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# Alkylation of 2- and 3-alkoxycarbonyl-4-quinolinones. DFT study on the regioselectivity

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ABSTRACT

The reaction of 2-alkoxycarbonyl-4-quinolinones (**1**) with a variety of alkylating reagents under different conditions, lead to the corresponding *O*-alkylated products. The behavior in basic medium of compounds **1** differs from the 3-alkoxycarbonyl-4-quinolinones (**4**) isomers suggesting that the position of the carboxylate group determines the regioselectivity of the reaction. DFT calculations allow us to conclude that for 3-alkoxycarbonyl-4-quinolinones, the *N*-alkylation would be thermodynamically and kinetically favored. But for 2-alkoxycarbonyl-4-quinolinones the side chain in the 2-position of the ring prevents the planar approximation to the contiguous heteroatom leading to a more favorable O-alkylation transition state. Crystal structure of an *O*-alkylated product is determined by single crystal X-ray diffractometry.



## 1. Introduction

4-Oxo-1,4-dihydroquinolines, also known as 4-quinolinones [1] (Fig. 1) exhibit a wide variety of clinical applications including the treatment of urinary, respiratory, gastrointestinal and gynecologic infections, sexually transmitted diseases (STD), prostatitis, infections of skin, bone and soft tissue, and even as anti-proliferative agents in several cancer types, among others [2].

The antimicrobial activity of 4-quinolinones appears frequently associated with the presence of substituents attached to the nitrogen ($R^1$ = alkyl, alkenyl or alkynyl) (Fig. 1) [2a,g,h, 3]. Prototropic blockage achieved by the $R^1$ group ($R^1 \neq$ H) allows not only to modify the properties of these compounds, but also has important application in synthetic sequences and in obtaining models for spectroscopic and computational analysis [3,4]. For this reason the selective alkylation of *N*-unsubstituted 4-quinolinones ($R^1$ = H), where the pyridone ⇌ hydroxypyridine tautomerism occurs, has been extensively studied [2i,5]. 4-Quinolinones, as well as lactams, are able to act as ambidentate nucleophiles in alkylation reactions yielding *N*- and/or *O*-alkylated products (Scheme 1).

Several authors have concluded that the regioselectivity of the alkylation of 4-quinolinones depends on the presence of substituents on the heterocyclic ring ($R^2$ and $R^3$). Thus, different alkylating agents, reaction conditions and substrates, lead to different yields of *N*-alkylated [3a,4c,5c,f,g] and/or *O*-alkylated [2f,i,j,k,4b,f,j] products. Generally, when only one substituent is present, the nucleophilic center not adjacent to the substituent is alkylated, but in some cases a mixture of both products occurs, being difficult to rationalize the regioselectivity. In some cases it has been observed that the presence of certain substituents on the adjacent aromatic ring can also modify the regioselectivity [6].

Reaction conditions can modify the regioselectivity because of the different mechanisms at which the reaction can go through. It is usually accepted that in neutral medium, nitrogen and oxygen nucleophilicity varies according to the tautomeric equilibrium, which depends on the solvent polarity [7]. In these conditions, it is commonly found that the most reactive center is the non-protonated heteroatom [7a]. When alkylation is carried out in basic medium (assuming an $S_N2$ reaction), the molecule can react through the *N*- or *O*-center of the ambidentate anion. The observed regioselectivity has been rationalized in terms of the total charge

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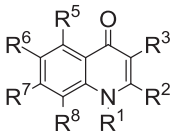
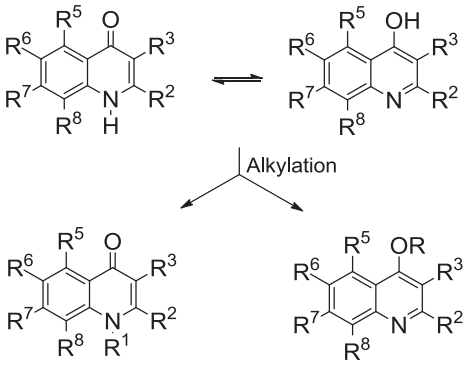


**Fig. 1.** 4-Quinolinones.




**Scheme 1.** Compounds obtained by alkylation of 4-quinolinones.

distribution and frontier orbital theory [5c], but this analysis could not be extended to structurally related compounds.

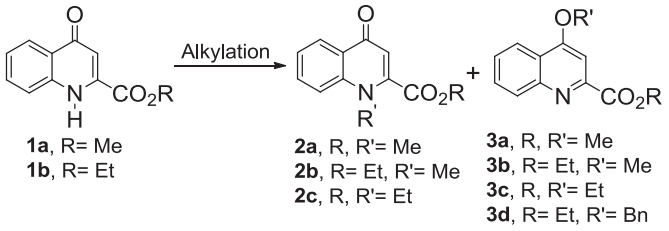
Frank et al. [5b] studied the reaction of 4-quinolinones with trimethyl phosphate (TMP) demonstrating that the *O*-alkylated derivative is formed first in a kinetically controlled process, with subsequent thermal isomerization, through a quaternary salt, to the more stable *N*-alkylated product. Makara et al. [5c] studied the reaction of 3-ethoxycarbonyl-4-quinolinones and related 1,8-naphthyridinones, in neutral and basic media, yielding in all cases *N*-alkylated derivatives as the only products. Through computational analysis they concluded that the formation of the ambidentate anion increases the energy of the HOMO determining an orbital-controlled reaction, where the alkylating agent reacts through the softer center of the molecule, *i.e.* nitrogen. The authors obtained a good correlation between the HSAB principle [8], Klopman's theorem for chemical reactivity [9] and their experimental results.

As part of our ongoing research using esters and amides derived from kynurenic acid **1** (4-oxo-1,4-dihydroquinoline-2-carboxylic acid) [10] as precursors of new potentially bioactive heterocyclic compounds, we report herein the results of the alkylation of esters **1a**,**b** with a variety of electrophilic reagents under different conditions (Scheme 2). As an attempt to rationalize the observed regioselectivity, DFT calculations of the reaction pathways are also presented.

## 2. Material and methods

### 2.1. General considerations

Melting points were taken on a Büchi capillary apparatus and are uncorrected. $^{1}H$ and $^{13}C$ NMR spectra were measured in $CDCl_3$ solutions on a Bruker MSL 300 MHz spectrometer at 25 °C. Standard concentration of the samples was 10 and 20 mg/mL respectively. Chemical shifts are reported in ppm ($\delta$) relative to TMS as an internal standard. Coupling constant ($J$) values are given in Hz. Splitting multiplicities are reported as singlet (s), broad doublet (bd), doublet (d), triplet (t), quartet (q), double doublet (dd), double double doublet (ddd) and broad multiplet (bm). MS (EI) were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating




**Scheme 2.** Compounds obtained by alkylation of 4-oxo-1,4-dihydroquinoline-2-carboxylic acid alkyl esters (**1**).

at 20 eV. High resolution mass spectra (HMRS), were acquired with a model GCT (Waters, Milford, MA, USA), operating at 8000 resolving power (50% valley definition) using heptacose (*m/z* 219) as the reference compound. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer. Preparative thin layer separations (PLC) were carried out by centrifugally accelerated radial chromatography using Chromatotron model 7924T. The rotors were coated with Silica Gel 60 PF254 and the layer thickness was 2 mm. Chloroform and increasing percentages of methanol were used as eluent. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures. The assignment of some selected compounds (**2a**, **3c**,**d**) was performed by heteronuclear correlation NMR spectra.

### 2.2. Reaction of 4-oxo-1,4-dihydroquinoline-2-carboxylic acid alkyl esters (*1*) with diazomethane. General procedure

4-Oxo-1,4-dihydroquinoline-2-carboxylic acid alkyl ester (**1**, 1 mmol), was dissolved in anhydrous methanol (5 mL) (ice bath) and an ethereal solution of diazomethane was added with stirring in small portions until the solution acquired a pale yellow color. After 2 h at room temperature, the reaction mixture was concentrated *in vacuo*. Products were isolated by chromatographic methods. Results are presented in Table 2.

### 2.3. Reaction of 4-oxo-1,4-dihydroquinoline-2-carboxylic acid alkyl esters (*1*) with alkylating agents. General procedures

#### 2.3.1. Without added base

A mixture of 4-oxo-1,4-dihydroquinoline-2-carboxylic acid alkyl ester (**1**, 1 mmol), the corresponding alkyl iodide (5 mmol) and anhydrous DMF (5 mL) was stirred at the appropriate temperature. After a specified time (Table 2), the mixture was poured into ice-water. If the product crystallized, the resulting solid was filtered, washed with water and purified by recrystallization or by chromatographic methods. If not, the suspension was extracted with chloroform and the organic layer was washed with water, dried and concentrated *in vacuo*. Products were isolated and purified by chromatographic methods. Results are presented in Table 2.

#### 2.3.2. In basic media

A mixture of 4-oxo-1,4-dihydroquinoline-2-carboxylic acid alkyl ester (**1**, 1 mmol), base (1.3 mmol), the corresponding alkylating agent (alkyl iodide, 1.5 mmol; others, 1.2 mmol) and anhydrous DMF (5 mL) was stirred at the appropriate temperature and monitored by TLC (DCM:MeOH 4.7:0.3). After a specified time (Table 2), the mixture was carefully poured into ice-water. The compounds obtained were isolated and purified as was indicated above. Alkylating agents, bases and solvents are presented in Table 2.