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4-HYDROXY-2-QUINOLONES 125*. ETHYL 3-BROMO-2,4-DIOXO-1,2,3,4-TETRAHYDROQUINOLINE-3-CARBOXYLATES AS POTENTIAL BROMINATING AGENTS

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The spatial structural features of 3-bromo-3-ethoxycarbonyl-2,4-dioxo-1,2,3,4-tetrahydroquinolines have been studied by X-ray analysis. It has been experimentally confirmed that these compounds can be regarded as potential brominating agents.

Keywords: 3-bromo-2,4-dioxo-1,2,3,4-tetrahydroquinolines, brominating agents, X-ray structural analysis.

The bromination route of ethyl 1R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids using molecular bromine in acetic acid depends on the presence of water in the reaction mixture. Its presence predetermines the formation of 1-R-3-bromo-3-ethoxycarbonyl-2,4-dioxo-1,2,3,4-tetrahydroquinolines. This reaction occurs instantly upon addition of bromine. On the other hand, after thorough dehydration of the reagents and solvent an electrophilic attack occurs only at position 6 of the quinolone ring and in this case completion of the bromination requires several hours [2]. In practice, carrying out the reaction with a strictly stoichiometric ratio of the reacting material and in absolutely anhydrous conditions could not always be achieved. As a consequence there was sometimes observed a partial formation of the 3-bromo-substituted isomers which, in contrast to the colorless 6-bromoquinolines, are bright yellow in color. This process does not, however, cause a significant problem since the high solubility in most organic solvents allows a ready removal of the unwanted admixture from the target 6-bromo derivatives.

This formation of the 6-bromoquinolines has been confirmed by us *via* a counter synthesis using intermediate products with a well known position for the bromine atom in the molecule [3], e.g. from X-ray analysis. At the same time, the steric structural features of their 3-bromo-substituted isomers has remained obscure for a long time.

In one of the bromination experiments [2] of ethyl 4-hydroxy-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylate (**1**), prolonged cooling of the filtrate remaining after separation of the basic 6-bromoquinoline **2** at -25ºC caused the growth of several yellow single crystals which were subjected to X-ray analysis.

* For Communication 124 see [1].

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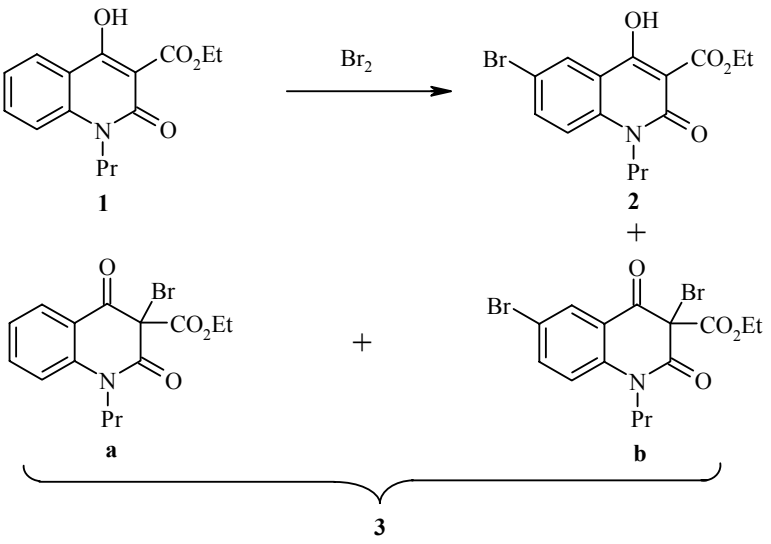
Although, in fact, the obtained crystals prove to be mixed this did not hinder their detailed study since the mono and dibromo derivatives **3a** and **3b** are found in the ratio 85: 15 in the same states.



The remoteness of the second bromine atom from the substituted tetrahydropyridinedione fragment governs the uniform structure of the latter (Fig. 1, Tables 1, 2) which is found in a chair conformation in both molecules (folding parameters: $S = 0.32$, $\theta = 47.4°$, $\Psi = 2.3°$ [4]). The deviation of atom $C_{(2)}$ from the mean plane of the remaining atoms is 0.30 Å. The bromine atom at $C_{(2)}$ has an axial orientation (torsional angle $Br_{(1)}–C_{(2)}–C_{(3)}–C_{(4)}$ 89.6(5)º). The ester substituent is orientated equatorially (torsional angle $N_{(1)}–C_{(1)}–C_{(2)}–C_{(13)}$ 151.4(5)º) and is twisted relative to the $C_{(1)}–C_{(2)}$ bond by 115.7(8)º (torsional angle $C_{(1)}–C_{(2)}–C_{(13)}–O_{(2)}$). The ethyl group is disordered into two *-ac* -and *ap*-conformations relative to the $O_{(3)}–C_{(13)}$ bond with a population density of 42: 58% (torsional angle $C_{(13)}–O_{(3)}–C_{(14)}–C_{(15)}$ -115(2)º for the *-ac* and -158(1)º for the *ap*-conformation

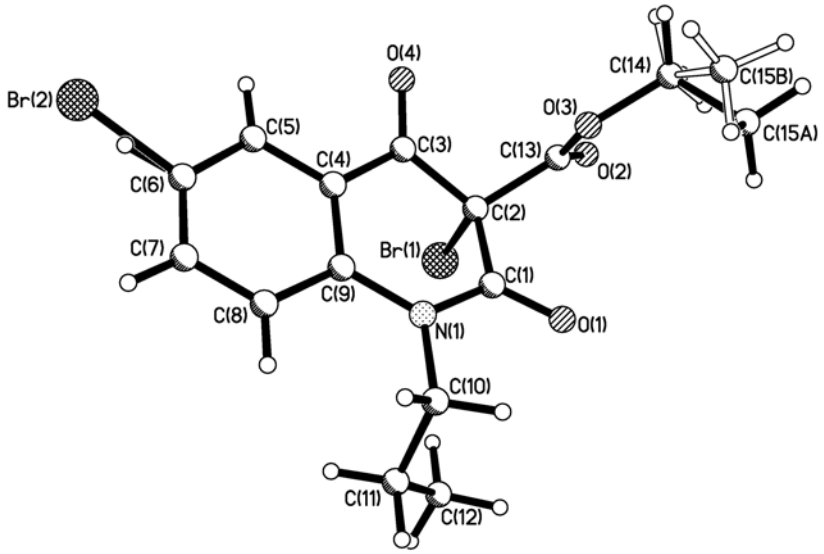


Fig. 1. Structure of the molecule of the mixed ester **3** with atomic numbering.

TABLE 1. Bond Lengths (*l*) in the Mixed Ether Structure **3**

Bond	*l*, Å	Bond	*l*, Å
$Br_{(1)}–C_{(2)}$	1.957(5)	$Br_{(2)}–C_{(6)}$	1.876(5)
$N_{(1)}–C_{(1)}$	1.359(9)	$N_{(1)}–C_{(9)}$	1.40(1)
$N_{(1)}–C_{(10)}$	1.481(9)	$O_{(1)}–C_{(1)}$	1.201(9)
$O_{(2)}–C_{(13)}$	1.177(8)	$O_{(3)}–C_{(13)}$	1.291(8)
$O_{(3)}–C_{(14)}$	1.47(1)	$O_{(4)}–C_{(3)}$	1.213(8)
$C_{(1)}–C_{(2)}$	1.527(9)	$C_{(2)}–C_{(3)}$	1.509(9)
$C_{(2)}–C_{(13)}$	1.564(8)	$C_{(3)}–C_{(4)}$	1.445(9)
$C_{(4)}–C_{(5)}$	1.395(1)	$C_{(4)}–C_{(9)}$	1.40(1)
$C_{(5)}–C_{(6)}$	1.37(1)	$C_{(6)}–C_{(7)}$	1.31(1)
$C_{(7)}–C_{(8)}$	1.33(1)	$C_{(8)}–C_{(9)}$	1.41(1)
$C_{(10)}–C_{(11)}$	1.53(1)	$C_{(11)}–C_{(12)}$	1.517(9)
$C_{(14)}–C_{(15A)}$	1.52(1)	$C_{(14)}–C_{(15B)}$	1.519(9)

respectively). The propyl substituent on $N_{(1)}$ is placed virtually perpendicularly to the heterocyclic plane (torsional angle $C_{(9)}–N_{(1)}–C_{(10)}–C_{(11)}$ 83.8(9)º) and is found in a +*sc* -conformation relative to the $N_{(1)}–C_{(10)}$ (torsional angle $N_{(1)}–C_{(10)}–C_{(11)}–C_{(12)}$ 63(1)º). There is a repulsion between the $N_{(1)}$ substituent and the neighboring carbonyl group and hydrogen atom in the *peri* position of the benzene ring [intramolecular contacts $O_{(1)}\cdots H_{(10b)}$ 2.33 (sum of van der Waal radii 2.46 [5]), $C_{(8)}\cdots H_{(10a)}$ 2.57 (2.87), $C_{(8)}\cdots C_{(11)}$ 3.34 (3.42), $C_{(8)}\cdots H_{(11b)}$ 2.82 (2.87), $H_{(8a)}\cdots C_{(10)}$ 2.49 (2.87), $H_{(8a)}\cdots H_{(10a)}$ 2.06 (2.34), $H_{(8a)}\cdots C_{(11)}$ 2.78 (2.87), and $H_{(8a)}\cdots H_{(11b)}$ 2.24 (2.34 Å)] and this leads to a shortening of the $N_{(1)}–C_{(9)}$ bond 1.40(1) Å when compared with the mean value 1.335 Å [6].

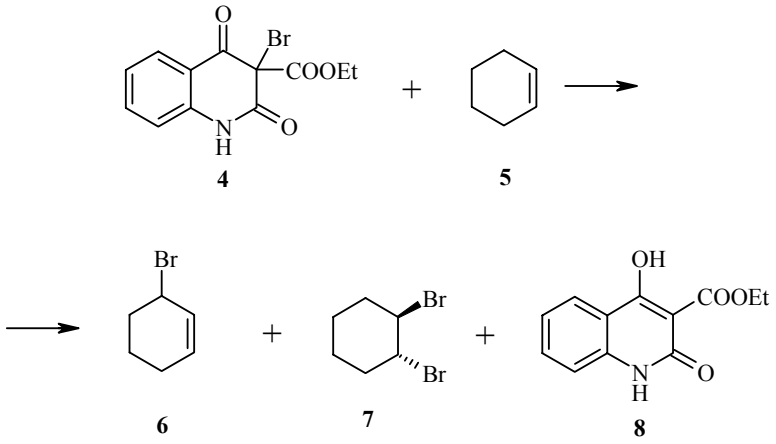
The crystal of mixed ester **3** shows an intermolecular hydrogen bond $C_{(12)}–H_{(12b)}\cdots Br_{(2')}$ (*x*, *y*, 1+*z*) H···Br' 2.19 Å, C–H···Br' 127ºC together with shortening of the intermolecular contacts: $Br_{(1)}\cdots O_{(4')}$ (0.5+*x*, 0.5-*y*, 0.5+*z*) 2.85 (3.26), $Br_{(2)}\cdots C_{(1')}$ (1-*x*, -*y*, 1-*z*) 3.64 (3.68), $Br_{(2)}\cdots C_{(6')}$ (2-*x*, -*y*, 1-z) 3.58 (3.68), $Br_{(2)}\cdots C_{(7')}$ (2-*x*, -*y*, 1-*z*) 3.49 (3.68), $Br_{(2)}\cdots H_{(10b')}$ (1-*x*, -*y*, 1-*z*) 3.19 (3.23), $H_{(12a)}\cdots Br_{(2')}$ (*x*, *y*, 1+*z*) 2.78 (3.23), $H_{(15a)}\cdots Br_{(2')}$ (1-*x*, -*y*, 1-*z*) 3.09 (3.23), and $H_{(15b)}\cdots Br_{(1')}$ (*x*-1, *y*, *z*) 2.83 (3.23 Å).

TABLE 2. Valence Angles (ω) in the Mixed Ether Structure **3**

Valence angle	ω, deg	Valence angle	ω, deg
$C_{(1)}–N_{(1)}–C_{(9)}$	123.3(6)	$C_{(1)}–N_{(1)}–C_{(10)}$	117.3(6)
$C_{(9)}–N_{(1)}–C_{(10)}$	119.3(6)	$C_{(13)}–O_{(3)}–C_{(14)}$	114.0(6)
$O_{(1)}–C_{(1)}–N_{(1)}$	124.1(7)	$O_{(1)}–C_{(1)}–C_{(2)}$	118.6(6)
$N_{(1)}–C_{(1)}–C_{(2)}$	117.2(6)	$C_{(3)}–C_{(2)}–C_{(1)}$	117.0(5)
$C_{(3)}–C_{(2)}–C_{(13)}$	110.3(5)	$C_{(1)}–C_{(2)}–C_{(13)}$	111.2(5)
$C_{(3)}–C_{(2)}–Br_{(1)}$	104.2(4)	$C_{(1)}–C_{(2)}–Br_{(1)}$	103.4(4)
$C_{(13)}–C_{(2)}–Br_{(1)}$	110.2(4)	$O_{(4)}–C_{(3)}–C_{(4)}$	124.6(6)
$O_{(4)}–C_{(3)}–C_{(2)}$	120.0(6)	$C_{(4)}–C_{(3)}–C_{(2)}$	115.3(5)
$C_{(5)}–C_{(4)}–C_{(9)}$	119.5(7)	$C_{(5)}–C_{(4)}–C_{(3)}$	118.9(7)
$C_{(9)}–C_{(4)}–C_{(3)}$	121.6(6)	$C_{(6)}–C_{(5)}–C_{(4)}$	116.1(7)
$C_{(7)}–C_{(6)}–C_{(5)}$	126.3(7)	$C_{(7)}–C_{(6)}–Br_{(2)}$	123.2(8)
$C_{(5)}–C_{(6)}–Br_{(2)}$	110.4(7)	$C_{(6)}–C_{(7)}–C_{(8)}$	118.2(8)
$C_{(7)}–C_{(8)}–C_{(9)}$	121.7(9)	$C_{(4)}–C_{(9)}–N_{(1)}$	121.1(6)
$C_{(4)}–C_{(9)}–C_{(8)}$	118.2(7)	$N_{(1)}–C_{(9)}–C_{(8)}$	120.7(7)
$N_{(1)}–C_{(10)}–C_{(11)}$	113.7(6)	$C_{(12)}–C_{(11)}–C_{(10)}$	114.2(7)
$O_{(2)}–C_{(13)}–O_{(3)}$	128.3(6)	$O_{(2)}–C_{(13)}–C_{(2)}$	123.5(6)
$O_{(3)}–C_{(13)}–C_{(2)}$	108.0(5)	$O_{(3)}–C_{(14)}–C_{(15A)}$	108(1)
$O_{(3)}–C_{(14)}–C_{(15B)}$	107.2(8)		

Analysis of the carbon-bromine bond lengths in the structure of the mixed ester **3** shows that they are fairly typical ($Br_{(1)}$–$C_{(2)}$ 1.957(5) and $Br_{(2)}$–$C_{(6)}$ 1.876(5) Å) and can be compared with the mean values of the bond lengths of the type Br–C_{sp3} 1.966 and Br–C_{ar} 1.875 Å). It is clear than one on these bonds (in fact the $Br_{(1)}$–$C_{(2)}$ is cleaved quite readily due its three carbonyl group neighbors. In fact, in a study of the chemical properties of 1-R-3-bromo-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylate esters we have noted the ease with which they oxidize hydrazine hydrate [7]. Many N-haloimides and amides react in just the same way with hydrazine hydrate. In addition the oxidative properties of their N-bromo derivatives are often used for preparative purposes [8]. At least in the case of N-bromosuccinimide it can be shown that its oxidative and brominating effects are due to the formation of molecular bromine in small amounts. Hence it is quite logical to propose that the oxidative properties of the 3-bromo-2,4-dioxoquinolines **3** can be based on the same reasoning. Hence such compounds can be considered as brominating agents.

We have studied the reaction product of ethyl 3-bromo-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (**4**) with cyclohexene (**5**) in anhydrous carbon tetrachloride in the presence of a catalytic amount of peroxide using chromato-mass spectrometry. The product is a mixture, the main components of which are 3-bromocyclohexene (**6**, 11%) and *trans*-1,2-dibromocyclohexane (**7**, 78%).



Hence the experiment carried out unambiguously confirms the brominating ability of 3-bromo-2,4-dioxo-1,2,3,4-tetrahydroquinolines. Naturally this does not currently relate to the preparative value of the given reaction since many of its features remain unstudied. For example, why does the addition reaction predominate over allylic bromine substitution, whether the direction of the reaction depends on the solvent, what role is played by the catalyst etc. None the less, the fact that brominating properties appear with organic compounds in which the halogen is bonded not to a nitrogen atom but rather directly to a carbon is undoubtedly of theoretical interest.

EXPERIMENTAL

Chromato-mass spectroscopic investigation was carried out on a Varian 1200L instrument for total scanning in the range 35-700 m/z with 70 eV electron ionization, a CP-SIL 8CB column of length 50 m and internal diameter 0.25 mm, polysiloxane film stationary phase (5% diphenylpolysiloxane, 95% dimethylpolysiloxane) of thickness 0 33 μm, helium gas carrier, injector temperature 300ºC, and ion source temperature 250ºC. Water was removed from commercial carbon tetrachloride using P_2O_5. Ethyl 3-bromo-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (**4**) was prepared by the method given in [9].

Bromination of Cyclohexene (5) Using Ethyl 3-Bromo-2,4-dioxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (4). A mixture of the 3-bromo-substituted ester **4** (3.12 g, 0.01 mol), cyclohexene freshly distilled over P_2O_5 (1.1 ml, 0.01 mol), and several crystals of diperoxyazelaic acid in anhydrous CCl_4 (15 ml) was refluxed for 20 h. The product was cooled to room temperature and held at -25ºC for 1 day. The precipitated solid was filtered off and washed with a small amount of cold CCl_4. Crystallization from alcohol gave ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**8)** 1.03 g identified by the absence of a depression of melting point when mixed with a known sample [10]. Solvent and unreacted cyclohexene were distilled off from the combined filtrates at about 100ºC. The residue (0.76 g) underwent chromato-mass spectrometric investigation. The content of the 3-bromocyclohexene (**6**) was 11%. Mass spectrum, *m/z* (I_{rel}, %): 160 $[M]^+$ (2.6), 81 $[M\text{-}Br]^+$ (100), 65 (5), 53 (12). The content of *trans*-1,2-dibromocyclohexane (**7**) was 78%. Mass spectrum: 240 $[M]^+$ (4), 161 $[M\text{-}Br]^+$ (37), 81 $(M\text{-}Br\text{-}Br)^+$ (100). In both case the *m/z* values are given only for the ^{79}Br isotope. The experimental mass spectra of the 3-bromocyclohexene (**6**) and *trans*-1,2-dibromo-cyclohexane (**7**) are identical to the spectra of the corresponding standard samples taken from a mass spectrometry library. For comparison it should be noted that in the mass spectrum of *cis*-1,2-dibromo-cyclohexane the intensities of the molecular ion $[M]^+$ and $[M\text{-}Br]^+$ fragment ions are identical at 16%.

X-Ray Structural Investigation. Crystals of the mixed ester **3** are monoclinic, at 20ºC: a = 8.937(3), b = 16.615(5), c = 11.025(3) Å, β = 111.10(2)º, V = 1527.4(8) Å^3, M_r = 365.84, Z = 4, space group $P2_1/n$, d_{calc} = 1.591 g/cm^3, μ(MoKα) = 3.092 mm^{-1}, F(000) = 740. Unit cell parameters and intensities of 4514 reflections (2660 independent with R_{int} = 0.097) were measured on a Siemens P3/PC, four circle, automatic diffractometer (MoKα radiation, graphite monochromator, θ/2θ scanning to $2\theta_{max}$ = 50º).

The structure was solved by a direct method using the SHELXTL program package [11]. Absorption was included by a semi-empirical method *via* Ψ-scanning (T_{min} = 0.661, T_{max} = 0.987). For refinement of the disordered fragment and the second bromine atom limits were placed on the bond lengths of C_{sp3}–C_{sp3} 1.54(0.01) and C_{ar}–Br 1.90(0.005) Å. The positions of the hydrogen atoms were revealed from electron density difference synthesis and refined using the "riding" model with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bonded to the given hydrogen (n = 1.5 for methyl and hydroxyl groups and 1.2 for the remaining hydrogen atoms). The structure was refined in F^2 full matrix least squares analysis in the anisotropic approximation for non-hydrogen atoms with wR_2 = 0.145 for 2489 reflections (R_1 = 0.063 for 1765 reflections with $F>4\sigma(F)$, S = 1.026). The complete crystallographic information has been placed in the Cambridge structural data bank, reference CCDC 608697.

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