Substituted quinolinones. Part 23. Synthesis of 6-ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carboxaldehyde and its chemical behavior towards hydroxylamine hydrochloride

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Abstract

The synthesis of novel 6-ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carboxaldehyde is described *via Vilsmeier-Haack* reaction of 3-acetyl-1-ethyl-4-hydroxyquinolin-2(1*H*)-one. The reaction of titled aldehyde with hydroxylamine hydrochloride, under different conditions, revealed its distinctive chemical behavior and a variety of products were obtained. This study revealed existence of ring-opening ring-closure (RORC) on treatment with hydroxylamine hydrochloride in both acetic acid and/or ethanolic potassium hydroxide. The structure of the new products was deduced on basis of their analytical and spectral data.

Keywords: Pyrano[3,2-*c*]quinoline, Vilsmeier-Haack reaction, hydroxylamine, RORC

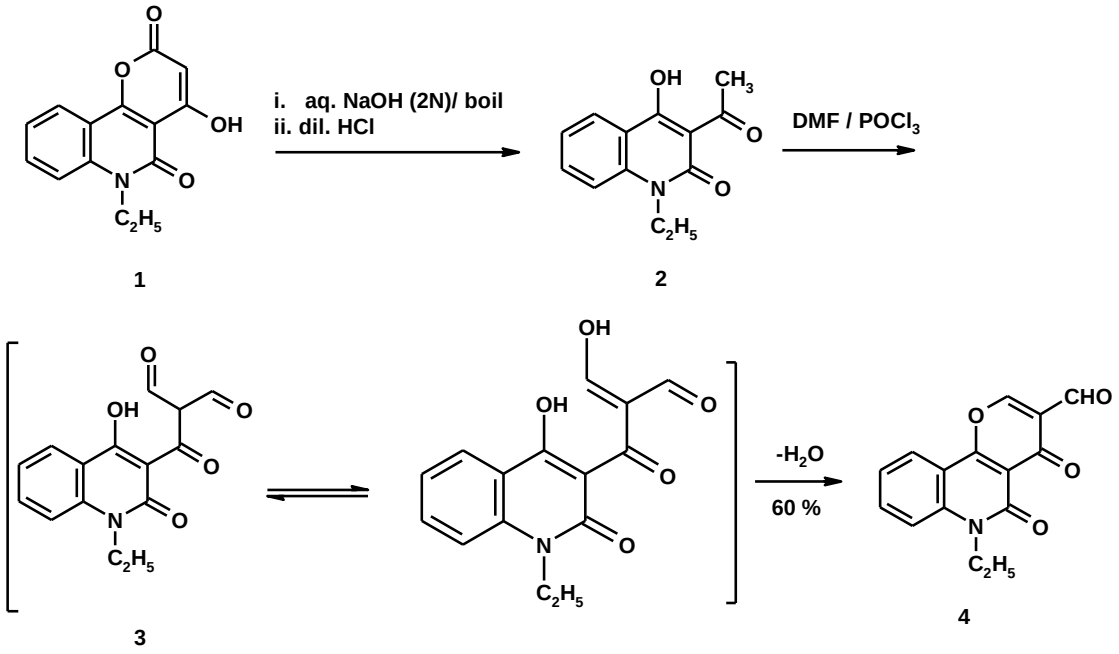
Introduction

4-Hydroxyquinolin-2(1*H*)-ones and their derivatives represent a class of heterocyclic compounds that have been associated with several biological activities.[1-6] The biological importance of quinolinones particularly fused heterocyclic derivatives of quinolinone inspired a rigorous synthetic research work for preparation of many new members of this class of compounds.[7-10] 4-Hydroxypyrano[3,2-*c*]quinoline-2,5-diones are used traditionally to prepare 3-acetyl-4-hydroxyquinolin-2(1*H*)-ones throughout boiling of which in aqueous sodium hydroxide solution.[11] In the present work, we have prepared 3-acetyl-1-ethyl-4-hydroxyquinolin-2(1*H*)-one using this literature route and utilized the Vilsmeier-Haack reaction to obtain the desired novel 6-ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carboxaldehyde. Our plan is to study the interesting behavior of this aldehyde towards different nucleophilic reagents and herein we

highlight its chemical behavior towards hydroxylamine hydrochloride under different reaction conditions. The reaction mechanisms of the novel products were also discussed.

Results and Discussion

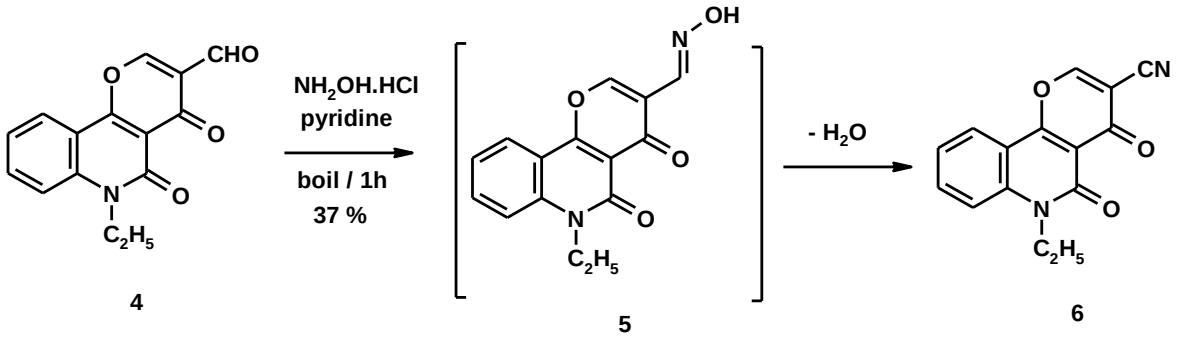
As depicted in Scheme 1, alkaline hydrolysis of 6-ethyl-4-hydroxypyrano[3,2-*c*]-quinoline-2,5(6*H*)-dione (**1**) afforded 3-acetyl-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**2**).[11] Formylation of acetylquinolinone **2** via Vilsmeier-Haack reaction, using dimethylformamide and phosphoryl chloride, led to the novel aldehyde; 6-ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]-quinoline-3-carboxaldehyde (**4**). It is clear that double formylation at the methyl group with subsequent *in situ* cyclization of the malonaldehyde intermediate **3** took place (Scheme 1).[12] Structure of aldehyde **4** was deduced from its correct elemental analysis and spectral data. The IR spectrum showed characteristic absorption bands attributed to three carbonyl groups at ν_{max} 1700 (HC=O), 1670 ($C=O_{\gamma\text{-pyrone}}$) and 1636 cm^{-1} ($C=O_{quinolone}$). The ^1H NMR spectrum of compound **4** showed characteristic singlet signals attributed to H-2 and aldehydic proton at δ 8.86 and 10.09, respectively. ^{13}C NMR spectrum showed three characteristic downfield signals at δ 183.4, 187.2, and 188.4, which are attributed to $C=O_{\gamma\text{-pyrone}}$, $C=O_{quinolone}$ and $C=O_{aldehyde}$, respectively. Furthermore, mass spectrum revealed the molecular ion peak at m/z 269 and the base peak at m/z 241, assigned to (M -28), due to loss of carbon monoxide or ethene molecule.



Scheme 1. Synthesis of the novel pyrano[3,2-*c*]quinoline-3-carboxaldehyde **4**.

Owing to structural features of aldehyde **4**, in which several sites are susceptible to nucleophilic attack, we designed a program to study its behaviour towards different nucleophilic reagents. Herein, we have considered its reaction with hydroxylamine hydrochloride under different reaction conditions.

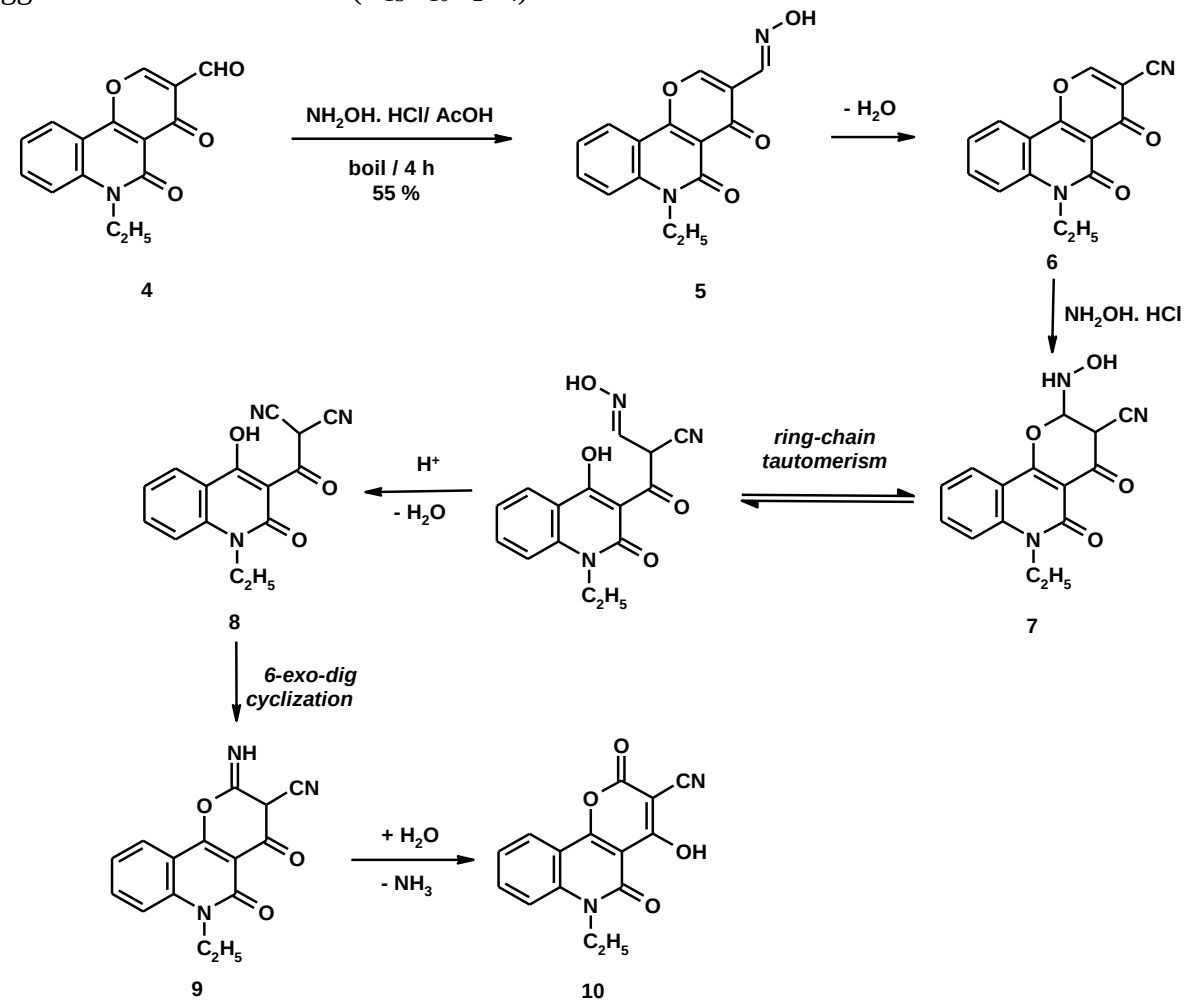
The reaction of aldehyde **4** with hydroxylamine hydrochloride, in boiling pyridine, afforded the corresponding carbonitrile derivative **6**, *via* first formation of non-isolable oxime **5**, which underwent *in situ* dehydration (Scheme 2). In this basic solvent; pyridine, we aimed to prepare oxime **5** but several trials to obtain the desired product afforded only the above carbonitrile **6**. In addition to elemental microanalysis which suggested that the molecular formula of the product is $C_{15}H_{10}N_2O_3$ (266.26), ^{1}H NMR spectrum of compound **6** showed characteristic singlet signal at δ 8.80 assigned to H-$2_{\gamma\text{-pyrone}}$. In the meantime ^{1}H NMR spectrum confirmed absence of both aldehydic and oxamic protons. IR spectrum indicated characteristic vibrational absorption band at ν_{max} 2226 cm^{-1} characteristic for nitrile function.



Scheme 2. Formation of pyrano[3,2-*c*]quinoline-3-carbonitrile derivative **6**.

It is known that condensation of hydroxylamine with aldehydes, in acidic media, usually leads to the corresponding carbonitrile derivatives.[13] Hence, we have repeated the previous reaction in acidic medium aiming to authenticate carbonitrile **6**. Albeit, it was found that treatment of aldehyde **4** with hydroxylamine hydrochloride, in glacial acetic acid, did not give either oxime **5** or carbonitrile **6**. Characterization of the product unexpectedly showed that 6-ethyl-5,6-dihydro-4-hydroxy-2,5-dioxo-*2H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (**10**) was obtained. The formation of the unusual product **10** may be explained if we take into consideration that two molecules of hydroxylamine step-wisely reacted with aldehyde **4**, leading to oxime **5** which dehydrated to carbonitrile **6**. The intermediate **6** is highly active cyclic push-pull system that quickly gave the adduct **7**, which in equilibrium in a ring-chain tautomerism. The oxime tautomer in such medium is easily dehydrated to the corresponding malononitrile intermediate **8**. Intramolecular 6-exo-dig cyclization of the latter intermediate **8**, followed by hydrolysis of its product 2-iminopyranoquinoline **9** furnished the final product **10** (Scheme 3). The structure of compound **10** was elucidated from interpretation of its spectral data. IR spectrum of compound **10** showed three characteristic absorption bands at ν_{max} 2235, 1756 and 1669 cm^{-1}, attributed to C≡N, C=$O_{\alpha\text{-pyrone}}$, and C=$O_{quinolone}$, respectively. ^{1}H NMR spectrum showed only signals attributed to sets of protons due to ethyl and benzo groups. Elucidatively, in this spectrum no singlet signals for either position 2 or aldehydic protons were observed. Furthermore, structure of compound **10** was further deduced from its mass spectrum which

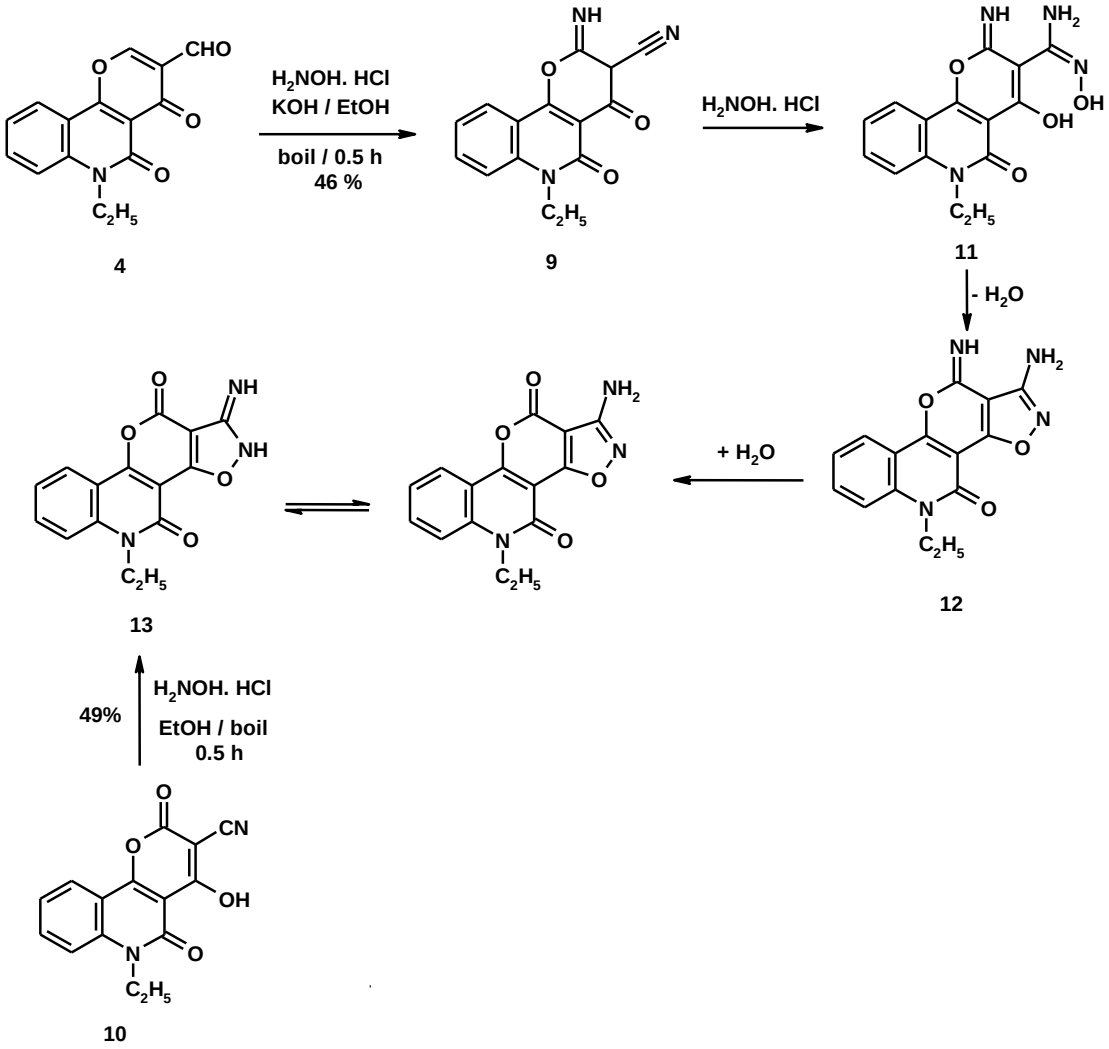
revealed the molecular ion peak, as the base peak, at m/z 282 which agreed well with its suggested molecular formula ($C_{15}H_{10}N_2O_4$).



Scheme 3. Formation of 4-hydroxypyrano[3,2-*c*]quinoline-3-carbonitrile derivative **10.**

Another novel and unexpected product was afforded when aldehyde **4** was treated with hydroxylamine hydrochloride, in ethanolic KOH solution (1%) as basic catalyst,[14,15] instead of acidic medium. As a consequence, this experiment led to 1-amino-5-ethylisoxazolo[5′,4′:4,5] pyrano[3,2-*c*]quinoline-4,11(5*H*)-dione (**13**), in 46 % yield. Herein again, we conclude that the reaction led to the same intermediate **9**, in a basic catalyzed route, which underwent addition with another molecule of hydroxylamine resulting in 6-ethyl-*N*,4-dihydroxy-2-imino-5-oxo-5,6-dihydro-2*H*-pyrano[3,2-*c*]quinoline-3-carboximidamide (**11**). Cyclization of this imidamide gave isoxazole derivative **12**. Hydrolysis of imine **12** took place as in the case of compound **10** leading to the final product **13** (Scheme 4). Compound **13** was authentically obtained from the reaction of carbonitrile derivative **10** with hydroxylamine hydrochloride in boiling ethanol. Structure of the product **13** was established on basis of elemental microanalysis and spectral data which revealed existence of amine-imine tautomerism (Scheme 4). IR spectrum of compound **13** showed characteristic absorption bands at ν_{max} 3446, 3159, 1731, 1646 and 1612 cm^{-1}, which are

attributed to N–H, C=$O_{\alpha\text{-pyrone}}$, C=$O_{quinolone}$ and C=N, respectively. ^{1}H NMR spectrum revealed two deuterium exchangeable protons at different chemical shifts δ 9.33 and 11.33 assigned to the N–H protons due to imino and 2*H*-isoxazoline. The predominance of the imino tautomer (Scheme 4) is very surprising to us according to literature reports which cited that the amino-form is more predominant than imino-form.[16] We decided the structure and presence of such tautomerism type (amine-imine) building on spectral results, in which the ^{1}H NMR was carried out in DMSO-d_6. We noticed presence of two different N-H protons which are replaceable with deuterium on treating with D_2O. If the two N-H protons are symmetrical (i.e. as NH_2) they should not appear different. Additionally, the IR spectrum showed the (N–H) stretching region at ν_{max} 3446, 3158 cm^{-1}. This findings supported that majority is due to imino tautomer in both (DMSO) solution and solid state. We think that the present case is distinctive and it is may be due to strong hydrogen bond (intramolecular, intermolecular, solute-solvent) interactions. In addition, there are differences between the parent isoxazol-3-amine as aromatic system and this annellated isoxazole fused heterocyclic system.



Scheme 4. Formation of 1-amino-5-ethylisoxazolo[5′,4′:4,5]pyrano[3,2-*c*]quinoline-4,11(5*H*)-dione **13**.

Conclusions

In conclusion, we have described a convenient one-pot synthesis of 6-ethyl-4,5-dioxo-5,6-dihydro-4H-pyrano[3,2-*c*]quinoline-3-carboxaldehyde using Vilsmeier-Haack reaction, which is applicable in similar *ortho*-hydroxyacetyl compounds. Correspondingly, we reported for reactivity of such pyrano[3,2-*c*]quinoline-3-carboxaldehyde towards hydroxylamine hydrochloride in which the products are extremely dependent on the reaction conditions.

Experimental Section

General. Melting points were determined on a digital Stuart SMP3 apparatus. Infrared spectra were taken on FT-IR Nicolet IS10 spectrophotometer (cm^{-1}), using KBr disks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured on Mercury-300BB, using DMSO-d_6 as a solvent and tetramethylsilane as an internal standard. Mass spectra were measured using GC-MS qp 1000 ex Shimadzu mass spectrometer instrument (70 eV). Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer at the Chemical War Department, Ministry of Defense, Egypt. Pyranoquinolinedione **1** and acetylquinolinone **2** were prepared according to a literature method.[11]

6-Ethyl-4,5-dioxo-5,6-dihydro-4*H*-pyrano[3,2-*c*]quinoline-3-carboxaldehyde (**4**)**.** Phosphoryl chloride (5 mL, 5.4 mmol) was added drop-wise to a stirred cold DMF (15 mL) in an ice-bath, then the mixture was stirred at room temperature for 30 min. A solution of 3-acetyl-1-ethyl-4-hydroxyquinolin-2(1*H*)-one (**2**) (1.1 g, 4 mmol), in DMF (10 mL) was added drop-wise with continuous stirring. After completion of addition, the reaction mixture was stirred at room temperature for 2 h and heated under reflux, on a boiling water-bath, for 2 h. The mixture was left to cool and poured onto crushed ice (*ca.* 50 g). The reddish solid so obtained was filtered, dried and crystallized from ethanol to give compound **4** as amber yellow crystals, yield 0.6 g (60 %), mp 220–222 °C. IR (KBr, cm^{-1}): ν_{max} 3076 (CH_{arom}), 2973, 2945, 2890 (CH_{aliph}), 1700 (HC=O), 1670 ($C=O_{\gamma\text{-pyrone}}$), 1636 ($C=O_{quinolone}$), and 1588 (C=C). ^{1}H NMR (DMSO-d_6), δ: 1.24 (t, 3H, *J* 7.5 Hz, CH_2CH_3), 4.37 (q, 2H, *J* 7.5 Hz, CH_2CH_3), 7.43 (t, 1H, *J* 7.8 Hz, H-9), 7.70 (d, 1H, *J* 8.7 Hz, H-7), 7.86 (t, 1H, *J* 7.5 Hz, H-8), 8.09 (d, 1H, *J* 7.2 Hz, H-10), 8.86 (s, 1H, H-2), 10.09 (s, 1H, CH=O). ^{13}C NMR (DMSO-d_6), δ: 12.6, 38.7, 107.1, 114.9, 122.4, 123.1, 123.7, 124.1, 134.3, 138.3, 163.1, 172.5, 183.4, 187.2, 188.4. Mass spectrum, m/z (I_r %): 269 (3) ($M^{+\cdot}$), 268 (11), 241 (100) (M - CO), 213 (13) (M - 2 CO), 185 (82), 171 (5), 132 (18), 120 (8), 115 (6), 89 (13) and 77 (8). Anal. Calcd. for $C_{15}H_{11}NO_4$ (269.26); C, 66.91; H, 4.12; N, 5.20%. Found: C, 66.80; H, 4.00; N, 4.90%.

6-Ethyl-5,6-dihydro-4,5-dioxo-4*H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (**6**)**.** A mixture of aldehyde **4** (0.54 g, 2 mmol) and hydroxylamine hydrochloride (0.13 g, 2 mmol) in dry pyridine (10 mL) was heated under reflux for 1 h. After cooling, the reaction mixture was poured onto crushed ice (*ca.* 50 g) and neutralized with cold dilute hydrochloric acid. The precipitate so formed was filtered and crystallized from ethanol to give compound **6** as pale yellow crystals, yield (0.20 g, 37%), mp 250–251 ºC. IR (KBr, cm^{-1}): ν_{max} 3071 (CH_{arom}), 2980, 2935 (CH_{aliph}), 2226 (C≡N), 1660 ($C=O_{\gamma\text{-pyrone}}$), 1636 ($C=O_{quinolone}$) and 1582 (C=C). ^{1}H NMR (DMSO-d_6), δ: 1.21 (t, 3H, *J* 6.9 Hz, CH_2CH_3), 4.28 (q, 2H, *J* 6.9 Hz, CH_2CH_3), 7.35 (t, 1H, *J* 7.8 Hz, H-9), 7.63 (d, 1H, *J* 8.4 Hz, H-7), 7.81 (t, 1H, *J* 8.4 Hz, H-8), 8.14 (d, 1H, *J* 9 Hz, H-10), 8.97 (s, 1H, H-2). Anal. Calcd for $C_{15}H_{10}N_2O_3$ (266.26); C, 67.67; H, 3.79; N, 10.52%. Found: C, 67.80; H, 3.60; N, 10.20%.

6-Ethyl-5,6-dihydro-4-hydroxy-2,5-dioxo-*2H*-pyrano[3,2-*c*]quinoline-3-carbonitrile (**10**)**.** A mixture of aldehyde **4** (0.54 g, 2 mmol) and hydroxylamine hydrochloride (0.26 g, 4 mmol), in glacial acetic acid (5 mL), was heated under reflux for 4 h. The solid so obtained after cooling was filtered and crystallized from ethanol to give compound **10** as sandy yellow crystals, yield (0.30 g, 55 %), mp 270–271 ºC. IR (KBr, cm^{-1}): ν_{max} 3480 (br, O–H), 2986, 2945 (CH_{aliph}), 2234 (C≡N), 1756 ($C=O_{\alpha\text{-pyrone}}$), 1669 ($C=O_{quinolone}$), and 1615 (C=C). ^{1}H NMR (DMSO-d_6), δ: 1.26 (t, 3H, *J* 6.3 Hz, CH_2CH_3), 4.39 (q, 2H, *J* 6.3 Hz, CH_2CH_3), 7.53 (t, 1H, *J* 7.8 Hz, H-9), 7.86 (d, 1H, *J* 8.4 Hz, H-7), 7.94 (t, 1H, *J* 7.5 Hz, H-8), 8.18 (d, 1H, *J* 8.4 Hz, H-10). Mass spectrum, *m/z* (I_r %): 282 (100) ($M^{+\cdot}$), 254 (86) (M – CO or C_2H_4), 226 (95) (M - 2 CO), 216 (33), 210 (14), 187 (34), 132 (35), 119 (54), 91 (33), 77 (61), 76 (42). Anal. Calcd for $C_{15}H_{10}N_2O_4$ (282.26): C, 63.83; H, 3.57; N, 9.92%. Found: C, 63.60; H, 3.70; N, 9.60%.

1-Amino-5-ethylisoxazolo[5′,4′:4,5]pyrano[3,2-*c*]quinoline-4,11(5*H*)-dione (**13**)

Procedure *a*. A mixture of aldehyde **4** (0.54 g, 2 mmol) and hydroxylamine hydrochloride (0.26 g, 4 mmol), in ethanol (10 mL) containing aqueous potassium hydroxide (1 %) solution (5 mL), was heated under reflux for 0.5 h. The solid that obtained after cooling, was filtered and crystallized from ethanol to give compound **13** as yellow crystals, yield (0.25 g, 46 %), mp 220–221 ºC. IR (KBr, cm^{-1}): ν_{max} 3446, 3158 (2NH), 2980, 2930 (CH_{aliph}), 1731 ($C=O_{\alpha\text{-pyrone}}$), 1646 ($C=O_{quinolone}$), and 1587 (C=N). ^{1}H NMR (DMSO-d_6), δ: 1.30 (t, 3H, *J* 7.5 Hz, CH_2CH_3), 4.43 (q, 2H, *J* 7.5 Hz, CH_2CH_3), 7.55-7.59 (m, 2H, H-7 and H-8), 7.93 (t, 1H, *J* 7.5 Hz, H-6), 8.21 (d, 1H, *J* 7.8 Hz, H-9), 9.33 (bs, 1H, NH, exchangeable with D_2O), and 11.33 (bs, 1H, NH, exchangeable with D_2O). Mass spectrum, m/z (I_r %): 298 (2) (M+1), 297 (11) ($M^{+\cdot}$), 282 (3), 263 (11), 179 (8), 105 (100), 90 (9), 77 (46), 64 (7). Anal. Calcd for $C_{15}H_{11}N_3O_4$ (297.27); C, 60.61; H, 3.73; N, 14.14 %. Found: C, 60.40; H, 3.60; N, 14.05%.

Procedure *b*. A mixture of compound **10** (0.56 g, 2 mmol) and hydroxylamine hydrochloride (0.13 g, 2 mmol) in ethanol (20 mL) was heated under reflux for 0.5 h. The solid that separated after cooling was filtered off and crystallized from ethanol to give compound **13** as yellow crystals, yield 0.29 (49%), mp 220–221 ºC.

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