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# 4-HYDROXY-2-QUINOLONES 130*. THE REACTIVITY OF ETHYL 4-HYDROXY-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLATES

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*The high reactivity of ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates is governed by the simultaneous presence of the 4-OH and 2-C=O groups in the pyridine part of the molecule.*

**Keywords:** ethyl hydroxyquinolinecarboxylates, X-ray structural analysis, reactivity.

Ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates are known to be quite powerful acylating agents. They readily react with primary and many secondary aliphatic, aromatic, and heterocyclic amines to form the corresponding amides in high yields [2-5]. The almost unlimited potential for modification of the quinolone and amide parts of the molecule allows a targeted change to the physicochemical and hence biological properties of the indicated compounds. This has led to increased interest from the viewpoint of chemists and pharmacologists engaged in a search for novel biologically active compounds based on them and which can give rise to medicinal compounds with improved properties

There is also interest in the theoretical question regarding the reason for the high reactivity of the ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates which are key in such investigations because the reason remains unclear. Our report attempts to answer the question.

The first step in our investigation was a comparative analysis of the steric structural features of the simplest member of the homologous series, i.e. ester **1** and of the isomers 4-ethoxycarbonyl-3-hydroxy-2-oxo-1,2-dihydroquinoline (**2**) and 3-ethoxycarbonyl-4-hydroxy-1-oxo-1,2-dihydroisoquinoline (**3**) stable to amidation. With this aim, all three esters were studied by X-ray structural analysis. Hence in the case of the isoquinoline derivative **3** it was found that the heterocyclic fragment is planar to within 0.022 Å (see Fig. 1). The atoms $O_{(1)}$ and $O_{(2)}$ deviated from the isoquinoline ring plane by -0.072 and +0.023 Å respectively.

The ethoxycarbonyl group is placed virtually in the plane of the bicycle (torsional angles $C_{(4)}$–$C_{(3)}$–$C_{(11)}$–$O_{(3)}$ -2.7(3), $C_{(3)}$–$C_{(11)}$–$O_{(4)}$–$C_{(12)}$ 178.5(2), and $C_{(11)}$–$O_{(4)}$–$C_{(12)}$–$C_{(13)}$ 172.0(2)º). This substituent location is likely due to the formation of an intramolecular hydrogen bond $O_{(2)}$–$H_{(2)}$···$O_{(3)}$ 1.82(2) Å (angle $O_{(2)}$–$H_{(2)}$···$O_{(3)}$ 144(3)º). The ester **3** molecule forms centrosymmetric dimers in the crystal via an intermolecular hydrogen bond $N_{(2)}$–H···$O_{(1)}$ (1-*x*, 1-*y*, 1-*z*) 2.04(3) Å (angle N–H···O 166(3)º).

* For Communication 129 see [1].

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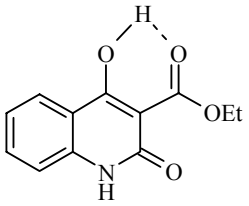
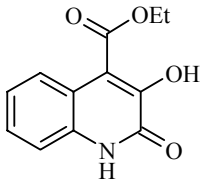
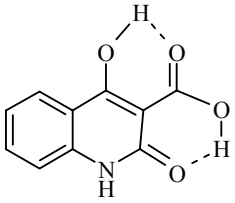
Similar parameters were found in the 4-hydroxy-2-oxoquinoline ester **1** [6]. One significant difference was noted in the structure of the 4-ethoxycarbonyl compound **2** in which the carbonyl group of the ester function deviated markedly from the plane of the bicycle leading to a disturbance to the conjugation and so to lengthening of the C–COO and shortening of the C=O bonds [7]. Evidently this fact serves partially to explain the low reactivity of ester **2** when reacting with amines.



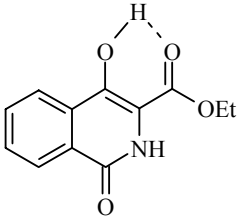
**1** p*K*a = 8.64 ± 0.03



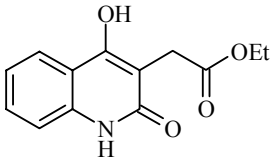
**2** p*K*a = 10.36 ± 0.05



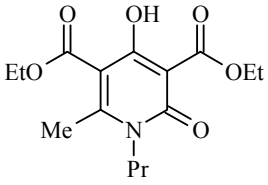
**4** p*K*a$^{OH}$ = 13.53 ± 0.06
p*K*a$^{COOH}$ = 7.16 ± 0.03



**3** p*K*a > 13



**5** p*K*a = 8.75 ± 0.04



**6**

Useful information was also obtained when studying the acidic properties of esters **1-3**. It was found that 4-hydroxy-2-oxo derivative **1** in 80% aqueous dioxane shows the properties of a weak acid (see Scheme).

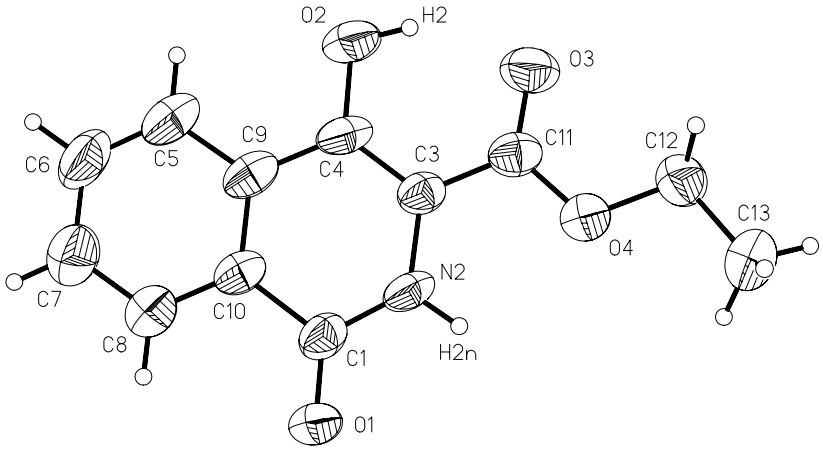



Fig. 1. Structure of the isoquinoline ester **3** with atomic numbering.

With a change of the ester group for a carboxyl (acid **4**) the acidic properties of the 4-OH group are strongly lowered by four orders and this is likely connected with the appearance in the X-ray analysis [8] of an additional intramolecular hydrogen bond between the carboxyl and 2-carbonyl groups. A similar effect, but limited by the impossibility of polar conjugation of the anion with the heteroatom, also changes with the position of the nitrogen atom relative to the hydroxyl group (esters **2** and **3**) and this agrees with the σ- constants for a nitrogen heteroatom as substituent ($\sigma_4$ = 0.85, $\sigma_3$ = 0.53 [9]). These results allow us to propose a direct relationship between the reactivity of the carbethoxy groups of esters **1-3** and the acidity of their OH groups. However, the next example (the quinoline-3-acetate ester **5**) which is known for its inertness to amines [10] is inconsistent with such a conclusion. The introduction of an isolating methylene linkage into the side chain leads to a systematic weakening of the acid dissociation process due to the decreased inductive effect from the ester side. However, the effect of this modification has proved very limited. At least, the lowering in the acidity of the 4-OH group observed when changing from the quinoline-3-carboxylate ester **1** (p$K_a$ 8.64) to the quinoline-3-acetate ester **5** (p$K_a$ 8.75) can scarcely be considered as the principal reason for this fall in reactivity.

None the less, the activating effect of the 4-OH group on the acylating properties of ester **1** is not in doubt since its removal, alkylation, participation in salt formation [11], or substitution by halogen, methyl [12], primary [13] or secondary [14] amino group fully deactivate the ester fragment. It was interesting that removal of the carbonyl group from position 2 of the quinoline ring produced a similar effect. The amidation of ethyl 4-hydroxyquinoline-3-carboxylate by alkylamines in refluxing ethanol did not occur. Also very significant was the fact that the diethyl ester of 4-hydroxy-6-methyl-2-oxo-1-propyl-1,2-dihydropyridine-3,5-dicarboxylic acid (**6**) was amidated exclusively at the 3-ethoxycarbonyl group [15].

TABLE 1. Bond Lengths (*l*) in the Isoquinoline Ester **3**

| Bond | *l*, Å | Bond | *l*, Å |
|---|---|---|---|
| $O_{(1)}$–$C_{(1)}$ | 1.2298(19) | $C_{(3)}$–$C_{(4)}$ | 1.375(2) |
| $O_{(2)}$–$C_{(4)}$ | 1.356(2) | $C_{(3)}$–$C_{(11)}$ | 1.439(2) |
| $O_{(2)}$–$H_{(2)}$ | 0.86(2) | $C_{(4)}$–$C_{(9)}$ | 1.444(3) |
| $O_{(3)}$–$C_{(11)}$ | 1.2418(19) | $C_{(5)}$–$C_{(6)}$ | 1.356(3) |
| $O_{(4)}$–$C_{(11)}$ | 1.334(2) | $C_{(5)}$–$C_{(9)}$ | 1.411(2) |
| $O_{(4)}$–$C_{(12)}$ | 1.462(2) | $C_{(6)}$–$C_{(7)}$ | 1.382(3) |
| $C_{(1)}$–$N_{(2)}$ | 1.363(2) | $C_{(7)}$–$C_{(8)}$ | 1.384(3) |
| $C_{(1)}$–$C_{(10)}$ | 1.492(2) | $C_{(8)}$–$C_{(10)}$ | 1.381(3) |
| $N_{(2)}$–$C_{(3)}$ | 1.407(2) | $C_{(9)}$–$C_{(10)}$ | 1.404(2) |
| $N_{(2)}$–$H_{(2n)}$ | 0.8519 | $C_{(12)}$–$C_{(13)}$ | 1.491(2) |

TABLE 2. Valence Angles (ω) in the Isoquinoline Ester **3**

| Angle | ω, deg | Angle | ω, deg |
|---|---|---|---|
| $C_{(4)}$–$O_{(2)}$–$H_{(2)}$ | 105.2(14) | $C_{(5)}$–$C_{(6)}$–$C_{(7)}$ | 120.97(18) |
| $C_{(11)}$–$O_{(4)}$–$C_{(12)}$ | 116.23(14) | $C_{(6)}$–$C_{(7)}$–$C_{(8)}$ | 119.3(2) |
| $O_{(1)}$–$C_{(1)}$–$N_{(2)}$ | 122.16(14) | $C_{(10)}$–$C_{(8)}$–$C_{(7)}$ | 121.29(18) |
| $O_{(1)}$–$C_{(1)}$–$C_{(10)}$ | 122.86(17) | $C_{(10)}$–$C_{(9)}$–$C_{(5)}$ | 119.03(19) |
| $N_{(2)}$–$C_{(1)}$–$C_{(10)}$ | 114.98(16) | $C_{(10)}$–$C_{(9)}$–$C_{(4)}$ | 118.65(14) |
| $C_{(1)}$–$N_{(2)}$–$C_{(3)}$ | 124.91(14) | $C_{(5)}$–$C_{(9)}$–$C_{(4)}$ | 122.32(17) |
| $C_{(4)}$–$C_{(3)}$–$N_{(2)}$ | 119.94(16) | $C_{(8)}$–$C_{(10)}$–$C_{(9)}$ | 118.96(15) |
| $C_{(4)}$–$C_{(3)}$–$C_{(11)}$ | 120.29(15) | $C_{(8)}$–$C_{(10)}$–$C_{(1)}$ | 119.60(15) |
| $N_{(2)}$–$C_{(3)}$–$C_{(11)}$ | 119.76(14) | $C_{(9)}$–$C_{(10)}$–$C_{(1)}$ | 121.43(17) |
| $O_{(2)}$–$C_{(4)}$–$C_{(3)}$ | 122.91(17) | $O_{(3)}$–$C_{(11)}$–$O_{(4)}$ | 122.57(17) |
| $O_{(2)}$–$C_{(4)}$–$C_{(9)}$ | 117.05(14) | $O_{(3)}$–$C_{(11)}$–$C_{(3)}$ | 122.59(16) |
| $C_{(3)}$–$C_{(4)}$–$C_{(9)}$ | 120.01(15) | $O_{(4)}$–$C_{(11)}$–$C_{(3)}$ | 114.84(15) |
| $C_{(6)}$–$C_{(5)}$–$C_{(9)}$ | 120.38(19) | $O_{(4)}$–$C_{(12)}$–$C_{(13)}$ | 106.82(15) |

Hence the high reactivity of ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates occurs only with the simultaneous presence in the pyridine part of the molecule of the 4-OH and 2-C=O groups. In fact, they can be considered in their behavior as cyclic analogs of a methanetricarboxylic mono ester (more precisely its enol form). If such an approach is also used in the analysis of the structure of esters **2**, **3**, and **5** it appears that they are synthetic analogs of the mono ester enol forms of succinic acid (esters **2** and **5**) or acylaminomalonic acid (ester **3**). In these cases the inertness of their ester groups becomes apparent.

## EXPERIMENTAL

Ethyl 4-hydroxy-1-oxo-1,2-dihydroisoquinoline-3-carboxylate (**3**) was prepared by rearrangement of ethyl phthalimidoacetate [16]. Investigation of the acid-base equilibria was carried out by method [17] using 80% aqueous dioxane as solvent. Freshly, doubly distilled dioxane for UV spectroscopy, freed from $CO_2$, from the Labscan company was used in the preparation of the mixed solvent. The titrant was 0.01 molar aqueous KOH freed from $CO_2$. The concentrations of the titrations solutions at half neutralization point were 0.0005 molar. Potentiometric titrations were carried out on a SevenEasy S-20-K Mettler Toledo steady state pH meter using an InLab 413 combination electrode at 25ºC. Titrations were carried out three times for each compound. The accuracy of the results obtained was evaluated by a mathematical statistics method [18].

**X-ray Structural Investigation**. Crystals of the isoquinoline-3-carboxylate ester (**3**) are monoclinic (ethanol), at 20ºC: $a$ = 13.848(9), $b$ = 4.403(2), $c$ = 18.591(15) Å, β = 105.03(2)º, $V$ = 1094.8(12) Å$^3$, $M_r$ = 233.22, $F$(000) = 488, $Z$ = 4, $d_{calc}$ = 1.415 g/cm$^3$, space group $P2/n$, μ(MoKα) = 0.108 mm$^{-1}$. Measurement of the intensities was carried out on a Siemens P3/PC, four circle automatic diffractometer using molybdenum irradiation and graphite monochromator (2θ/θ scanning in the range $5 \leq 2\theta \leq 50$º, 2 control reflections for all each of the 98 reflexes). 1925 Intensities were measured of which 1850 were independent with $R_{int}$ = 0.0557 and 947 with $I > 2\sigma(I)$. For conversion of intensities to structural factors the Lorentz and polarization factors carried out using a Lehmann-Larsen profile were included.

The structure was solved by a direct method and refined in $F^2$ full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms. The final accuracy factors were $R$ = 0.0343, $wR_2$ = 0.0502 for the observed and $R$ = 0.1187, $wR_2$ = 0.0625 for all independent reflections. Calculations were carried out using the SHELX97 program package [19]. The full crystallographic information has been deposited in the Cambridge structural data bank (reference CCDC 619707). Interatomic distances and valence angles are given in Tables 1 and 2.

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