2-ones bearing various functional groups in position 3 through pyrone ring opening, followed by decarboxylation [11,12]. In continuation to previous research on 4-hydroxyquinolin-2(1H)-ones [13-18], the present paper reports the synthesis of the new 3-[(1-ethyl-1,4-hydroxy-2-oxo-2H]-quinolin-3-yl)-3-oxo-propanoic acid (2) and the study of its chemical reactivity towards some ortho-hydroxyaldehydes and ortho-aminoaldehydes, in search of new quinolinone derivatives of potential biological activity.

2. Experimental

2.1. Instrumentation

Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were measured on a Perkin-Elmer 293 spectrophotometer (cm⁻¹), using KBr disks. 1H NMR spectra were measured on Gemini-200 (200 MHz) and/or Mercury-300BB (300MHz) spectrometers, using DMSO-d₆ as solvent and TMS (δ) as internal standard. Mass spectra were obtained using a GC-2010 Shimadzu Gas chromatography-mass spectrometer (70 eV) instrument. Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer.

2.2. 3-[(1-Ethyl-1,4-hydroxy-2-oxo-2H]-quinolin-3-yl)-3-oxopropanoic acid (2)

A solution of 6-ethyl-4-hydroxy-2H-pyrano[3,2-c]quinoline-2,5(6H)-dione (1) (25.7 g, 100 mmol) in 1N sodium hydroxide aqueous solution (250 mL) was warmed at 40-50 °C for 30 min (Scheme 1). The solution so formed was filtered and the clear solution was acidified with 10% HCl. The precipitate so formed was filtered, washed several times with water, air dried and crystallized from acetic acid to give 2 as yellow crystals. M.p.: 226 °C. Yield: 21 g, 76%. IR (KBr, cm⁻¹): 3910 (C=Ocarboxy), 1769 (C=Oquinolinone), 13.41 (br, 1H exchangeable with D₂O), 1613 (C=Oketone). 1H NMR spectra were obtained using a GC-2010 Shimadzu Gas chromatography-mass spectrometer (70 eV) instrument. Elemental microanalyses were performed on a Perkin–Elmer CHN-2400 analyzer.

2.3. 2-[(1-Ethyl-1,4-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl)carbonyl]-3-(2-hydroxy phenyl) prop-2-enoic acid (3)

A mixture of β-ketoacid (0.55 g, 2 mmol) and salicylaldehyde (0.21 mL, 2 mmol), in glacial acetic acid (10
mL) and freshly fused sodium acetate (0.2 g), was heated at reflux for 3 h (Scheme 2). The yellow crystals obtained after cooling were filtered and recrystallized from acetic acid to give 3 as yellow crystals. M.p.: 256 °C. Yield: 0.37 g, 49%. IR (KBr, cm⁻¹): 3429 (OH), 3045 (CH₂(α)), 2975, 2890 (CH₃, CH₂), 1724 (C=O(carbonyl)), 1642 (C=O(quinoline)), 1603 (C=O(hetero)). ¹H NMR (DMSO-d₆, δ): 1.14 (t, 3H, J=6.8 Hz, CH₃), 4.17 (q, 2H, J=6.8 Hz, CH₂), 5.70 (s, 1H, CH methine), 7.36–7.88 (m, 6H, Ar-H), 8.15–8.18 (m, 2H, Ar-H), 11.72 (br, 1H exchangeable with D₂O, OH(salicylaldehyde)), 14.69 (br, 2H exchangeable with D₂O, OH(quinoline) and OH(carbonyl)). Anal. Calcd for C₂₁H₁₇NO₆ (379.36): C, 66.49; H, 1.13; N, 3.69%. Found: C, 66.42; H, 4.36; N, 3.46%.

2.5. 2-[1-Ethyl-4-hydroxy-2-oxo-1,2-dihydro-quinolin-3-yl(carbonyl)]-3-(1-hydroxy naphthalen-2-yl)-prop-2-enoic acid (6)

A mixture of β-ketocacid 2 (0.55 g, 2 mmol) and 2-hydroxy-1-naphthaldehyde (0.344 g, 2 mmol), in glacial acetic acid (10 mL) and freshly fused sodium acetate (0.2 g), was heated under reflux for 4 h (Scheme 3). The yellow crystals obtained after cooling were filtered and recrystallized from acetic acid to give 6 as yellow crystals. M.p.: 280 °C. Yield: 0.39 g, 45%. IR (KBr, cm⁻¹): 3496, 3350, 3200 (30H), 3063 (CH(α)), 2979, 2885 (CH₃, CH₂), 1719 (C=O(carbonyl)), 1617 (C=O(quinoline) and C=O(hetero)). ¹H NMR (DMSO-d₆, δ): 1.13 (t, 3H, J=7.8 Hz, CH₃), 4.14 (q, 2H, J=7.8 Hz, CH₂), 5.60 (s, 1H, CH methine), 7.33–8.10 (m, 8H, Ar-H), 8.58–9.11 (m, 2H, CH methine), 10.81 (br, 1H exchangeable with D₂O, OH(naphthalene)), 13.50 (br, 2H exchangeable with D₂O, OH(quinoline) and OH(carbonyl)). Anal. Calcd for C₂₅H₂₀N₂O₆ (493.43): C, 69.92; H, 4.46; N, 3.26%. Found: C, 69.60; H, 4.66; N, 3.08%.

2.4. 6-Ethyl-3-(2-hydrobenzylidene)-2H-pyran-3,2-c/quinoline-2,4,5(3H,6H)trione (4)

2.4.1. Method A

Compound 3 (0.379 g, 1 mmol) in concentrated H₂SO₄ (5 mL) was heated on a water bath for 2 h. After cooling, the reaction mixture was poured onto ice/water, the precipitate so formed was filtered, washed several times with H₂O and crystallized from DMF to give 4 as yellow crystals. M.p.: 240–241 °C. Yield: 0.23 g, 64% (Scheme 2).

2.4.2. Method B

A mixture of compound 1 (0.514 g, 2 mmol) and salicylaldehyde (0.21 mL, 2 mmol), in glacial acetic acid (10 mL) and freshly fused sodium acetate (0.2 g), was heated at reflux for 3 h, the yellow crystals obtained after cooling were filtered and recrystallized from DMF to give 4 as yellow crystals (Scheme 2). M.p.: 241 °C. Yield: 0.41 g, 57%. IR (KBr, cm⁻¹): 3430 (OH), 3044 (CH₂(α)), 2976, 2920 (CH₃, CH₂), 1725 (OC=O), 1642 (C=O(quinoline), 1611 (C=O(hetero)). ¹H NMR (DMSO-d₆, δ): 1.13 (t, 3H, J=6.9 Hz, CH₃), 4.13 (q, 2H, J=6.9 Hz, CH₂), 7.29–7.43 (m, 4H, Ar-H), 7.54 (d, 1H, J=8.4 Hz, Ar-H), 7.69 (t, 1H, J=7.5 Hz, Ar₆), 7.78–8.82 (m, 2H, Ar-H), 8.13 (s, 1H, CH methine). ¹C NMR (DMSO-d₆, δ): 124 (CH₃), 36.2 (CH₃), 106.5 (C₆), 114.8 (C₆), 116.1 (C₆), 118.3 (C₆), 120.5 (C₆), 122.1 (C₆), 125.6 (C₆), 125.3 (C₆), 129.1 (C₆), 130.1 (C₆), 132.5 (C₆), 135.2 (C₆), 139.0 (C₆), 140.4 (CH methine), 153.3 (C₁₀ as C₆), 1574 (C₆), 168.9 (C₆) as C=O). 173.3 (C₆ as C=O), 201.5 (C₆ as C=O). M/z (relative intensity): 362 (M⁺+1, 28), 361 (M⁺, 100), 332 (22), 304 (11), 288 (67), 261 (11), 188 (25), 160 (8), 132 (10), 118 (6), 101 (3), 77 (2). Anal. Calcd for C₂₅H₂₀N₂O₆ (361.35): C, 69.80; H, 4.18; N, 3.88%. Found: C, 69.43; H, 4.42; N, 3.79%.

2.6. 2-Ethyl-3-{[2-hydroxy naphthalen-1-yl](methyldiene)}-2H-pyran-3,2-c/quinoline-2,4,5(3H,6H)trione (7)

2.6.1. Method A

Compound 6 (0.429 g, 1 mmol) in concentrated H₂SO₄ (5 mL) was heated on a water bath for 2 h. After cooling the reaction mixture was poured onto ice/water, the precipitate so formed was filtered, washed several times with H₂O and crystallized from acetic acid to give 7 as yellow crystals. M.p.: 177 °C. Yield: 0.28 g, 68% (Scheme 3).

2.6.2. Method B

A mixture of compound 1 (0.514 g, 2 mmol) and 2-hydroxy-1-naphthaldehyde (0.344 g, 2 mmol), in glacial acetic acid (10 mL) and freshly fused sodium acetate (0.2 g), was heated under reflux for 4 h. The yellow crystals obtained after cooling were filtered and recrystallized from DMF to give 7 as white crystals (Scheme 3). M.p.: 177 °C. Yield: 0.46 g, 56%. IR (KBr, cm⁻¹): 3432 (OH), 3055 (CH₂(α)), 2976, 2927 (CH₃, CH₂), 1715 (OC=O), 1673 (C=O(quinoline), 1619 (C=O(hetero)). ¹H NMR (DMSO-d₆, δ): 1.24 (t, 3H, J=7.4 Hz, CH₃), 4.36 (q, 2H, J=7.4 Hz, CH₂), 7.48–7.99 (m, 10H, Ar-H), 8.23 (s, 1H, CH methine), 14.45 (br, 1H exchangeable with D₂O, OH(naphthalene)). Anal. Calcd for C₂₅H₂₀N₂O₆ (411.41): C, 72.99; H, 4.16; N, 3.40%. Found: C, 72.52; H, 4.08; N, 3.28%.
2.7. 6-Ethyl-3-(4-hydroxy-1-phenyl-2-oxo-1,2-dihydroquinolin-3-yl)methylidene)-2H-pyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (10)

A mixture of β-ketoacid 2 (0.275 g, 1 mmol) and 4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxaldehyde (8) (0.265 g, 1 mmol) in DMF (5 mL) containing few drops of pipерidine was heated at reflux for 2 h. The solid deposited after cooling was filtered and recrystallized from DMF to give 10 as yellow crystals (Scheme 4). M.p.: 215 °C. Yield: 0.20 g, 47%. IR (KBr, cm⁻¹): 3445 (OH), 3058 (CH arom.), 2934, 2859 (CH₂, CH₃), 1660 (C=O). Anal. Calcd for C₂₃H₁₅N₃O₆ (429.38): C, 64.33; H, 3.51; N, 9.79%. Found: C, 71.32; H, 3.87; N, 5.90%.

2.8. 6-Ethyl-3-[(2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrroloidin-3-yl)methylidene]-2H-pyrano[3,2-c]quinoline-2,4,5(3H,6H)-trione (11)

A mixture of β-ketoacid 2 (0.275 g, 1 mmol) and 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-carboxaldehyde (9) (0.19 g, 1 mmol) in DMF (5 mL) containing few drops of pipерidine was heated at reflux for 2 h. The solid deposited after cooling was filtered and recrystallized from DMF to give 11 as orange crystals (Scheme 4). M.p.: 215 °C. Yield: 0.20 g, 47%. IR (KBr, cm⁻¹): 3407 (OH), 3060 (CH arom.), 2978, 2927 (CH₃, CH₂), 1732 (OCO=O), 1671 (C=O), 1623 (C=O). NMR (DMSO-d₆, δ): 1.29 (t, 3H, CH₃), 3.49 (q, 2H, CH₂), 7.30-7.92 (m, 7H, Ar-H), 8.02 (s, 1H, CH methine), 8.08 (d, 1H, J=7.2 Hz, Ar-H). 14.14 (bs, 1H exchangeable with D₂O, OH). Anal. Calcd for C₂₇H₂₀N₂O₆ (468.46): C, 69.22; H, 4.30, N, 5.98%. Found: C, 67.24; H, 3.65; N, 6.20%.

For compound 14b: M.p.: 213 °C. Yield: 43-51%. IR (KBr, cm⁻¹): 3438 (NH₁), 3076 (CH arom.), 2972, 2929 (CH₃, CH₂), 1736 (OCO=O), 1661 (C=O). NMR (DMSO-d₆, δ): 1.31 (t, 3H, CH₃), 3.76 (br, 2H, CH₂), 4.37 (q, 2H, CH₂), 5.18 (m, 2H, CH=CH₂), 6.15 (m, 1H, CH=CH₂), 7.25-7.94 (m, 7H, Ar-H), 8.04 (s, 1H, CH methine), 8.71 (br, 1H exchangeable with D₂O, 1H of NH₁). 9.92 (br, 1H exchangeable with D₂O, 1H of NH₁). Anal. Calcd for C₁₉H₁₇N₂O₆ (486.46): C, 69.22; H, 4.30, N, 5.98%. Found: C, 69.02; H, 4.07; N, 5.72%.

3. Results and Discussion

In the course of the present work, we found, warming pyranooquinoline (1) in sodium hydroxide solution (1N) at 40-50 °C for 30 min. afforded the novel 3-(1-ethyl-4-hydroxy-2-oxo-2H-1,10-quinolin-3-yl)-3-propanoic acid (2) in 76% yield (Scheme 1). Structure of compound 2 was confirmed from its correct elemental analysis and spectral data. The 1H NMR spectrum showed a characteristic singlet signal at δ 5.56 ppm attributed to the active methylene protons, in addition to two exchangeable signals at δ 12.02 and 13.41 ppm assigned to 2H protons. The mass spectrum of compound 2 did not show the molecular ion peak at m/z 275 but showed a peak at m/z 257 which was in agreement with its molecular mass after loss of one molecule of water, and the base peak at m/z 229.

Some new quinoline derivatives were prepared from the reaction of β-ketoacid 2 with different ortho-hydroxyalkyldehydes and ortho-aminoalkdehydes. Thus, condensation of 2 with salicylaldehyde in glacial acetic acid containing freshly fused sodium acetate gave the Knoevenagel condensation product 3 (Scheme 2). The 1H NMR spectrum of compound 3 revealed the presence of two exchangeable signals at δ 11.71 (OHsalicylaldehyde) and 14.69 ppm (OHquinolinone and OHcarboxy). Compound 3 can undergo intramolecular cyclization in the presence of concentrated H₂SO₄ leading to either pyranooquinoline derivative 4 or coumarine derivative 5 (Scheme 2). The product obtained from this reaction was found to be identical (the same mp, mixed mp and identical spectra) with the product obtained from the reaction of pyranooquinoline 1 and salicylaldehyde, in glacial acetic acid and freshly fused sodium acetate. Therefore, cyclization of compound 3 in concentrated
H$_2$SO$_4$ yielded 6-ethyl-3-(2-hydroxybenzylidene)pyrano[3,2-c]quinoline-2,4,5-(3H,6H)-trione (4) not the coumarine derivative 5. The reaction of pyranooquinoline 1 with salicylaldehyde proceeds through the tautomeric 1,3-dione form, which in turn possesses an active methylene group. The IR spectrum of compound 4 showed characteristic absorption bands at 3450 (OH), 1725 (C=O) and 1642 cm$^{-1}$ (C=O). The methine proton observed at $\delta$ 8.13 ppm in the $^1$H NMR spectrum, while the methine carbon appeared at $\delta$ 140.4 ppm in the $^1$C NMR spectrum. The structure of compound 4 was further deduced from its mass spectrum which revealed the molecular peak at m/z 361 as the base peak, which is coincident with the formula weight (361.35) and support the identity of the structure.

Similarly, condensation of $\beta$-ketocacid 2 with 2-hydroxy-1-naphthaldehyde, in glacial acetic acid and freshly fused sodium acetate, afforded the Knoevenagel condensation product 6 which underwent intramolecular cyclization in the presence of concentrated H$_2$SO$_4$ to yield 6-ethyl-3-(2-hydroxy-1-naphthylidyne)pyrano[3,2-c]quinoline-2,4,5-(3H,6H)-trione (7). Compound 7 was also obtained from the condensation of 4-hydroxypyranooquinoline derivative 1 with 2-hydroxy-1-naphthaldehyde (Scheme 3).

Interestingly, condensation of $\beta$-ketocacid 2 with 4-hydroxy-2-oxo-1-phenyl-1,2-dihydroquinoline-3-carboxaldehyde (8) [19] and 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxaldehyde (9) [20] in boiling DMF, containing few drops of piperidine, furnished directly the cyclized products, 6-ethyl-3-[[4-(hydroxy-1-phenyl-2-oxo-1,2-dihydroquinolin-3-yl)methylhydine-2H-pyran][3,2-c]quinoline-2,4,5-(3H,6H)-trione 10 and 6-ethyl-3-[[2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidin-3-ylmethylhydine-2H-pyran][3,2-c]quinoline-2,4,5-(3H,6H)-trione 11, respectively, in one step reactions. Under these reaction conditions the Knoevenagel condensation intermediates were not isolated, but underwent intramolecular nucleophilic lactonization to form the cyclized products 10 and 11 (Scheme 4).

On the other hand, when $\beta$-ketocacid 2 was subjected to react with 2-amino-chromone-3-carboxaldehyde (12a) [21] and its 8-allyl analog 12b, [22] in boiling DMF containing few drops of piperidine as a catalyst, pyranooquinoline derivatives 14a, b or chromonopyridine derivatives 15a, b were expected as products for this reaction (Scheme 5). Herein again, the reaction proceeds initially via Knoevenagel condensation to produce the intermediates 13a and 13b, respectively. These intermediates can undergo intramolecular nucleophilic lactonization forming pyranooquinoline derivatives 14a, b or lactonization forming chromonopyridine derivatives 15a, b. The elemental and mass analyses of the products are not differential because both structures are isomers. The $^1$H NMR spectra were used to distinguish the structure of the products. The signals assigned to the OH and NH protons of compounds 15a, b were not observed in the spectra, and therefore structures 15a, b were excluded. The spectra of compounds 14a, b showed characteristic exchangeable signals attributed to the NH$_2$ protons. Compounds 14a and 14b were also obtained from the reaction of pyranooquinoline 1 with 2-aminochromone-3-carboxaldehydes (12a, b) in glacial acetic acid and freshly fused sodium acetate.

In continuation to our previous work on the chemistry of chromone-3-carbonitrile [23], we found that 2-amino-3-formylchromone is chemically equivalent to chromone-3-carbonitrile under certain nucleophilic conditions. Thus, treating $\beta$-ketocacid 2 with chromone-3-carbonitriles (16a, b) [21,22] in boiling DMF containing few drops of piperidine afforded compounds 14a, b. Formation of compounds 14a, b from carbonitriles 16a, b was accomplished via a tandem cyclization reaction through Michael addition of the active methylene group in compound 2 to the $\gamma$-pyrone moiety of carbonitriles 16a, b producing intermediates A (non-isolable). The base-mediated retro-Michael reaction of A gave the open chain intermediates B (non-isolable), the attack of hydroxyl group onto the nitrile function gave intermediates C (non-isolable) which underwent lactonization leading to 14a, b. The transformation of 16 into 14 can be regarded as a domino "Michael / retro-Michael / nitrile-addition / lactonization" as shown in Scheme 6 [24].

4. Conclusion

We have developed a new and convenient method for the synthesis of novel pyranoo[3,2-c]quinolodine derivatives via condensation reactions of 3-(1-ethyl-4-hydroxy-2-oxo-2H-quinolin-3-yl)-3-oxopropanoic acid with some ortho-hydroxylaldehydes and ortho-alkoaldehydes.

References