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# 4-HYDROXY-2-QUINOLONES. 41.* REACTION OF HYDRAZIDES OF 1-R-2-OXO-4-HYDROXYQUINOLINE-3-CARBOXYLIC ACIDS WITH ETHYL ORTHOFORMATE

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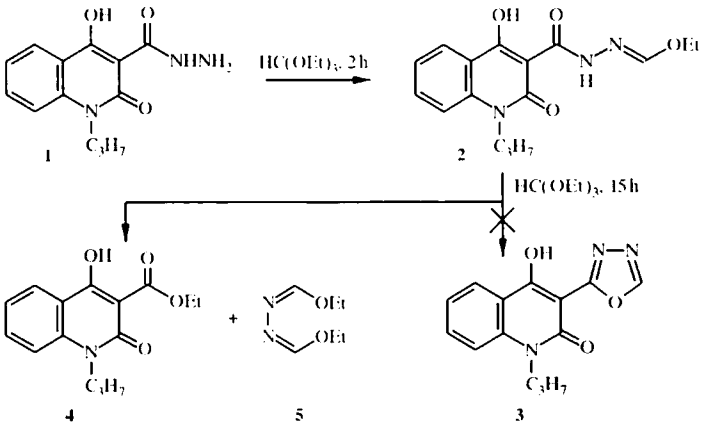
*The boiling of hydrazides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids in an excess of ethyl orthoformate leads to the formation of ethyl esters of the corresponding quinoline-3-carboxylic acids, the structure of which was confirmed by X-ray diffraction analysis.*

**Keywords:** hydrazide, carbostyryl, 4-hydroxyquinolone, ethyl formate, X-ray diffraction analysis.

Depending on the reaction conditions and the chemical structure, hydrazides of carboxylic acids react with ethyl orthoformate to form various products [2]. A general method, developed by Ainsworth [3], for the synthesis of 1,3,4-oxadiazoles involves the boiling of hydrazides of different aryl(heteryl)carboxylic acids in an excess of the orthoester, whereby it was shown that the corresponding intermediate alkoxyalkylidene derivatives can also be isolated if required.




Experiments showed that the brief (2 h) boiling of the hydrazide of 1-propyl-2-oxo-4-hydroxyquinoline-3-carboxylic acid (**1**) in an excess of ethyl orthoformate leads, as expected, to the "normal" product of such a reaction – the ethoxymethylidenehydrazide (**2**). When the reaction time was increased to 15 h, ethyl 1-propyl-2-

* For the Communication 40, see [1].

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oxo-4-hydroxyquinoline-3-carboxylate (**4**) was isolated with a high yield instead of the expected oxadiazole (**3**). The data obtained indicate that the esterification is undergone by the ethoxymethylidene derivative **2**, and not by the initial hydrazide **1**. The formation of the ester **4** apparently proceeds by a mechanism analogous to transesterification, although the conversion of amides to esters is usually associated with significant difficulties [4]. Such a ready reaction course can be explained by several factors. In the first place, as was established [5, 6], the amides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids are characterized by a strong intramolecular hydrogen bond between the 4-OH group and the oxygen atom of the carbonyl group at the position 3 of the quinolone ring, leading to significant lengthening of the C=O bond which should, in turn, substantially facilitate attack by the ethoxide ion at the carbonyl carbon atom of the amide portion. On the other hand, if the investigated reaction actually goes through by a type of transesterification, then the equilibrium mixture of the ester **4** and the ethoxymethylidene derivative **2** should be formed in principle. Nevertheless, the utilization of an excess of ethyl orthoformate guarantees the binding of the hydrazine released, apparently in the ethoxymethylidenazine (**5**), thereby shifting the equilibrium in favor of the formation of the ester.

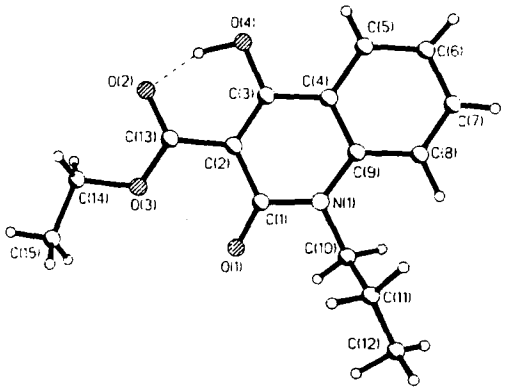


Fig. 1. The structure of the ester **4**.

TABLE 1. Coordinates of Non-hydrogen Atoms (Å × $10^4$) and Equivalent Isotropic Thermal Parameters (Å$^2$ × $10^3$) in the Structure of the Ester **4**

| Atom | x | y | z | $U_{eq}$ |
|---|---|---|---|---|
| $N_{(1)}$ | 4118(2) | 3648(1) | 7341(2) | 50(1) |
| $O_{(1)}$ | 3809(2) | 2361(1) | 7392(2) | 66(1) |
| $O_{(2)}$ | 354(2) | 2613(1) | 9665(2) | 68(1) |
| $O_{(3)}$ | 1750(2) | 1789(1) | 8708(2) | 51(1) |
| $O_{(4)}$ | 807(2) | 4017(1) | 9638(2) | 66(1) |
| $C_{(1)}$ | 3428(2) | 2992(1) | 7760(2) | 45(1) |
| $C_{(2)}$ | 2252(2) | 3123(1) | 8579(2) | 40(1) |
| $C_{(3)}$ | 1896(2) | 3863(1) | 8934(2) | 43(1) |
| $C_{(4)}$ | 2700(2) | 4515(1) | 8559(2) | 43(1) |
| $C_{(5)}$ | 2364(3) | 5267(1) | 8960(3) | 56(1) |
| $C_{(6)}$ | 3182(3) | 5879(1) | 8637(3) | 67(1) |
| $C_{(7)}$ | 4335(3) | 5755(1) | 7920(3) | 64(1) |
| $C_{(8)}$ | 4670(3) | 5028(1) | 7490(3) | 60(1) |
| $C_{(9)}$ | 3842(2) | 4389(1) | 7790(2) | 44(1) |
| $C_{(10)}$ | 5144(3) | 3514(1) | 6298(3) | 55(1) |
| $C_{(11)}$ | 6731(3) | 3394(2) | 7185(3) | 62(1) |
| $C_{(12)}$ | 7697(3) | 3246(2) | 6029(4) | 69(1) |
| $C_{(13)}$ | 1385(2) | 2494(1) | 9026(2) | 47(1) |
| $C_{(14)}$ | 840(3) | 1172(1) | 9116(3) | 58(1) |
| $C_{(15)}$ | 1460(3) | 434(1) | 8682(4) | 67(1) |

TABLE 2. Bond Lengths ($l$) in the Structure of the Ester **4**

| Bond | $l$, Å | Bond | $l$, Å |
|---|---|---|---|
| $N_{(1)}$–$C_{(9)}$ | 1.388(3) | $N_{(1)}$–$C_{(11)}$ | 1.397(2) |
| $N_{(1)}$–$C_{(10)}$ | 1.487(3) | $O_{(1)}$–$C_{(11)}$ | 1.218(2) |
| $O_{(2)}$–$C_{(13)}$ | 1.235(3) | $O_{(3)}$–$C_{(13)}$ | 1.319(2) |
| $O_{(3)}$–$C_{(14)}$ | 1.459(2) | $O_{(4)}$–$C_{(3)}$ | 1.328(2) |
| $C_{(11)}$–$C_{(2)}$ | 1.459(2) | $C_{(2)}$–$C_{(3)}$ | 1.381(3) |
| $C_{(2)}$–$C_{(13)}$ | 1.464(3) | $C_{(3)}$–$C_{(4)}$ | 1.437(3) |
| $C_{(4)}$–$C_{(9)}$ | 1.400(3) | $C_{(4)}$–$C_{(5)}$ | 1.406(3) |
| $C_{(5)}$–$C_{(6)}$ | 1.373(4) | $C_{(6)}$–$C_{(7)}$ | 1.379(4) |
| $C_{(7)}$–$C_{(8)}$ | 1.376(4) | $C_{(8)}$–$C_{(9)}$ | 1.410(3) |
| $C_{(10)}$–$C_{(11)}$ | 1.501(4) | $C_{(11)}$–$C_{(12)}$ | 1.527(3) |
| $C_{(14)}$–$C_{(15)}$ | 1.492(4) | | |

Investigation of the structure of the ester **4** by X-ray diffraction showed that the pyridone ring occurs in the conformation of the compressed sofa. The $N_{(1)}$ atom deviates from the plane of the remaining ring atoms by -0.07 Å. The reason for the disturbance in the planarity of the given portion is probably the repulsion between the trans-disposed propyl substituents, the carbonyl group, and the hydrogen atom in the peri position of the benzene ring, whereby the shortened intramolecular contact for $H_{(10B)}\cdots O_{(1)}$ is 2.33 Å and that of $H_{(10A)}\cdots H_{(8)}$ is 2.04 Å, where the sums of the van der Waals radii [7] are 2.46 Å and 2.32 Å correspondingly. The ethoxy group has the *s-cis* conformation in relation to the endocyclic $C_{(2)}$=$C_{(3)}$ double bond. Such a disposition of the substituent is determined by the formation of the strong intramolecular $O_{(4)}$–$H_{(4O)}\cdots O_{(2)}$ hydrogen bond of 1.48 Å, where the O–H···O angle is 156°. On account of this, significant changes of the bond lengths are also observed in the portions under consideration. The $C_{(2)}$–$C_{(3)}$ bond of 1.381(3) Å and the $C_{(13)}$–$O_{(2)}$ bond of 1.235(3) Å are lengthened by comparison with the mean values [8] of 1.343 Å and 1.211 Å, and the $C_{(3)}$–$O_{(4)}$ and $C_{(13)}$–$C_{(14)}$ bonds are shortened, with the mean values of 1.36 Å and 1.453 Å correspondingly.

Shortened intermolecular contact for $O_{(1)}$–$H_{(5)}$ (1-$x$, -0.5+$y$, 1.5-$z$) of 2.37 Å is also found in the crystal of compound **1**.

TABLE 3. Bond Angles ($\omega$) in the Structure of the Ester **4**

| Angle | $\omega$, deg | Angle | $\omega$, deg |
|---|---|---|---|
| $C_{(9)}$–$N_{(1)}$–$C_{(11)}$ | 123.7(2) | $C_{(9)}$–$N_{(1)}$–$C_{(10)}$ | 120.6(2) |
| $C_{(11)}$–$N_{(1)}$–$C_{(10)}$ | 115.7(2) | $C_{(13)}$–$O_{(3)}$–$C_{(14)}$ | 116.0(2) |
| $O_{(1)}$–$C_{(11)}$–$N_{(1)}$ | 119.0(2) | $O_{(1)}$–$C_{(11)}$–$C_{(12)}$ | 124.6(2) |
| $N_{(1)}$–$C_{(11)}$–$C_{(12)}$ | 116.3(2) | $C_{(3)}$–$C_{(2)}$–$C_{(11)}$ | 120.2(2) |
| $C_{(3)}$–$C_{(2)}$–$C_{(13)}$ | 117.3(2) | $C_{(11)}$–$C_{(2)}$–$C_{(13)}$ | 122.4(2) |
| $O_{(4)}$–$C_{(3)}$–$C_{(2)}$ | 122.8(2) | $O_{(4)}$–$C_{(3)}$–$C_{(4)}$ | 116.0(2) |
| $C_{(2)}$–$C_{(3)}$–$C_{(4)}$ | 121.2(2) | $C_{(9)}$–$C_{(4)}$–$C_{(5)}$ | 120.3(2) |
| $C_{(9)}$–$C_{(4)}$–$C_{(3)}$ | 118.6(2) | $C_{(5)}$–$C_{(4)}$–$C_{(3)}$ | 121.2(2) |
| $C_{(6)}$–$C_{(5)}$–$C_{(4)}$ | 120.2(2) | $C_{(5)}$–$C_{(6)}$–$C_{(7)}$ | 119.8(2) |
| $C_{(8)}$–$C_{(7)}$–$C_{(6)}$ | 121.2(2) | $C_{(7)}$–$C_{(8)}$–$C_{(9)}$ | 120.3(2) |
| $N_{(1)}$–$C_{(9)}$–$C_{(4)}$ | 119.6(2) | $N_{(1)}$–$C_{(9)}$–$C_{(8)}$ | 122.2(2) |
| $C_{(4)}$–$C_{(9)}$–$C_{(8)}$ | 118.2(2) | $N_{(1)}$–$C_{(10)}$–$C_{(11)}$ | 112.9(2) |
| $C_{(10)}$–$C_{(11)}$–$C_{(12)}$ | 109.4(2) | $O_{(2)}$–$C_{(13)}$–$O_{(3)}$ | 121.1(2) |
| $O_{(2)}$–$C_{(13)}$–$C_{(2)}$ | 122.0(2) | $O_{(3)}$–$C_{(13)}$–$C_{(2)}$ | 116.9(2) |
| $O_{(3)}$–$C_{(14)}$–$C_{(15)}$ | 106.8(2) | | |

## EXPERIMENTAL

The $^1$H NMR spectra of the compounds synthesized were recorded on the Bruker WP-100 SY instrument in DMSO-$d_6$ with TMS as the internal standard. The hydrazide of 1-propyl-2-oxo-4-hydroxyquinoline-3-carboxylic acid **1** was synthesized by the method [10].

**Ethoxymethylidenehydrazide of 1-Propyl-2-oxo-4-hydroxyquinoline-3-carboxylic Acid (2).** The solution of hydrazide of 1-propyl-2-oxo-4-hydroxyquinoline-3-carboxylic acid **1** (2.61 g, 0.01 mol) in ethyl orthoformate (30 ml) is boiled for 2 h, after which the excess of orthoester is distilled off under reduced pressure. The residue is crystallized from ethanol. The yield is 2.34 g (76%); mp 163-165°C. $^1$H NMR spectrum: 12.97 (1H, s, OH); 11.10 (1H, s, NH); 8.09 (1H, d, 5-H); 7.81 (1H, t, 7-H); 7.64 (1H, d, 8-H); 7.36 (1H, t, 6-H); 7.21 (1H, s, C<u>H</u>–OEt); 4.27 (4H, m, $NCH_2$ + $OCH_2$); 1.64 (2H, m, $NCH_2C\underline{H}_2$); 1.32 (3H, t, $OCH_2C\underline{H}_3$); 0.96 ppm (3H, t, $NCH_2CH_2C\underline{H}_3$). Found, %: C 60.68; H 5.96; N 13.35. $C_{16}H_{19}N_3O_4$. Calculated, %: C 60.56; H 6.03; N 13.24.

**Ethyl Ester of 1-Propyl-2-oxo-4-hydroxyquinoline-3-carboxylic Acid (4). ($C_{15}H_{17}NO_4$).** This compound is synthesized by an analogous method. The reaction time is 15 h. Yield 83%; mp 86-88°C (diethyl ether). The mixed test with a sample of the ester **4** obtained by the method [11] does not give a depression of the melting temperature. The $^1$H NMR spectra of these compounds are identical.

**X-Ray Diffraction Investigation.** Crystals of the ester **4** are monoclinic. At 20°C, $a$ = 9.242(2) Å, $b$ = 17.378(5) Å, $c$ = 8.789(2) Å; β = 103.89(2)°; V = 1370.3(6) Å$^3$; $d_{calc}$ = 1.334 g/cm$^3$; space group $P2_1/c$; $Z$ = 4. Parameters of the elementary cell and intensities of the 3914 independent reflections ($R_{int}$ = 0.038) were measured on the Siemens P3/PC automatic four-circle diffractometer (λMoKα, graphite monochromator, θ/2θ-scanning, $2\theta_{max}$ = 60°). The structure was interpreted by the direct method with the utilization of the SHELX97 complex of programs [9]. Positions of the hydrogen atoms were calculated geometrically and specified by the "rider" model with the fixed $U_{iso}$ = n$U_{eq}$ of the non-hydrogen atom connected with the given atom of hydrogen (n = 1.5 for the methyl groups, and 1.2 for the remaining hydrogen atoms). The specification for $F^2$ by the full-matrix MLS in the anisotropic approximation for non-hydrogen atoms from the 3914 reflections was conducted to the $wR_2$ = 0.216 ($R_1$ = 0.078 from 2323 reflections with the $F > 4\sigma(F)$, S = 1.02). The final coordinates of non-hydrogen atoms are presented in Table 1, and the bond lengths and bond angles are presented in the Tables 2 and 3.

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