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Preparation and Some Reactions with 3-(Quinolin-3-yl)-3-Oxopropanoic Acid

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Abstract. Preparation of quinolinyl-3-oxopropanoic acid **2** was accomplished by hydrolysis of pyranoquinolinedione **1** in aqueous alkaline medium. The chemical behavior of this β-keto acid **2** towards nitrosation, coupling with a diazonium salt, esterification, condensation with 2,2-dimethoxyethanamine, hydrazinolysis, Knoevenagel condensation with isatine, salisyaldehyde, 3-formylquinolones, and 3-formylchromone, was investigated. Also many of the products of these reactions were found obtainable using either pyranoquinolinedione **1** or β-keto acid **2**, under the same conditions.
Key words: Quinolin-2(1*H*)-one, β-Keto-carboxylic acid, Pyrano[3,2-*c*]quinoline, Knoevenagel condensation, heterocyclization reactions.

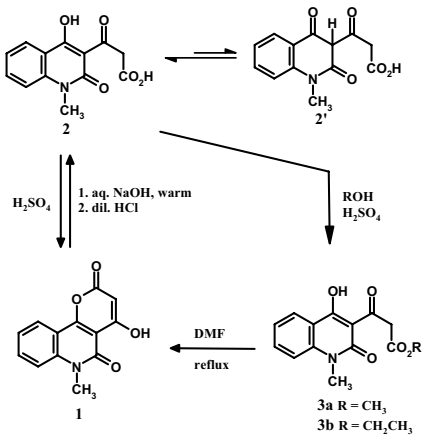
Resumen. La preparación del ácido quinolinil-3-oxopropanoico **2** se realizó por hidrólisis de la piranoquinolindiona **1** en medio acuoso alcalino. Se investigó el comportamiento químico de este β-cetoácido **2** en reacciones de nitrosación, acoplamiento con sales de diazonio, esterificación, condensación con 2,2-dimethoxyethanamine, hidrazinólisis, condensación de Knoevenagel con isatina, salicilaldehido, 3-formilquinolones y 3-formilchromonas. Muchos de los productos de estas reacciones pueden obtenerse mediante el uso ya sea de la piranoquinolindiona **1** o del β-cetoácido **2**, bajo las mismas condiciones.
Palabras clave: Quinolin-2(1*H*)-ona, ácido β-ceto-carboxílico, pirano [3,2-*c*] quinolina, condensación de Knoevenagel, reacciones de heterociclización.

Introduction

In the recent years, an increasing interest in the synthesis of functionalized 4-hydroxyquinolin-2(1*H*)-ones, with promising biological properties has been observed. A broad number of important pharmacological activities have been associated with 3-substituted 4-hydroxyquinolin-2(1*H*)-ones [1-5]. Many derivatives of this heterocyclic category are biologically active naturally occurring compounds, which were found as useful intermediates for many medicinal products [6-8]. It had been reported that *N*-methyl derivatives of 4-hydroxyquinolin-2(1*H*)-one are associated with significant biological activity [9-11], and many derivatives of 6-methylpyrano[3,2-*c*]quinolinone are known as pharmaceutical active ingredients, e.g. the well-known alkaloids: *veprisines* and *flindersines* [12,13]. Pyrano[3,2-*c*]quinolinones were found to be active against certain immuno-reaction diseases, in particular against immediate hypersensitivity reactions (anaphylaxis). Furthermore, they were distinguished by a strong systemic antiallergic action and therefore, they are suitable for the treatment and the prophylaxis of allergy diseases [14]. In general, most of these medicines include 4-hydroxyquinolin-2(1*H*)-one as the stem heterocyclic system. Thus, the majority of the viable syntheses of this category of compounds employed the cyclization of the corresponding 4-hydroxyquinolin-2(1*H*)-ones. In turn these pyranoquinolinones were used on wide range to obtain 4-hydroxyquinolin-2(1*H*)-one and 3-acetyl-4-hydroxyquinolin-2(1*H*)-one derivatives [15]. So that 4-hydroxypyrano[3,2-*c*]quinoline-2,5(6*H*)-diones are very important synthones to obtain several 3-substituted 4-hydroxyquinolin-2(1*H*)-ones especially 3-acyl derivatives [16-18]. Earlier Bowman *et al.* [19] had reported one pot synthesis of 4-hydroxypyrano[3,2-*c*]quinoline-2,5(6*H*)-diones by condensation of the appropriate aniline with excess diethyl malonate, a technique which is still the most successful procedure to obtain such heterocyclic system and we apply to this methodology in order to prepare our starting material; pyranoquinolinone **1**. In connection to our program work which deals with substituted quinolinones, our attention was directed to obtain new multi-functionalized quinolinone derivatives of expected biological activity especially as antimalarial and antiparasitic [1, 2]. In the present work we describe the synthetic utility of pyranoquinolinone **1** and its alkaline hydrolysis product; 3-(quinolin-3-yl)-3-oxopropanoic acid **2** to obtain new heterocyclic derivatives incorporating quinolin-2-one moiety of expected antiparasitic activity.

Results and Discussion

It was reported that boiling of pyranoquinolinone **1** in aqueous sodium hydroxide results in 3-acetyl-4-hydroxyquinolin-2(1*H*)-one in which ring-opening is followed by decarboxylation [14, 20]. Our attempts to obtain a quinolinone bearing β-keto carboxylic acid group at position-3 met success, starting from pyranoquinolinone **1**. A convenient facile basic hydrolysis of pyranoquinolinone **1** was carried out *via* warming its aqueous sodium hydroxide solution at about 50 ºC, to give 3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid (**2**) in 94 % yield (Scheme 1). The structure of the product was established on basis of the following analytical and spectral results; satisfactory elemental microanalysis for C, H, and N elements is within ±0.2 %, IR spectrum revealed the presence of absorption bands at $\bar{\nu}$ 3447 and 1734 cm^{-1} due to CO_2H group, ^1H NMR spectrum, in dimethylsulfoxide

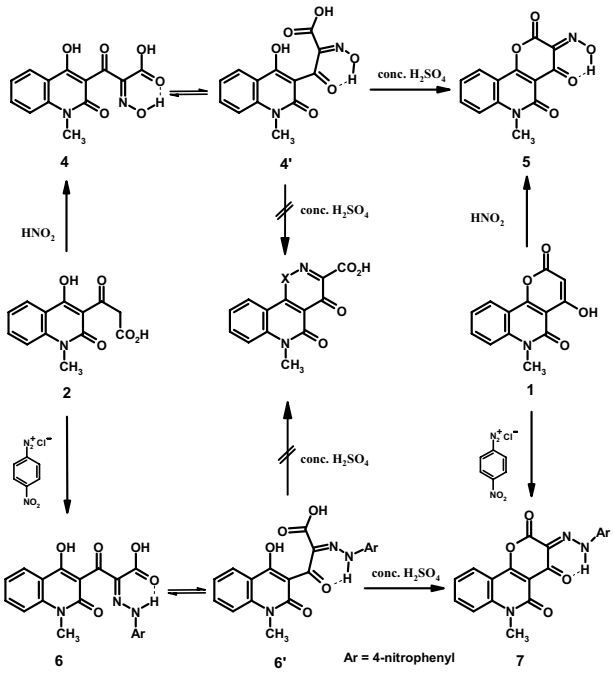


Scheme 1.

(DMSO-d_6), showed that it exists as 4-hydroxyquinolin-2-one form, while in chloroform ($CDCl_3$) it exists as 2,4-quinolinedione form. In $CDCl_3$ the proton at position-3 was observed at δ 5.66, and mass spectrum presented molecular ion peak M^+ at m/z 261 and a peak at m/z 243 due to $(M-H_2O)^+$ ion of a recyclized pyranoquinoline fragment (Table 1).

Alkyl 3-(quinolinyl)-3-oxopropanoates **3a,b** were obtained *via* esterification of the β-keto acid **2** with alcohols *viz*; methanol and ethanol, in presence of concentrated sulfuric acid, in 84 ± 1 % yields (Scheme 1). ^{1}H NMR spectrum of compound **3a** (R = Et) showed signals at δ 3.48 due to (NCH_3), 3.52 due to (α-CH_2CO_2Me), and 3.62 due to (CO_2CH_3). An alternative route to obtain the ester **3b** (R = Et) was described *via Claisen* condensation reaction between diethyl carbonate and 3-acetyl-4-hydroxy-1-methylquinolin-2(1*H*)-one [21]. However, the present preparation from compound **2** is convenient and advantageous because *Claisen* condensation, in which many by-products are formed and purification of the product is inconvenient, with overall yield ~44 %, starting from pyranoquinoline **1**, a nearly half of the present preparation yield [17].

Nitrosation of the β-keto acid **2**, using sodium nitrite and dilute hydrochloric acid at 0-5 °C, furnished the oxime **4**. As depicted in Scheme 2, the oxime **4** may exist in two forms; *Z*-form **4** and/or *E*-form **4'**. ^{1}H NMR spectrum of the oxime **4** showed three signals at δ 12.8, 13.4, and 17.6 (Table 1). Since the three chemical shifts disappear on addition of deuterium oxide (D_2O), they attributed to three OH groups of oxime, quinolinol, and carboxylic acid, respectively. The dehydration reaction of the oxime **4**, in concentrated sulfuric acid, is expected to give one or more than one product. The structures which are suggested as possible products for such reaction include; 3-hydroxyiminopyrano[3,2-*c*]quinolinetrione **5** and 1,2-oxazino[5,6-*c*]quinoline-3-carboxylic acid, (Scheme 2). In addition to chemical tests, IR and ^{1}H NMR spectral data of the product showed no evidences for presence of CO_2H. So it is concluded that the product of this reaction is the compound **5**. Moreover, these results were clearly supported by obtaining of the pyranoquinoline **5** directly from nitrosation of pyranoquinoline **1** (Scheme 2).



Scheme 2.

The coupling reaction of β-keto acid **2** with *p*-nitrobenzenediazonium chloride afforded an orange colored product. IR spectrum of the product showed a medium absorption band broaden between 3206-2434 cm^{-1} due to H-bonded N-H and O-H, in addition to two strong stretching bands at 1737 and 1640 cm^{-1} due to C=O of carboxylic acid and quinolinone. ^{1}H NMR spectrum revealed the presence of three D-exchangeable protons at δ 9.17, 12.37, and 15.23 refer to N-H of hydrazone and O-H of quinolinol and carboxylic acid. Building on above the structure of the product was determined as the hydrazone **6**. Herein again the *Z*-form **6** and *E*-form **6'** are possible as depicted in scheme 2. The structures of compounds **4** and **6** as seen need further study using X-ray single crystal analysis but unfortunately we did not succeed in getting suitable crystals for such analysis.

When the hydrazone **6** was subjected to dehydration using concentrated sulfuric acid only 3-hydrazonopyrano[3,2-*c*]quinolinetrione **7** was obtained. For such reaction one can also expect to get pyridazino[4,3-*c*]quinoline by the possible intramolecular heterocyclization between hydrazone nitrogen and quinolinol hydroxyl group. All analytical and spectral data showed that carboxylic group was involved in cyclization and structure of the product contains an N-H appeared at δ 9.64 (exchangeable on addition of deuterium oxide). Moreover, these results were definitely confirmed when the same hydrazone derivative **7** was obtained *via* coupling of the pyranoquinolinedione **1** with p-nitrobenzenediazonium chloride (Scheme 2).

The reaction of the β-keto acid **2** with 2,2-dimethoxyethanamine (2-aminoacetaldehyde dimethyl acetal), in boiling DMF, was carried out to obtain a 2-(quinolin-3-yl)pyrrole-3-carboxylic acid derivative. Unexpectedly, characterization of

Table 1. IR, ^{1}H NMR, and Mass Spectral Data of the New Compounds.

Compd. No.	IR (KBr), $\bar{\nu}$/cm^{-1}	^{1}H NMR (DMSO-d_6), δ†	Mass, m/z (%)
2	3447-2951 (OH), 1734 ($C=O_{carboxylic}$), 1672 ($C=O_{ketone}$), 1615 ($C=O_{quinolone}$)	($CDCl_3$): 3.79 (s, 3H, NCH_3), 3.88 (s, 2H, CH_2), 5.66 (s, 0.5H, 3-H), 7.26 (d, 1H, *J* = 8, 8-H), 7.50 (dd, 1H, *J* = 7.8, 2.0, 6-H), 7.8 (dd, 1H, *J* = 7.8, 2.0, 7-H), 8.32 (d, 1H, *J* = 8, 5-H), 13.60 (s, 0.5H, OH), 15.60 (s, 1H, $OH_{carboxylic}$)	261 (4.1) (M^+), 243 (M^+ - H_2O) (22.8), 245 (3.6), 244 (8.4), 217 (23.3), 215 (100), 216 (17.6), 131 (32.4), 106 (11.3), 89 (37.3), 76 (26.3), 65 (22.7), 53 (39.4), 50 (44.2)
3a	3444 (OH), 1735 ($C=O_{ester}$), 1672 ($C=O_{ketone}$), 1644 ($C=O_{quinolone}$), 1162 (C-O-C_{ether})	3.48 (s, 3H, NCH_3), 3.52 (s, 2H, CH_2), 3.62 (s, 3H, OCH_3), 7.44 (t, 1H, *J* = 6.2, 6- H), 7.64 (d, 1H, *J* = 8, 8-H), 7.76 (t, 1H, *J* = 6.2, 7-H), 8 (d, 1H, *J* = 8, 5-H), 13.4 (s, 1H, OH)	275 (4.8) (M^+), 276 (1.5), 274(1.9), 261 (9.6), 245 (18.3), 217 (12.4), 203 (13.8), 175 (100), 161 (17.6), 145 (24.4), 117 (16.2), 93 (28.1), 77 (23.2), 64 (16.0), 51 (45.0)
4	3446- 2500 (OH, NH), 1739 ($C=O_{carboxylic}$), 1671 ($C=O_{ketone}$ + $C=O_{quinolone}$)	3.50 (s, 3H, NCH_3), 7.52 (t, 1 H, *J* = 6.4, C7-H), 7.79 (d, 1H, *J* = 8, C8-H), 7.90 (t, 1H, *J* = 6.4,C6-H), 8 (d, 1H, *J* = 8, C5-H), 12.8 (s, 1H, OH_{oxime}), 13.4 (s, 1H, OH), 17.6 (s, 1H, $OH_{carboxylic}$)	290 (M^+) (4.9), 291 (1.3), 285 (15.4), 229 (5.4), 228 (13.6), 216 (23.0), 215 (40.3), 202 (18.1), 134 (18.5), 106 (15.7), 77 (75.9), 51 (100)
5	3432 (OH), 1737 ($C=O_{pyrone}$), 1649 ($C=O_{quinolone}$), 1618 (C=N)	3.50 (s, 3H, NCH_3), 7.25–7.32 (t, 1H, 7-H), 7.45 (d, 1H, 8-H), 7.76 (t, 1H, 6-H), 7.98 (d, 1H, 5-H), 12.8 (s, 1H, OH_{oxime})	272 (M^+) (52.1), 273 (7.2), 255 (43.5), 244 (66.7), 229 (45.9), 173 (100), 157 (32.8), 133 (33.5), 105 (23.3), 76 (78.9)
6	3206-2434 ($OH_{carboxylic}$), 1737 ($C=O_{carboxlic}$), 1640 ($C=O_{quinolone}$), 1503, 1481 (NO_2)	3.73 (s, 3H, NCH_3), 7.30–8.05 (m, 8H, H_{arom}), 9.17 (s, 1H, NH), 12.37 (s, 1H, OH), 15.23 (s, 1H, $OH_{carboxylic}$)	410 (M^+) (5.1), 411(2.3), 394 (20.4), 365 (10.7), 349 (17.9), 321 (32.6), 230 (100), 217 (34.7), 203 (31.8), 175 (56.9)
7	3404 (NH), 1725 –1673 ($C=O_{pyrone}$), 1631 ($C=O_{quinolone}$), 1571, 1495 (NO_2)	3.73 (s, 3H, NCH_3), 7.33–8.02 (m, 8H, H_{arom}), 9.40 (s, 1H, NH)	392 (M^+) (3.6), 393 (1.8), 347 (8.7), 256 (18.0), 243 (100), 230 (10.4), 217 (40.1), 203 (30.2), 189 (63.3), 175 (34.2), 161 (32.0)
8	3227 (OH, NH), 1742 ($C=O_{carboxylic}$), 1674 ($C=O_{quinolone}$)	3.28 (s, 3H, NCH_3), 3.63 (s, 3H, OCH_3), 6.89 (d, 1H, *J* = 8.2, 2-$H_{pyrrole}$), 7.09 (d, 1H, *J* = 8.2, 3-$H_{Pyrrole}$), 7.51 (t, 1H, *J* = 7.9, 6-H), 7.82 (m, 2H, 7-H + 8-H), 8.10 (d, 1H, *J* = 7.8, 5-H), 9.64 (s, 1H, NH), 13.8 (b, 1H, $OH_{carboxylic}$)	298 (M^+) (15.9), 299 (5.0), 297 (8.4), 283 (2.9), 269 (8.5), 267 (15.2), 266 (12.0), 254 (21.2), 215 (20.3), 199 (12.2), 159 (14.5), 131 (11.0), 77 (21.1), 76 (18.6), 75 (100)
10	3429, 3243 (OH, NH), 1740 ($C=O_{carboxylic}$), 1730 ($C=O_{indolone}$), 1650 ($C=O_{quinolone}$)	3.71 (s, 3H, NCH_3), 6.92–8.34 (m, 8H, H_{arom}), 10.42 (b, 1H, NH), 12.40 (s, 1H, OH), 14.2 (s, 1H, $OH_{carboxylic}$)	390 (M^+) (8.6), 391 (2.6), 346 (34.0), 330 (22.1), 316 (20.2), 173 (34.6), 159 (43.8), 145 (32.7)
11	3157 (NH), 1752 ($C=O_{pyrone}$), 1652 ($C=O_{indolone}$, $C=O_{quinolone}$)	3.52 (s, 3H, NCH_3), 7.04–8.70 (m, 8H, H_{arom}), 12.01 (b, 1H, NH)	372 (M^+) (4.6), 373 (1.7), 331 (23.3), 317(12.5), 255 (100), 241 (10.7), 229 (21.9), 201 (13.3), 200 (15.2), 173 (18.6), 145 (20.2), 78 (21.3)
12	3435 (OH), 1730 ($C=O_{pyrone}$), 1636 ($C=O_{quinolone}$)	3.49 (s, 3H, NCH3), 7.37–7.84 (s, 8H, H_{arom}), 8.16 (s, 1H, 4-$H_{coumarin}$), 14.80 (b, 1H, OH)	347 (M^+) (100), 348 (36.0), 349 (6.7), 319 (39.6), 275 (61.9), 202 (38.4), 173 (57.6), 134 (46.5), 90 (23.6), 77 (71.4), 63 (46.8)
13	3423,(OH), 1670, 1651 ($C=O_{pyrone}$), 1644 ($C=O_{quinolone}$)	3.52 (s, 3H, NCH_3), 7.15–7.97 (m, 8H, H_{arom}), 5.68 (s, 1H, $H_{methine}$), 12.00 (s, 1H, OH)	347(M^+) (60), 348 (14.8), 329 (34.8), 319 (64.5), 301 (16.4), 211 (18.3), 201 (78.1), 175 (11.3), 174 (100), 133 (22.4), 94 (46.2)
17a	3415 (OH), 1717 ($C=O_{pyrone}$), 1670 ($C=O_{quinolone}$)	3.70 (s, 3H, NCH_3), 3.77 (s, 3H, NCH_3), 5.82 (s, 1H, $H_{methine}$), 7.30–8.33 (m, 8H, H_{arom}), 13.4 (b, 1H, OH)	428 (M+) (38.3), 429 (9.4), 400 (31.2), 399(10.9), 385(6.8), 268(16.4), 254 (29.6), 226 (8.3), 214 (11.3), 202 (20.4), 199 (60.6), 172 (14.3), 117 (14.2), 115 (24.0), 104 (38.5), 77 (100), 76 (29.7), 64 (23.3)
17b	3438, 3158 (OH), 1752 ($C=O_{pyrone}$), 1657 ($C=O_{quinolone}$)	2.43 (s, 3H, $6CH_3$), 3.49 (s, 3H, NCH_3), 5.44 (s, 1H, $H_{methine}$), 7.31–8.05 (m, 7H, H_{arom}), 12.11 (s, 1H, NH), 13.80 (s, 1H, OH)	428 (M+) (100), 429 (25.3), 430 (10.6), 427 (11.3), 400 (74.2), 399 (18.2), 372 (27.3), 226 (21.4), 200 (25.4), 199 (97.6), 186 (22.6), 39 (12.8), 104 (55.6), 77 (99.9)
20	3051 (C–H_{arom}), 1748 ($C=O_{pyrone}$), 1644 ($C=O_{pyrone}$), 1622 ($C=O_{quinolone}$)	($CDCl_3$) 3.84 (s, 3H, NCH_3), 6.94 (s, 1H, $H_{methine}$), 7.12 (d, 1H, *J* = 7.9, 6-$H_{quinolone}$), 7.44 -7.53 (m, 4H, H_{arom}), 7.74 (d, 1H, *J* = 8.2, 8-$H_{chromone}$), 8.17 (d, 1H, *J* = 8.0, 5-$H_{quinolone}$), 8.37 (d, 1H, *J* = 8.2, 5-$H_{chromone}$), 8.70 (s, 1H, 2-$H_{chromone}$)	399 (M^+) (5.4), 400 (2.2), 398 (25.4), 397 (100), 396 (35.8), 368 (30.4), 277 (81.6), 276 (18.3), 104 (11.4), 93 (28.2), 77 (36.2), 65 (67.2)

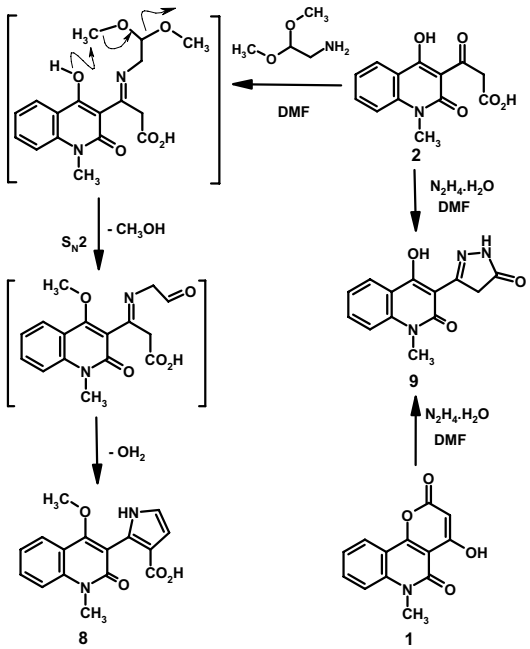
† All ^{1}H NMR experiments were carried out in DMSO-d_6 unless cited.

structure of the product using elemental and spectral analyses indicated the existence of a methoxy and a carboxylic acid functions. Mass fragmentation pattern revealed peaks at m/z 267 due to $(M - OCH_3)^+$ ion and m/z 254 due to $(M - CO_2)^+$ ion (Table 1). ^{1}H NMR spectrum showed a singlet signal at δ 3.63 due chemical shift of OCH_3 in addition to two deuterium replaceable protons appeared at δ 9.64 and 13.8 due to pyrrole N-H and carboxylic O-H (Table 1). As depicted in Scheme 3, *Friedländer* cyclo-condensation reaction took place, giving the corresponding azomethine intermediate, which underwent an intramolecular S_N2 *O*-methylation of 4-hydroxyquinolin-2-one, accompanied by loss of methanol. The presumed aldehyde intermediate underwent smooth cyclization, leading to 2-(4-methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrrole-3-carboxylic acid (**8**) (Scheme 3).

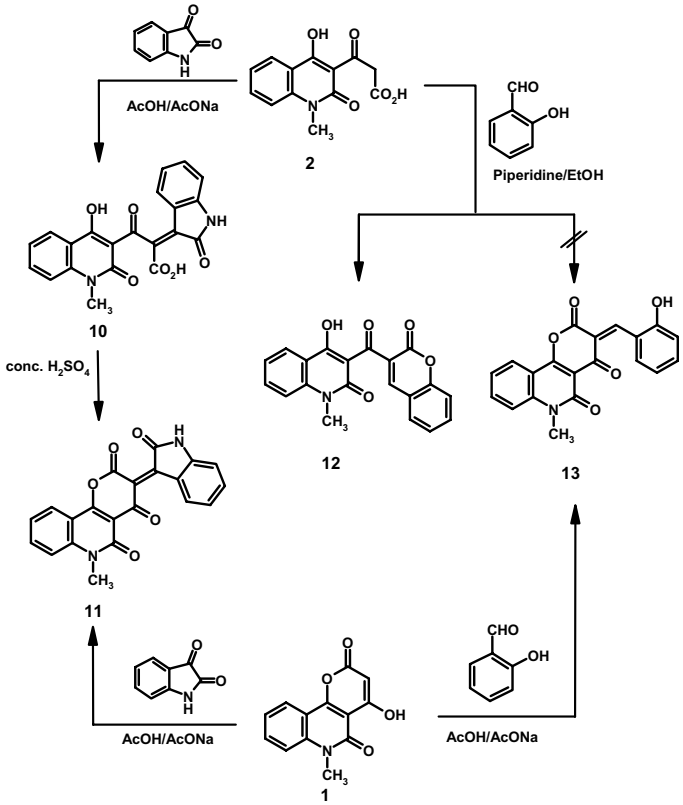
As illustrated in scheme 3, when the β-keto acid **2** was subjected to react with hydrazine hydrate, in boiling DMF, the pyrazolinylquinoline **9** was obtained, in moderate yield (56 %). The same compound was also obtained starting from the pyranoquinolinedione **1** as previously described [16]. Even, the reported preparation yield (92%) is higher than the present but usage of β-keto acid **2** in preparation is mandatory for estimation of orientation of cyclization. In case of γ-hydroxy-α-pyrone, the nucleophilic attack starts at lactone C=O followed by cyclization with nucleophilic replacement of the γ-enol OH, while in case of β-keto acid this attack should start at the β-C=O followed by cyclization *via* condensation with the carboxylic group. Anyhow in case of treatment with hydrazine no difference is noticed but we expect that both compounds **1** and **2** may give different products on use of unsymmetrical 1,2-binucleophiles like mono-substituted hydrazine and hydroxylamine.

Treatment of the β-keto acid **2** with isatine was carried out under *Knoevenagel* reaction conditions using fused sodium acetate and glacial acetic acid. The product of this reaction was characterized as 2-(indol-3-ylidene)propanoic acid **10** (Scheme 4). Under this acidic conditions, it was expected to obtain the cyclization product; indolylidenepyranoquinoline **11**. However, when the product **10** was consequently treated with concentrated sulfuric acid, this cyclization took place and the compound **11** was formed. Interestingly, when the pyranoquinoline **1** was subjected to react with isatine, in presence of fused sodium acetate and glacial acetic acid, the same compound **11** was afforded, in 88 % yield (Scheme 4).

Since benzopyrones are well thought-out as useful synthones to get diverse heterocyclic derivatives through ring-opening ring closure (RORC) reactions [22-25], it was planned to obtain a new quinolinone derivatives in which benzopyrone nucleus was constructed as substituent at position-3. Thus, β-keto acid **2** was subjected to react with salicylaldehyde, in presence of piperidine in boiling ethanol. Both coumarin derivative **12** and pyranoquinoline derivative **13** were expected as products of this reaction (Scheme 4). For such reaction the plausible *Knoevenagel* condensation intermediate was suggested due to the reactivity of methylene of the β-keto acid **2**. This intermediate can undergo intramolecular nucleophilic lactonization, forming either coumarin derivative **12** or pyranoquinoline derivative **13**. The elemental and mass analyses of the product are not differential because both expected structures are isomers. ^{1}H NMR spectrum of the product gave important information



Scheme 3.

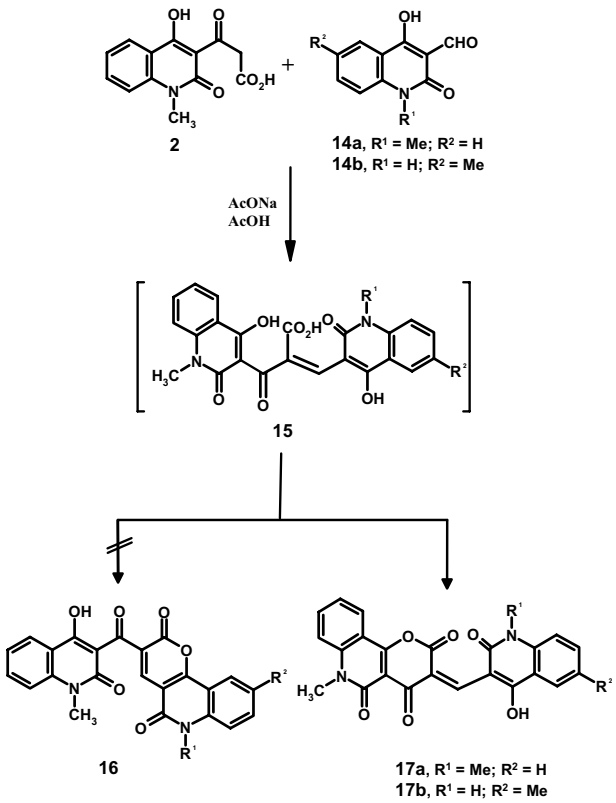


Scheme 4.

about characterization of its structure. Thus, it exhibited a singlet signal at δ 8.16, which is characteristic for chemical shift of C-H at position 4 of α-pyrone. This indicates that the structure of the product is the coumarin **12** (Scheme 4). Interestingly, we checked this result by an alternate route when we carried out the reaction of salicylaldehyde with pyranoquinoline **1**, in acidic medium to retain the pyrone nucleus during the reaction. This reaction was constructed building on the presence of 4-hydroxy-2-pyrone as malonyl heterocycles, a tautomeric 1,3-dione form, which possesses an active methylene site. Thus, this condensation was carried out, in presence of fused sodium acetate and glacial acetic acid, to give a single product which was found to be different from the coumarin derivative **12**. Again ^{1}H NMR was used to distinguish the structure of the product in which a methine proton was observed in the normal olefinic region as singlet at δ 5.68. These results confirmed that the latter product is the expected structure of 3-benzylidenepyrano[3,2-*c*]quinolinetrione **13** (Scheme 4).

Knoevenagel condensation of the β-keto acid **2** with quinoline-3-carbaldehydes **14a,b** was carried out, in the presence of freshly fused sodium acetate in glacial acetic acid aiming to get the acrylic acid derivative **15**. Albeit, the expected acrylic acid derivative **15** was not isolated, its cyclized products 3-(quinolinylmethylene)pyrano[3,2-*c*]quinolinetriones **17a,b** were obtained (Scheme 5). The structure of the products was established on basis of their spectral and analytical data, which showed the disappearance of the carboxylic group and the presence of only one hydroxyl group. It is worthwhile to take into account the other reasonable isomeric structure **16**. Elemental microanalyses and IR spectra did not give significant information to deduce which structure **16** or **17** is the product. ^{1}H NMR spectrum showed singlet peak due to chemical shift of olefinic C-H proton appeared at δ 5.82 corresponding to compound **17a**, and at δ 5.44 corresponding to compound **17b**. These results confirmed the proposed lactonization, excluding formation of structure **16**. There is no explanation for these results other than the formation of *Z*-intermediate **15** which is stabilized through the extended conjugation of the chain HO-C=C-CH=C-C=OOH, in addition to additional stabilization comes from intramolecular H-bonding between carboxylic function and its neighbouring hydroxy and oxo functions (Scheme 5)

The β-keto acid **2** was subjected to react with 4-oxo-4*H*-chromene-3-carbaldehyde (**18**), in presence of fused sodium acetate. This reaction led to the formation of two isolable products. Characterization of the two products proved that the major product is 3-(chromenylmethylene)pyrano[3,2-*c*]quinoline **20**. The minor product, which was separated from the DMF filtrate of crystallization of reaction product, was characterized as 3-(3-chromenyl)acryloylquinoline **21** (Scheme 6). The structure of the major product pyranoquinoline **20** was inferred from its elemental and spectral analytical data. Microanalysis for C, H, and N elements showed satisfactory results (within ± 0.4 %) of the calculated values (Table 2). IR spectrum represented strong stretching band at $\bar{\nu}$ 1748 correlated to C=O groups of α-pyrone, and 1644-1622 cm^{-1} due to C=O groups of γ-pyrone and quinolone. ^{1}H NMR spectrum showed singlet signal at

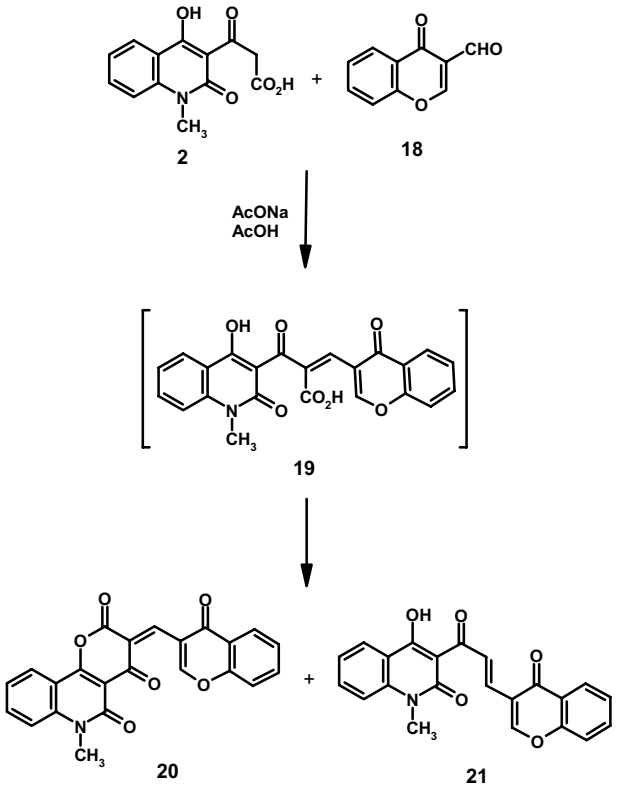


Scheme 5.

δ 6.94 due to chemical shift of a methine proton. Moreover, three signals were also observed at more down field shifts at δ 8.17 as doublet due to C5-H of quinoline, 8.37 as doublet due to C5-H of γ-chromone, and δ 8.70 as singlet characteristic for C2-H of chromone (Table 1). Mass spectrum revealed molecular ion peak at m/z 399, which is in agreement with the calculated molecular weight for the formula (Table 2). The minor product 3-(3-chromenyl)acryloylquinoline **21** is a known compound previously prepared by condensation of 3-acetyl-4-hydroxy-1-methylquinolin-2(1*H*)-one and 4-oxo-4*H*-chromene-3-carbaldehyde (**18**) [26]. An authentic sample of the compound **21** was compared with this product and found completely identical. This showed that subsequent to condensation to form the intermediate **19**, partial decarboxylation took place to some extent affording the acryloylquinoline **21**, while the majority cyclized to give the major product pyranoquinoline **20** (Scheme 6).

Conclusion

4-Hydroxypyranoquinolinedione **1** and its alkaline hydrolysis product β-keto acid derivative **2** are useful synthones to obtain some new 3-heterocyclic substituted quinolin-2(1*H*)-one derivatives in good yields. Usage of either compound **1** or **2** in condensation reaction with aldehydes can lead to the same products since a facile lactonization of the β-keto acid products takes place in acid media. The β-keto acid derivative **2** showed



Scheme 6.

distinctive cyclization behavior when treated with some aldehydes and ketones.

Experimental

General

Melting points were determined on a digital Stuart-SMP3 apparatus. IR spectra were taken on a Perkin-Elmer FT-IR 1650 in KBr disks. ^{1}H NMR spectra were recorded on Varian Gemini-200 NMR-spectrometer (200 MHz), using DMSO-d_6 or $CDCl_3$ as solvents and TMS as internal reference. Mass spectra were determined on a Shimadzu GC-MS-QP 1000 EX mass spectrometer at 70 eV. Elemental microanalyses were performed on a Perkin Elmer CHN-2400 Analyzer. All reactions were monitored by thin-layer chromatography (TLC) on 0.2-mm silica gel F-254 (Merck) plates, using UV light (254 and 366 nm) for detection. Authentic samples of compounds **1** [27], **3b** [21], **9** [16], **14a** [28], **14b** [29], **18** [30] and **21** [26] were prepared according to the literature methods.

4-Hydroxy-6-methylpyrano[3,2-*c*]quinoline-2,5(6*H*)-dione (**1**)

Procedure A

The β-keto acid **2** (1.3 g, 5 mmol) was portion-wise added to concentrated sulfuric acid (10 mL) with continuous stirring

Table 2. Analytical Data of the New Compounds

Compd. No.	Yield %	M.p. °C	M. Formula M. Weight	Microanalysis Calcd./Found		
				C %	H %	N %
1	90[a]	255-7[c]	$C_{13}H_9NO_4$	64.20	3.73	05.76
	76[b]		243.22	64.00	3.70	0.560
2	94	225-7	$C_{13}H_{11}NO_5$	59.77	4.24	05.36
			261.24	59.80	4.20	05.40
3a	85	120-2	$C_{14}H_{13}NO_5$	61.09	4.76	05.09
			275.26	61.20	4.80	04.80
3b	83	130-2[d]	$C_{15}H_{15}NO_5$	62.28	5.23	04.84
			289.29	62.00	5.30	04.80
4	70	244-5	$C_{13}H_{10}N_2O_6$	53.80	3.47	09.65
			290.23	53.80	3.50	09.70
5	60[a]	190-1	$C_{13}H_8N_2O_5$	57.36	2.96	10.29
	76[b]		272.22	57.30	2.90	10.00
6	67	250-2	$C_{19}H_{14}N_4O_7$	55.61	3.44	13.65
			410.35	55.50	3.30	13.40
7	81[a]	275-6	$C_{19}H_{12}N_4O_6$	58.17	3.08	14.28
	80[b]		392.33	58.10	3.10	14.40
8	67	200-1	$C_{16}H_{14}N_2O_4$	64.42	4.73	09.39
			298.30	64.40	4.60	09.20
9	56	284-5[e]	$C_{13}H_{11}N_3O_3$	60.70	4.31	16.33
			257.25	60.50	4.40	16.00
10	75	>300	$C_{21}H_{14}N_2O_6$	64.62	3.62	07.18
			390.36	64.50	3.50	07.00
11	70[a]	>300	$C_{21}H_{12}N_2O_5$	67.74	3.25	07.52
	88[b]		372.34	67.70	3.20	07.50
12	90	290-2	$C_{20}H_{13}NO_5$	69.16	3.77	04.03
			347.33	69.30	3.60	03.80
13	79	>300	$C_{20}H_{13}NO_5$	69.16	3.77	04.03
			347.33	69.10	3.70	04.00
17a	74[a]	>300	$C_{24}H_{16}N_2O_6$	67.29	3.76	06.54
	65[b]		428.40	67.50	3.50	06.40
17b	79[a]	>300	$C_{24}H_{16}N_2O_6$	67.29	3.76	06.54
	68[b]		428.40	67.40	3.60	06.40
20	65	>300	$C_{23}H_{13}NO_6$	69.17	3.28	03.51
			399.36	69.10	3.00	03.40
21	13	224-6[f]	$C_{22}H_{15}NO_5$	70.77	4.05	03.75
			373.37	70.60	3.80	03.50

[a] Yield according to *Procedure A,* [b] Yield according to *Procedure B,* [c] Literature [28] m.p. 257 °C. [d] Literature [21] m.p. 132 °C. [e] Literature [3] m.p. 287-288 °C. [f] Literature [26] m.p. 226 °C.

where the internal temperature was kept 60-65 ºC by means of thermostated water-bath. After completion of addition the mixture was stirred at the ambient temperature for 2 hr, and then poured onto crushed ice to give a brown precipitate. The precipitate so formed was filtered, washed with cold ethanol and crystallized from dioxane [27].

Procedure B

The ester derivative **3a** (0.29 g, 1 mmol), in DMF (10 mL), was heated under reflux for 4 h. Then, the reaction mixture was left to cool, at room temperature, and the crystalline precipitate so formed was filtered and recrystallized from dioxane.

3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoic acid (**2**)

The compound **1** (2.43 g, 10 mmol) was dissolved in sodium hydroxide solution (20 mL, 2M) and warmed at ~ 50 ºC for 30 min, and then the solution so obtained was filtered off. The clear solution was precipitated by dilute hydrochloric acid. The precipitate was filtered, washed with water, dried and crystallized from DMF.

Methyl 3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoate (**3a**) and Ethyl 3-(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxopropanoate (**3b**)

To a suspension of the compound **2** (2.61 g, 10 mmol), in the proper alcohol *viz*; absolute methanol and/or ethanol (20 mL), concentration sulfuric acid (5 mL) was added and stirred up at room temperature overnight. The precipitate so formed was filtered, washed with water, dried, and crystallized from dioxane to give the esters **3a** and **3b**.

3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-hydroxyimino-3-oxopropionic acid (**4**)

To a previously cooled solution (0-5 ºC) of the β-keto acid **2** (1.3 g, 5 mmol), in aqueous sodium carbonate (50 mL, 1M), was drop-wise added nitrous acid (freshly prepared from solution of sodium nitrate (0.35 g, 5 mmol) in ice-cold water (10 mL), and hydrochloric acid (60 mL, 1M) with continuous stirring for about 30 min. After completion of addition, the mixture was stirred at room temperature. The bright orange precipitate that formed was filtered, washed several times with cold water, dried and crystallized from chloroform.

3-Hydroxyimino-6-methylpyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**5**)

Procedure A

The compound **4** (0.58 g, 2 mmol) was portion-wise added to concentrated sulfuric acid (5 mL) and stirred at room temperature for 2 h. The dark brick red solution so formed was poured onto crushed ice. The separated deep orange deposits were filtered, washed with cold water several time, dried and crystallized from DMSO.

Procedure B

To a previously cooled solution (0-5 ºC) the compound **1** (1.22 g, 5 mmol), in aqueous sodium carbonate (50 mL, 1M), was drop-wise added nitrous acid (freshly prepared from solution of sodium nitrate (0.35 g, 5 mmol) in ice-cold water (10 mL), and hydrochloric acid (60 mL, 1M) with continuous stirring for about 30 min. After completion of addition at, the mixture was stirred at the ambient temperature. The deep orange precipitate that formed was filtered, washed several times with cold water, dried and crystallized from DMSO.

3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-2-[(4-nitrophenyl)hydrazono]-3-oxopropionic acid (**6**)

To a previously cooled solution (0-5 ºC) of the β-keto acid **2** (1.3 g, 5 mmol,) in sodium carbonate (50 mL, 1 M), was added a solution of *p*-nitrophenyldiazonium chloride, freshly prepared from *p*-nitroaniline (0.7 g, 5 mmol) and hydrochloric acid (60 mL, 1M), with continuous stirring for about 30 min. After completion of addition, the mixture was stirred at the ambient temperature for 1 hr. The shining orange precipitate that formed was filtered, washed several times with cold water, dried and crystallized from ethanol.

6-Methyl-3-(4-nitrophenyl)hydrazonopyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**7**)

Procedure A

The compound **6** (0.82 g, 2 mmol) was portion-wise added to concentrated sulfuric acid (5 mL) and stirred at room temperature for 2 hr. The dark brick red solution so formed was poured onto crushed ice and the separated reddish-orange deposits were filtered, washed with cold water several time, dried and crystallized from DMF.

Procedure B

To a previously cooled solution (0-5 ºC) of the compound **1** (1.22 g, 2 mmol,) in sodium carbonate (50 mL, 1 M), was added a solution of *p*-nitrophenyldiazonium chloride, freshly prepared from *p*-nitroaniline (0.7 g, 5 mmol) and hydrochloric acid (60 mL, 1M), with continuous stirring for about 30 min. After completion of addition, the mixture was stirred at the ambient temperature for 1 hr. The reddish-orange precipitate that formed was filtered, washed twice with cold water, dried and crystallized from DMF.

2-(4-Methoxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-1*H*-pyrrole-3-carboxylic acid (**8**)

A mixture of the compound **2** (0.26 g, 1 mmol) and 2,2-dimethoxyethanamine (0.22 mL, 2 mmol), in DMF (10 mL), was heated under reflux for 6 hr. Then the solvent was evaporated in vacuum. The residual semi-solid material was triturated with cold ethanol (5 mL). The solid material so formed was filtered and crystallized from DMF.

4-Hydroxy-1-methyl-3-(5-oxo-4,5-dihydro-1*H*-pyrazol-3-yl)quinolin-2(1*H*)-one (**9**)

To a solution of the β-keto acid derivative **2** (0.52 g, 2 mmol), in DMF (10 mL), was added hydrazine hydrate (0.1 mL, 2 mmol), and then the mixture was heated under reflux for 2 hr. The solid product, that formed, was filtered and crystallized from DMSO.

3-(4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-3-oxo-2-(2-oxoindolin-3-ylidene)propanoic acid (**10**)

A mixture of the compound **2** (0.26 g, 1 mmol), isatine (0.15 g, 1 mmol), and fused sodium acetate (0.5 g, 6 mmol) in acetic acid (20 mL), was heated under reflux for 4 hr. The brown crystalline material so formed was filtered and recrystallized from acetic acid.

6-Methyl-3-(2-oxoindolin-3-ylidene)-2*H*-pyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**11**)

Procedure A

The compound **10** (0.29 g, 1 mmol) was portion-wise added to concentrated sulfuric acid (5 mL) and stirred at room temperature for 2 h. The dark green solution so formed was poured onto crushed ice and the separated pale-yellow deposits were filtered, washed with cold water several time, dried and crystallized from DMF.

Procedure B

A mixture of the compound 1 (0.25 g, 1 mmol), isatine (0.15 g, 1 mmol), and fused sodium acetate (0.5 g, 6 mmol) in acetic acid (20 mL), was heated under reflux for 4 hr. The pale-yellow crystalline material so formed was filtered and recrystallized from DMF.

4-Hydroxy-1-methyl-3-(2-oxo-2*H*-chromene-3-carbonyl)quinolin-2(1*H*)-one (**12**)

A mixture of the β-keto acid **2** (2.61 g, 10 mmol), salicylaldehyde (1 mL, 10 mmol), and piperidine (0.2 mL), in ethanol (50 mL), was heated under reflux for 4 hrs. The pastel-yellow precipitate so obtained was filtered, washed thoroughly with cold ethanol and crystallized from DMSO.

3-(2-Hydroxybenzylidene)-6-methylpyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**13**)

A mixture of the compound **1** (2.43 g, 10 mmol), salicylaldehyde (1 mL, 10 mmol), and fused sodium acetate (2.05 g, 25 mmol), in acetic acid (20 mL), was heated under reflux for 4 hr. The pale-yellow precipitate so formed was filtered, washed twice with water and ethanol, and crystallized from acetic acid.

3-((4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-6-methyl-2*H*-pyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**17a**) and 3-((4-Hydroxy-6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-6-methyl-2*H*-pyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**17b**)

A mixture of the compound **2** (0.52 g, 2 mmol), the proper aldehyde derivative **14a** [28], **14b** [29], (0.41 g, 2 mmol), and freshly fused sodium acetate (0.82 g, 10 mmol), in glacial acetic acid (20 mL) was heated under reflux for 4 hr. The crystalline precipitate that formed was collected by filtration, washed with cold ethanol (10 mL) and diethyl ether (10 mL), and recrystallized from acetic acid to give the pyranoquinoline **17a, 17b**.

6-Methyl-3-((4-oxo-4*H*-chromen-3-yl)methylene)-2*H*-pyrano[3,2-*c*]quinoline-2,4,5(3*H*,6*H*)-trione (**20**) and (*E*)-4-Hydroxy-1-methyl-3-(3-(4-oxo-4*H*-chromen-3-yl)acryloyl)quinolin-2(1*H*)-one (**21**)

A mixture of the compound **2** (0.52 g, 2 mmol), 4-oxo-4*H*-chromene-3-carbaldehyde (**18**) [30] (0.35 g, 2 mmol), and freshly fused sodium acetate (0.82 g, 10 mmol), glacial acetic acid (20 mL), was refluxed for 5 hr. The brown precipitate so separated was filtered, washed with cold water, dried and crystallized from hot DMF (20 mL) to give reddish-brown prisms (0.52 g) of the chromenylpyranoquinoline **20**. The DMF-mother liquor filtrate of crystallization was evaporated to about one-third of its initial volume to give yellowish brown needles (0.10 g) of the chromenylacryloylquinoline **21** [26].

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