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4-HYDROXY-2-QUINOLONES. 109*. ALKYLATION OF 4-SUBSTITUTED ETHYL 2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLATES

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The alkylation of the ethyl esters of 4-methyl, 4-chloro-, and 4-amino substituted 2-oxo-1,2-dihydroquinoline-3-carboxylic acid by ethyl iodide in the system DMF/K_2CO_3 has been studied. Features of the structure of the starting compounds and their effect on the ratio of the N- and O-alkyl products formed are discussed.

Keywords: 2-oxo-1,2-dihydroquinolines, 1H-quinolin-2-ones, alkylation, X-ray structural analysis.

The alkylation of α-oxo(hydroxyl)azaheterocycles rarely proceeds uniquely. As a rule the result of such reactions are a mixture of the corresponding N- and O-alkyl substituted derivatives, frequently containing some of the starting material [2-5]. The predominant formation of one of the isomers is determined by many factors including the substituents in the alkylating substance, the structure and size of the introduced alkyl group (in the case of alkyl halides the halogen has an important effect), the base used for generating the anion, the solvent, and other experimental reaction conditions. Hence the effect of external and structural factors on the alkylation of α-oxo(hydroxy)azaheterocycles is of special interest and has become the subject of many investigations [5-7].

The experiments carried out by us have shown that alkylation of ethyl 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1a**) by ethyl iodide in the system DMF/K_2CO_3 (i.e. essentially the ambident anion **2a**) gives a mixture of reaction products. According to mass spectroscopic data the main component (70%) is the N-ethylquinolone **3a**. A minor residue (28%) was identified as 2-ethoxyquinoline **4a** with 2% of the non reacting starting NH-ester **1a**. As is known [6] ,the alkylation route for this type of compound depends to a large extent on the position of the tautomeric equilibrium. Through a detailed study of the structure of ester **1a** we have previously noted some of its features. In particular, a marked delocalization of electron density into the quinoline fragment is observed and this allowed us to suggest that the ester **1a** exists in neutral conditions in two tautomeric forms, i.e. aromatic and 1,2-dihydro with the latter predominating [8]. In basic medium the contribution of the aromatic tautomer towards the resonance hybrid is essentially unchanged and as a result the alkylation of ester **1a** gives a high yield of the 1-N-substituted product **3a**.

* For Communication 108 see [1].

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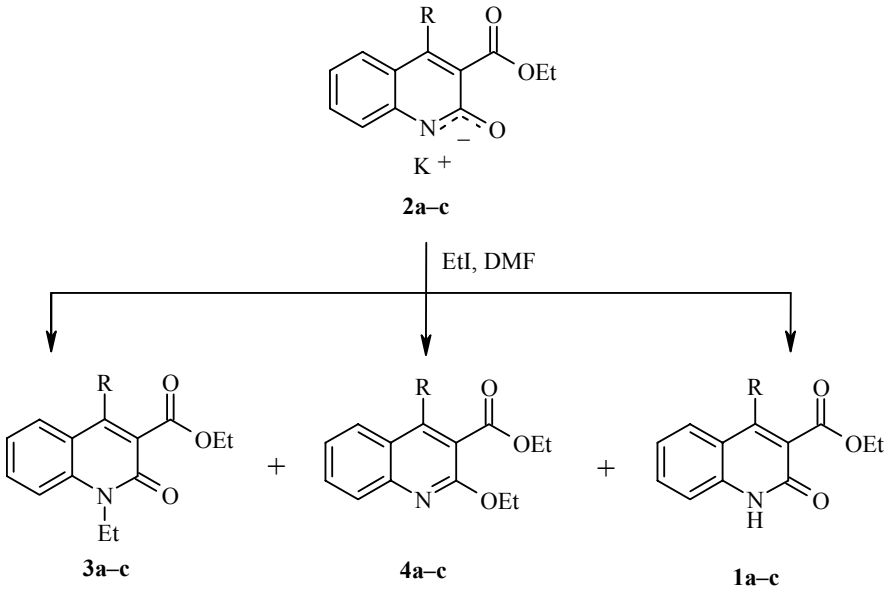

1-4: a	R = Me	70%	28%	2%
b	R = Cl	69%	31%	0
c	R = NH_2	1%	95%	4%

By contrast, in the structural analog of the 4-methyl-substituted ester **1a** (ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate **1b**) the double bond $C_{(7)}$–$C_{(8)}$ is localized according to X-ray analysis (Figure 1, Tables 1 and 2). Some lengthening of the $C_{(9)}$–$O_{(1)}$ carbonyl bond (1.242(4) Å, mean value 1.210 Å [9]) can be explained not by tautomerism but just by the formation of an intermolecular hydrogen bond $N_{(1)}$–$H_{(1)}$···$O_{(1)}$ (-1-*x*, 2-*y*, 1-*z*) H···O 1.98 Å, N–H···O 171°. The bicyclic fragment and atoms $O_{(1)}$ and $Cl_{(1)}$ lie in a single plane to within 0.01 Å. The ester group at atom $C_{(8)}$ is randomized into two positions **A** and **B** with a conformational population density of 54:46 as a result of rotation around the $C_{(8)}$–$C_{(10)}$ bond and in both conformers turned practically perpendicularly to the quinoline plane as in the 4-methyl-substituted ester **1a** (torsional angle $C_{(7)}$–$C_{(8)}$–$C_{(10)}$–$O_{(2)}$ -88(1)° in **A** and -108(1)° in **B**). The ethyl group in conformers **A** and **B** is found in an ap-position relative to the $C_{(10)}$–$C_{(8)}$ bond (torsional angles $C_{(11)}$–$O_{(3)}$–$C_{(10)}$–$C_{(8)}$ -166.3(9)° in **A** and -171(1)° in **B**). In the conformer **A** the $C_{(12)}$ atom is found in a position intermediate between *-ac* and *-ap* but in conformer **B** close to *+ac* (torsional angles $C_{(10)}$–$O_{(3)}$–$C_{(11)}$–$C_{(12)}$ -166(1)° in **A** and 147(2)° in **B**). Moreover, in conformer **A** a shortening of the intramolecular contact $H_{(11b)}$–$O_{(2a)}$ occurs (2.35 Å, sum of van der Waal radii 2.46 Å, [10]). The molecule also shows a shortened $H_{(5)}$···$Cl_{(1)}$ contact of 2.71 Å (3.06 Å). In other words, the X-ray analysis of the chloro-substituted ester **1b** does not permit conformation of any marked presence of an aromatic tautomeric form in the crystal. Hence in the alkylation of this quinolone by ethyl iodide it would be logical to expect, if not exclusively formation of the N-ethyl-substituted compound **3b** then at least a higher yield than in the preceding example. None the less chromatographic analysis of the composition of the reaction mixture obtained showed that the corresponding 2-ethoxy isomer **4b** is formed and its yield proved even slightly higher (31%) than in the case of the 4-methyl derivative.

The 4-amino-substituted ester also exists in the crystal exclusively in the 1,2-dihydro form [11]. However its reaction with octyl bromide in the system DMF/K_2CO_3 gives a mixture of N- and O-alkylation products moreover with a predominance of the aromatic 2-alkoxy derivative [3]. One of the reasons for this result would be a consequence of the rather large size of the alkyl group in the octyl bromide. However, after alkylation of ethyl 4-amino-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1c**) by ethyl iodide in the same conditions only traces of the N-ethyl-substituted isomer **3c** were found.

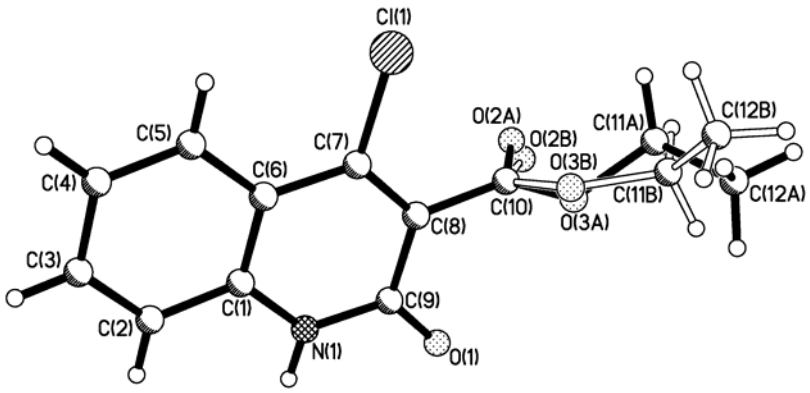

Fig. 1. Structure of the ester **1b** molecule with atomic numbering.

TABLE 1. Bond Lengths (*l*) in the Ester **1b** Structure

Bond	*l*, Å	Bond	*l*, Å
$Cl_{(1)}–C_{(7)}$	1.730(3)	$N_{(1)}–C_{(9)}$	1.349(4)
$N_{(1)}–C_{(1)}$	1.375(4)	$O_{(1)}–C_{(9)}$	1.242(4)
$O_{(2A)}–C_{(10)}$	1.206(5)	$O_{(3A)}–C_{(10)}$	1.314(7)
$O_{(3A)}–C_{(11A)}$	1.472(9)	$C_{(11A)}–C_{(12A)}$	1.507(9)
$O_{(2B)}–C_{(10)}$	1.206(5)	$O_{(3B)}–C_{(10)}$	1.322(8)
$O_{(3B)}–C_{(11B)}$	1.464(9)	$C_{(11B)}–C_{(12B)}$	1.51(1)
$C_{(1)}–C_{(6)}$	1.396(4)	$C_{(1)}–C_{(2)}$	1.406(4)
$C_{(2)}–C_{(3)}$	1.360(5)	$C_{(3)}–C_{(4)}$	1.395(5)
$C_{(4)}–C_{(5)}$	1.358(5)	$C_{(5)}–C_{(6)}$	1.404(4)
$C_{(6)}–C_{(7)}$	1.430(4)	$C_{(7)}–C_{(8)}$	1.354(4)
$C_{(8)}–C_{(9)}$	1.456(4)	$C_{(8)}–C_{(10)}$	1.492(4)

TABLE 2. Valence Angles (ω) in the Ester **1b** Structure

Angle	ω, deg.	Angle	ω, deg.
$C_{(9)}–N_{(1)}–C_{(1)}$	124.8(2)	$C_{(10)}–O_{(3A)}–C_{(11A)}$	111.3(8)
$O_{(3A)}–C_{(11A)}–C_{(12A)}$	105.5(9)	$C_{(10)}–O_{(3B)}–C_{(11B)}$	124(1)
$O_{(3B)}–C_{(11B)}–C_{(12B)}$	102(1)	$N_{(1)}–C_{(1)}–C_{(6)}$	120.6(3)
$N_{(1)}–C_{(1)}–C_{(2)}$	119.3(3)	$C_{(6)}–C_{(1)}–C_{(2)}$	120.1(3)
$C_{(3)}–C_{(2)}–C_{(1)}$	119.5(3)	$C_{(2)}–C_{(3)}–C_{(4)}$	120.7(3)
$C_{(5)}–C_{(4)}–C_{(3)}$	120.3(3)	$C_{(4)}–C_{(5)}–C_{(6)}$	120.7(3)
$C_{(1)}–C_{(6)}–C_{(5)}$	118.6(3)	$C_{(1)}–C_{(6)}–C_{(7)}$	115.9(3)
$C_{(5)}–C_{(6)}–C_{(7)}$	125.5(3)	$C_{(8)}–C_{(7)}–C_{(6)}$	122.8(3)
$C_{(8)}–C_{(7)}–Cl_{(1)}$	118.9(2)	$C_{(6)}–C_{(7)}–Cl_{(1)}$	118.3(2)
$C_{(7)}–C_{(8)}–C_{(9)}$	120.0(2)	$C_{(7)}–C_{(8)}–C_{(10)}$	122.6(3)
$C_{(9)}–C_{(8)}–C_{(10)}$	117.3(3)	$O_{(1)}–C_{(9)}–N_{(1)}$	121.5(3)
$O_{(1)}–C_{(9)}–C_{(8)}$	122.6(3)	$N_{(1)}–C_{(9)}–C_{(8)}$	115.9(3)
$O_{(2A)}–C_{(10)}–O_{(3A)}$	125(1)	$O_{(2B)}–C_{(10)}–O_{(3B)}$	124(1)
$O_{(2A)}–C_{(10)}–C_{(8)}$	124(1)	$O_{(2B)}–C_{(10)}–C_{(8)}$	122(1)
$O_{(3A)}–C_{(10)}–C_{(8)}$	110.3(6)	$O_{(3B)}–C_{(10)}–C_{(8)}$	113.3(7)

Hence from the results of the investigation given it follows that the structural features of the 1H-2-oxo-1,2-dihydroquinoline-3-carboxylate esters determined by X-ray analysis unfortunately give little information regarding a prediction of the direction of alkylation. Such a reaction needs an initial ionization of the N–H bond which is achieved by the addition of base and solvent. The anions of general formula **2** formed in this way have an ambident nature. Hence the actual ratio of the N- and O-alkylated isomers via their subsequent alkylation depends on the tautomeric equilibrium in the anion itself and it appears that it differs markedly from that in the neutral molecule in most cases.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury VX-200 (200 MHz) instrument with DMSO-d_6 as solvent and TMS as internal standard. Chromatographic mass spectrometric work was carried out on a Varian 1200L instrument in the full scanning mode in the range 35-700 m/z with electron impact ionization 70 eV, a CP-SIL 8CB chromatographic column of length 50 m and internal diameter 0.25 mm, a polysiloxane film coated phase (5% diphenylpolysiloxane, 95% dimethylpolysiloxane) of thickness 0.33 μm, gas carrier helium, injector temperature 300°C, and ion source temperature of 250°C. The synthesis of ethyl 4-chloro-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**3b**) has been reported in [12].

Ethyl 1-Ethyl-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (2a). Iodoethane (0.89 ml, 0.011 mol) was added to a mixture of ethyl 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1a**, 2.31 g, 0.01 mol) and K_2CO_3 (2.76 g, 0.02 mol) in DMF (20 ml) and stirred for 5 h at 90°C. The product was cooled and diluted with water. The precipitate formed was extracted with dichloromethane (3 × 20 ml). The organic extracts were combined, the solvent distilled off, and the residue was subjected to mass spectrometric analysis. For separation of the alkylation products formed the reaction mixture was treated with hexane (3 × 15 ml). Ether (30 ml) was added to the insoluble residue. The precipitate (starting NH-ester **1a**) was filtered off, washed with ether, and dried to give the ester **1a** (0.046 g, 2%). The ether extract was purified using carbon and the solvent was distilled off to give the N-ethyl-substituted ester **2a** (1.63 g, 63%); R_f 0.23 (Silufol UV-254, Et_2O–hexane, 2:1), mp 72-74°C (aqueous ethanol). Mass spectrum, *m/z* (I_{rel}, %): 259 $[M]^+$ (22), 258 $[M-H]^+$ (8), 230 $[M-C_2H_5]^+$ (8), 214 $[M-OEt]^+$ (53), 185 $[M-OEt-C_2H_5]^+$ (80), 157 $[M-OEt-C_2H_5-CO]^+$ (100), 143 (39), 130(55), 103 (40), 77 (30). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.90 (1H, d, *J* = 8.1 H-5); 7.69 (1H, td, *J* = 7.9 and 1.3, H-7); 7.61 (1H, d, *J* = 8.3, H-8); 7.33 (1H, td, *J* = 7.2 and 1.5, H-6); 4.29 (4H, m, NCH_2 + OCH_2); 2.39 (3H, s, 4-CH_3); 1.28 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$); 1.19 (3H, t, *J* = 7.1, $NCH_2C\underline{H}_3$). Found, %: C 69.62; H 6.78; N 5.53. $C_{15}H_{17}NO_3$. Calculated, %: C 69.48; H 6.61; N 5.40.

Ethyl 2-Ethoxy-4-methylquinoline-3-carboxylate (3a). The hexane extract remaining after removal of the N-ethyl-substituted ester **2a** (see above example) was purified using carbon and then the solvent was removed to give the 2-ethoxy derivative **3a** (0.57 g, 22%) as a colorless oily liquid with R_f 0.80 (Silufol UV-254, Et_2O–hexane, 2:1). Mass spectrum *m/z* (I_{rel}, %): 259 $[M]^+$ (12), 244 $[M-CH_3]^+$ (9), 230 $[M-C_2H_5]^+$ (11), 214 $[M-OEt]^+$ (27), 186 $[M-OEt-CO]^+$ (100), 159 (66), 143 (83), 130 (27), 103 (15), 77 (20). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.00 (1H, d, *J* = 8.3, H-5); 7.79-7.62 (2H, m, H-7,8); 7.47 (1H, t, *J* = 7.2, H-6); 4.41 (4H, m, NCH_2 + OCH_2); 2.55 (3H, s, 4-CH_3); 1.31 (6H, m, $OCH_2C\underline{H}_3$ + $NCH_2C\underline{H}_3$). Found, %: C 69.66; H 6.54; N 5.35. $C_{15}H_{17}NO_3$. Calculated, %: C 69.48; H 6.61; N 5.40.

Alkylation of Ethyl 4-Chloro- (1b) and 4-Amino- (1c) 2-oxo-1,2-dihydroquinoline-3-carboxylates using ethyl iodide was carried out similarly without preparative separation of the N- and O-alkyl isomers. Known N-ethyl esters **3b,c** were used as references for mass spectrometric investigation.

X-ray Analysis. Crystals of the ester **1b** obtained from ethanol were triclinic. At 20°C: *a* = 6.967(3), *b* = 7.397(3), *c* = 11.526(5) Å; α = 76.18(3), β = 85.99(4), γ = 81.17(3)°; *V* = 569.6(4) Å^3; d_{calc} = 1.467 g/cm^3; space group $P\bar{1}$; M_r = 251.66; *Z* = 2; μ(MoKα) = 0.330 mm^{-1}; *F*(000) = 60. The unit cell parameters and

intensities of 3214 reflections were measured on a Siemens P3/PC, four circle automatic diffractometer (λMoKα, graphite monochromator, θ/2θ scanning to $2\theta_{max} = 60°$).

Treatment of the experimental data was carried out by the Blessing method [13]. The structure was solved by a direct method using the program package SHELXTL [14]. For refinement of the structure, limits were set on the bond lengths in the randomized fragment: C_{sp^2}=O 1.210, C_{sp^2}–O 1.33, O–C_{sp^3} 1.45, and C_{sp^3}–C_{sp^3} 1.52 Å. The positions of the hydrogen atoms were revealed in electron density difference synthesis and for the randomized fragment were calculated geometrically and refined using the "riding" method with $U_{iso} = nU_{eq}$ for a non hydrogen atom bonded to the given hydrogen (n = 1.5 for methyl groups and n = 1.2 for remaining hydrogen atoms). The structure was refined in a full matrix least squares analysis for F_2 in the anisotropic approximation to $wR_2 = 0.186$ for 2923 reflections ($R_i = 0.077$ for 1765 reflections with $F > 4\sigma$ (F), $S = 1.060$). The full crystallographic data has been deposited in the Cambridge structural database (register no. CCDC 283293). Interatomic distances and valence angles are given in Tables 1 and 2.

Ethyl 4-Amino-1-ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (3c) was prepared by a known method [3]. Yield 75%; mp 200-202°C (ethanol). ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.16 (1H, d, J = 8.1, H-5); 8.01 (2H, s, 4-NH_2); 7.64 (1H, t, J = 7.8, H-7); 7.43 (1H, d, J = 8.6, H-8); 7.21 (1H, t, J = 7.5, H-6); 4.28-4.08 (4H, m, NCH_2 + OCH_2); 1.25 (3H, t, J = 7.1, CH_3); 1.12 (3H, t, J = 6.9, CH_3). Mass spectrum (direct introduction), m/z (I_{rel}, %): 260 $[M]^+$ (74), 259 $[M-H]^+$ (54), 232 $[M-CO]^+$ (23), 214 $[M-EtOH]^+$ (22), 213 $[M-H-EtOH]^+$ (51), 188 $[M-COOEt]^+$ (40), 187 $[M-H-COOEt]^+$ (36), 171 (37), 158 (100), 131 (33), 116 (46), 104 (82), 77 (76). Found, %: C 64.51; H 6.32; N 10.84. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.60; H 6.20; N 10.76.

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