Chemistry of Heterocyclic Compounds, Vol. 43, No. 9, 2007

4-HYDROXY-2-QUINOLONES

127.* SIMPLE METHOD FOR EXCHANGING CHLORINE FOR HYDROXYL IN 1-R-4-CHLORO-3-ETHOXYCARBONYl-2-OXO-1,2-DIHYDRO-QUINOLINES

I. V. Ukrainets[1], N. L. Bereznyakova[1], and S. V. Shishkina[2]

Treatment of ethyl 1-R-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylates with sodium nitrite in DMSO is a convenient method for their conversion to the corresponding 4-hydroxy derivatives.

Keywords: 4-chloro-2-oxo-1,2-dihydroquinolines, nitrous acid esters, X-ray analysis.

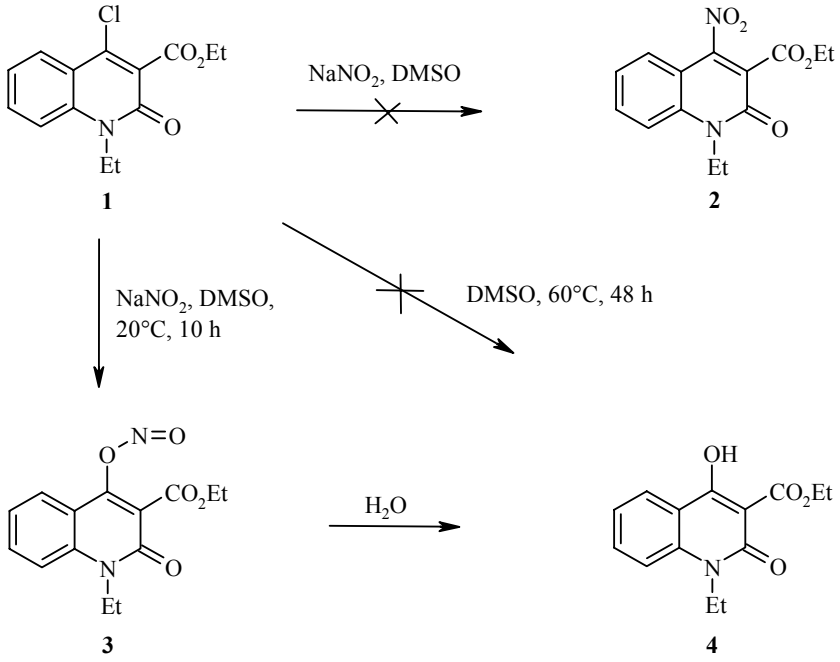
At this time several methods are known for the preparation of ethyl 1-alkyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates which are widely used in the synthesis of biologically active molecules [2-5]. With some considerable variety in the organic amines and 1,3-dicarbonyl compounds used in these methods, they all show the common feature of the N-alkyl substituent being introduced into the amine component before formation of the 4-hydroxy-2-oxo-1,2-dihydroquinoline ring. As is known, the N-alkylation of anilines occurs far from smoothly. Hence we previously attempted to synthesise 1-alkyl-substituted 3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinolines by a fundamentally different scheme proposing the introduction of the alkyl substituent into the previously prepared 1H-quinolone [6]. Direct alkylation did not give a positive result since it primarily gave the 4-alkoxyl derivative. With the use of a double excess of the alkylating agent the N-alkylation can indeed be achieved but removal of the 4-O-alkyl-protecting group without removal of the ethoxycarbonyl group remained a problem. On the other hand, the 4-O-acetyl protection is removed quite readily as a result of which about 20% of the alkyl halides are consumed in the formation of side alkyl acetates.

With this in mind, it seemed extremely promising to carry out a ready temporary modification of the 4-hydroxy group to a chlorine which would be inert to the conditions of the subsequent alkylation [7]. In fact, the N-alkylation of ethyl 4-chloro-1H-2-oxo-1,2-dihydroquinoline-3-carboxylates occurs in good yields [6]. However, as in the case with the 4-alkoxy derivatives, the return conversion of chlorine to a hydroxyl group is also significantly complicated by the lability of the ester reaction center in the molecule. None the less, we have unexpectedly discovered a very simple solution to this problem.

* For Communication 126 see [1].

[1]National University of Pharmacy, Kharkiv 61002, Ukraine; e-mail: uiv@kharkov.ua. [2]STC "Institute for Single Crystals", Ukraine National Academy of Sciences, Kharkiv 61001; e-mail: svet@xray.isc.kharkov.com. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1359-1364, September, 2007. Original article submitted May 18, 2006.

Being an ambident nucleophile the nitrite ion can react with organic halides in two ways. Depending on the conditions, the attack can occur at either the oxygen or a nitrogen atom leading to a nitrous acid ester or nitro derivative respectively [8]. Put differently, the reaction of ethyl 4-chloro-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) with sodium nitrite can theoretically form both the 4-nitroquinolone **2** and the hetarylnitrite **3**. Aprotic solvents cannot form hydrogen bonds and are thus unable to strongly solvate the anions formed on dissociation. As a result, when the reaction is carried out in DMSO the nitrite ion oxygen (as the center with the greatest charge density) proves more basic than the nitrogen and hence the O-substitution principally occurs.



The compound obtained gives a negative Beilstein test hence nucleophilic substitution of halogen in the chloroquinoline **1** has occurred successfully. However, X-ray analysis carried out by us (Figure 1, Tables 1, 2)

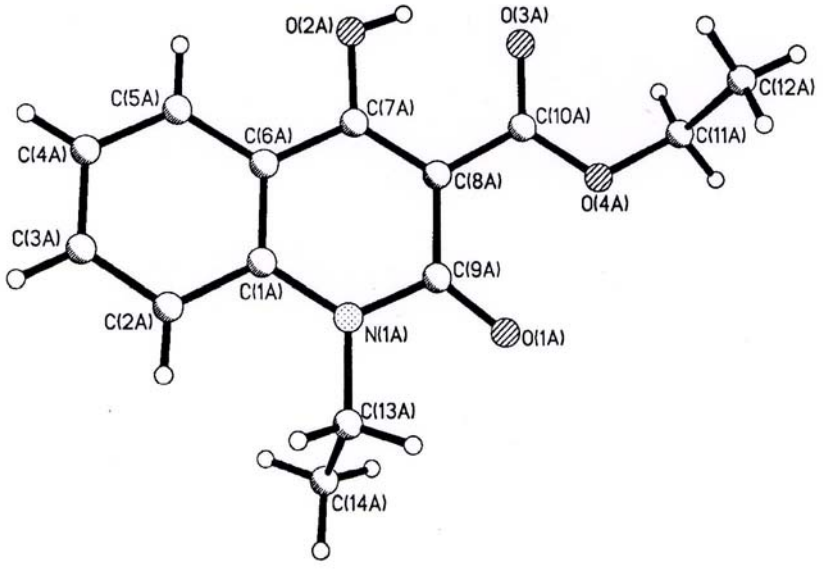


Fig. 1. Structure of the 4-hydroxy ester **4** molecule with atomic numbering.

TABLE 1. Bond Lengths (*l*) in the 4-Hydroxy Ester **4** Structure

Bond	*l*, Å	Bond	*l*, Å	Bond	*l*, Å
$N_{(1A)}$–$C_{(1A)}$	1.394(3)	$C_{(1B)}$–$C_{(6B)}$	1.402(3)	$C_{(8A)}$–$C_{(10A)}$	1.468(3)
$N_{(1A)}$–$C_{(13A)}$	1.466(3)	$C_{(2B)}$–$C_{(3B)}$	1.381(3)	$C_{(13A)}$–$C_{(14A)}$	1.515(3)
$O_{(2A)}$–$C_{(7A)}$	1.330(3)	$C_{(4B)}$–$C_{(5B)}$	1.371(3)	$N_{(1B)}$–$C_{(9B)}$	1.405(3)
$O_{(4A)}$–$C_{(10A)}$	1.315(3)	$C_{(6B)}$–$C_{(7B)}$	1.429(3)	$O_{(1B)}$–$C_{(9B)}$	1.221(3)
$C_{(1A)}$–$C_{(6A)}$	1.393(3)	$C_{(8B)}$–$C_{(9B)}$	1.467(3)	$O_{(3B)}$–$C_{(10B)}$	1.234(3)
$C_{(2A)}$–$C_{(3A)}$	1.370(3)	$C_{(11B)}$–$C_{(12B)}$	1.499(3)	$O_{(4B)}$–$C_{(11B)}$	1.457(3)
$C_{(4A)}$–$C_{(5A)}$	1.373(3)	$N_{(1A)}$–$C_{(9A)}$	1.407(3)	$C_{(1B)}$–$C_{(2B)}$	1.408(3)
$C_{(6A)}$–$C_{(7A)}$	1.434(3)	$O_{(1A)}$–$C_{(9A)}$	1.227(2)	$C_{(3B)}$–$C_{(4B)}$	1.379(4)
$C_{(8A)}$–$C_{(9A)}$	1.456(3)	$O_{(3A)}$–$C_{(10A)}$	1.236(3)	$C_{(5B)}$–$C_{(6B)}$	1.408(3)
$C_{(11A)}$–$C_{(12A)}$	1.496(3)	$O_{(4A)}$–$C_{(11A)}$	1.459(3)	$C_{(7B)}$–$C_{(8B)}$	1.378(3)
$N_{(1B)}$–$C_{(1B)}$	1.391(3)	$C_{(1A)}$–$C_{(2A)}$	1.408(3)	$C_{(8B)}$–$C_{(10B)}$	1.470(3)
$N_{(1B)}$–$C_{(13B)}$	1.466(3)	$C_{(3A)}$–$C_{(4A)}$	1.378(4)	$C_{(13B)}$–$C_{(14B)}$	1.514(3)
$O_{(2B)}$–$C_{(7B)}$	1.333(3)	$C_{(5A)}$–$C_{(6A)}$	1.402(3)		
$O_{(4B)}$–$C_{(10B)}$	1.321(3)	$C_{(7A)}$–$C_{(8A)}$	1.383(3)		

has shown that this compound is neither the nitroquinolone **2** nor the hetarylnitrite **3** but it is ethyl 1-ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**4**). In the symmetrically independent part of the unit cell this compound exists as two molecules (**A** and **B**), differing in some geometrical parameters.

TABLE 2. Valence Angles (ω) in the 4-Hydroxy Ester **4** Structure

Angle	ω, deg	Angle	ω, deg
$C_{(1A)}$–$N_{(1A)}$–$C_{(9A)}$	123.3(2)	$C_{(1A)}$–$N_{(1A)}$–$C_{(13A)}$	120.5(2)
$C_{(9A)}$–$N_{(1A)}$–$C_{(13A)}$	116.2(2)	$C_{(10A)}$–$O_{(4A)}$–$C_{(11A)}$	117.5(2)
$C_{(6A)}$–$C_{(1A)}$–$N_{(1A)}$	119.8(2)	$C_{(6A)}$–$C_{(1A)}$–$C_{(2A)}$	118.8(2)
$N_{(1A)}$–$C_{(1A)}$–$C_{(2A)}$	121.3(2)	$C_{(3A)}$–$C_{(2A)}$–$C_{(1A)}$	119.6(2)
$C_{(2A)}$–$C_{(3A)}$–$C_{(4A)}$	121.8(2)	$C_{(5A)}$–$C_{(4A)}$–$C_{(3A)}$	119.3(2)
$C_{(4A)}$–$C_{(5A)}$–$C_{(6A)}$	120.4(2)	$C_{(1A)}$–$C_{(6A)}$–$C_{(5A)}$	120.0(2)
$C_{(1A)}$–$C_{(6A)}$–$C_{(7A)}$	118.8(2)	$C_{(5A)}$–$C_{(6A)}$–$C_{(7A)}$	121.2(2)
$O_{(2A)}$–$C_{(7A)}$–$C_{(8A)}$	122.7(2)	$O_{(2A)}$–$C_{(7A)}$–$C_{(6A)}$	115.9(2)
$C_{(8A)}$–$C_{(7A)}$–$C_{(6A)}$	121.4(2)	$C_{(7A)}$–$C_{(8A)}$–$C_{(9A)}$	120.0(2)
$C_{(7A)}$–$C_{(8A)}$–$C_{(10A)}$	118.0(2)	$C_{(9A)}$–$C_{(8A)}$–$C_{(10A)}$	122.0(2)
$O_{(1A)}$–$C_{(9A)}$–$N_{(1A)}$	118.4(2)	$O_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	125.1(2)
$N_{(1A)}$–$C_{(9A)}$–$C_{(8A)}$	116.5(2)	$O_{(3A)}$–$C_{(10A)}$–$O_{(4A)}$	122.0(2)
$O_{(3A)}$–$C_{(10A)}$–$C_{(8A)}$	121.5(2)	$O_{(4A)}$–$C_{(10A)}$–$C_{(8A)}$	116.5(2)
$O_{(4A)}$–$C_{(11A)}$–$C_{(12A)}$	110.9(2)	$N_{(1A)}$–$C_{(13A)}$–$C_{(14A)}$	112.0(2)
$C_{(1B)}$–$N_{(1B)}$–$C_{(9B)}$	123.9(2)	$C_{(1B)}$–$N_{(1B)}$–$C_{(13B)}$	120.7(2)
$C_{(9B)}$–$N_{(1B)}$–$C_{(13B)}$	115.3(2)	$C_{(10B)}$–$O_{(4B)}$–$C_{(11B)}$	117.9(2)
$N_{(1B)}$–$C_{(1B)}$–$C_{(6B)}$	119.4(2)	$N_{(1B)}$–$C_{(1B)}$–$C_{(2B)}$	121.9(2)
$C_{(6B)}$–$C_{(1B)}$–$C_{(2B)}$	118.7(2)	$C_{(3B)}$–$C_{(2B)}$–$C_{(1B)}$	119.9(2)
$C_{(4B)}$–$C_{(3B)}$–$C_{(2B)}$	121.5(2)	$C_{(5B)}$–$C_{(4B)}$–$C_{(3B)}$	119.5(2)
$C_{(4B)}$–$C_{(5B)}$–$C_{(6B)}$	120.8(2)	$C_{(1B)}$–$C_{(6B)}$–$C_{(5B)}$	119.7(2)
$C_{(1B)}$–$C_{(6B)}$–$C_{(7B)}$	118.8(2)	$C_{(5B)}$–$C_{(6B)}$–$C_{(7B)}$	121.5(2)
$O_{(2B)}$–$C_{(7B)}$–$C_{(8B)}$	122.3(2)	$O_{(2B)}$–$C_{(7B)}$–$C_{(6B)}$	115.9(2)
$C_{(8B)}$–$C_{(7B)}$–$C_{(6B)}$	121.8(2)	$C_{(7B)}$–$C_{(8B)}$–$C_{(9B)}$	120.0(2)
$C_{(7B)}$–$C_{(8B)}$–$C_{(10B)}$	118.1(2)	$C_{(9B)}$–$C_{(8B)}$–$C_{(10B)}$	122.0(2)
$O_{(1B)}$–$C_{(9B)}$–$N_{(1B)}$	119.1(2)	$O_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	124.9(2)
$N_{(1B)}$–$C_{(9B)}$–$C_{(8B)}$	116.0(2)	$O_{(3B)}$–$C_{(10B)}$–$O_{(4B)}$	121.6(2)
$O_{(3B)}$–$C_{(10B)}$–$C_{(8B)}$	121.8(2)	$O_{(4B)}$–$C_{(10B)}$–$C_{(8B)}$	116.6(2)
$O_{(4B)}$–$C_{(11B)}$–$C_{(12B)}$	111.1(2)	$N_{(1B)}$–$C_{(13B)}$–$C_{(14B)}$	111.8(2)

In both molecules all of the non-hydrogen atoms lie within a single plane to an accuracy of 0.03 Å with the exception of $C_{(12)}$ and $C_{(14)}$ and an intramolecular hydrogen bond can be formed in both the **A** and **B** molecules *via* $O_{(2)}$–$H_{(2O)}$···$O_{(3)}$ (H···O 1.76 Å, O–H···O 148º). A shortened intramolecular contact $H_{(5)}$···$O_{(2)}$ of 2.43 in **A** and 2.44 Å in **B** additionally occurs (sum of the van der Waal radii 2.46 Å [9]). Overall, the bond lengths in the structure of ester **4** are similar to chose in the previously studied 4-hydroxy-2-oxoquinolines [10, 11].

The ethyl group of the ester substituent is placed perpendicularly to the plane of the bicyclic fragment (torsional angle $C_{(10)}$–$O_{(4)}$–$C_{(11)}$–$C_{(12)}$ 88.1(3) in **A** and 87.1(3) in **B**) with causes a shortened intramolecular contact $H_{(11b)}$···$O_{(3)}$ of 2.36 in **A** and 2.37 Å in **B** (2.46 Å).

The substituent on atom $N_{(1)}$ is also placed perpendicularly to the bicyclic plane (torsional angle $C_{(9)}$–$N_{(1)}$–$C_{(13)}$–$C_{(14)}$ -91.7(2) in **A** and -90.7(2)º in **B**) with repulsion between it and the neighboring carbonyl group and hydrogen atom in the *peri* position of the benzene ring [shortened intramolecular contacts $H_{(2)}$···$C_{(13)}$ 2.54 in **A**, 2.56 in **B** (2.87); $H_{(2)}$···$H_{(13b)}$ 2.02 **A**, 2.04 **B** (2.34), $H_{(13a)}$···$O_{(1)}$ 2.30 **A**, 2.28 **B** (2.46), $H_{(13b)}$···$C_{(2)}$ 2.55 **A** 2.56 **B** (2.87 Å)] leading to increased bond lengths $N_{(1)}$–$C_{(1)}$ 1.394(3) **A**, 1.391(3) **B** and $N_{(1)}$–$C_{(9)}$ 1.407(3) **A**, 1.405(3) Å **B** when compared with their mean values [12] (1.353 and 1.355 Å respectively). A shortened intermolecular contact $H_{(3a)}$···$H_{(14b)'}$ is also found between the molecules in the crystal of **4** (1-*x*, 1-*y*, 1-*z*) 2.31 Å (2.34 Å).

Formation of the 4-hydroxy ester **4** from the 4-nitroquinolone **2** is impossible hence it can be unambiguously proved that the first stage of the reaction of the chloro derivative **1** with sodium nitrite in DMSO is undoubtedly O-substitution to give the hetarylnitrite **3**. Being virtually an enol nitrous acid ester this compound is very readily hydrolyzed to give the 4-hydroxy ester **4** in high yield in the final step.

Attention should also be paid the fact that some halo derivatives, e.g. ethyl 4-chloroquinoline-3-carboxylate is converted to the hydroxyl compound under the action of just DMSO [13]. However, a similar reaction cannot be achieved with the 4-chloro-substituted ester **1** so we can exclude this conversion to the hydroxyl compound **4** from a number of options.

Hence, through the results of carrying out the workup with sodium nitrite in DMSO solution we can recommend this method as a preparative procedure for exchanging chlorine for a hydroxyl group in 1-R-2-oxo-4-chloro-3-ethoxycarbonyl-1,2-dihydroquinolines.

EXPERIMENTAL

Ethyl 1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (4). $NaNO_2$ (0.76 g, 0.011 mol) was added to a solution of the ethyl 4-chloro-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) [6] (2.79 g, 0.01 mol) in DMSO (15 ml), stirred until dissolved, and left for 10 h at room temperature. The reaction mixture was diluted with water. The precipitated 4-hydroxy ester **4** was filtered off, washed with water, and dried. Yield 2.38 g (91%). A single crystal suitable for X-ray analysis with mp 66-68ºC was obtained by crystallization from ether. When mixed with a known sample [4] the melting point was not depressed.

X-ray Analysis. Crystals of ester **4** are triclinic, at 20ºC: a = 7.348(2), b = 11.240(6), c = 16.426(4) Å, α = 87.72(3), β = 77.63(2), γ = 72.92(3)º, V = 1266.2(8), Å^3, M_r = 261.27, Z = 4, space group $P\bar{1}$, d_{calc} = 1.371 g/cm^3, μ(MoKα) = 0.101 mm^{-1}, F(000) = 552. The unit cell parameters and intensities of 11,456 reflections (5812 independent with R_{int} = 0.035) were measured on an Xcalibur-3, four circle automatic diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω scanning, $2\theta_{max}$ = 55º).

The structure was solved by a direct method using the SHELXTL [14] program package. The positions of the hydrogen atoms were revealed from the electron density difference synthesis and refined using the "riding" model with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bound with the given hydrogen (n = 1.5 for a methyl group and n = 1.2 for remaining hydrogen atoms). The structure was refined by F^2 full matrix least squares

analysis in the anisotropic approximation for non hydrogen atoms to wR_2 = 0.148 for 5773 reflections (R_1 = 0.056 for 2756 reflections with F > 4σ(F), S = 0.973). The complete crystallographic data have been placed in the Cambridge structural data base, reference CCDC 608699. The interatomic distances and valence angles are given in Tables 1 and 2.

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