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X-Ray Inside Clarifications Concerning the Acylation Reaction of 8-Hydroxyquinoline

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Abstract

We report here a thorough study concerning the acylation reaction products of 8-hydroxyquinoline with 2-chloroacyl chloride, with new insights and clarifications in respect to the obtained products brought by NMR and X-ray studies. According to the reaction conditions we employed, three compounds could be obtained: 1-(2-chloro-2-oxoethyl)pyridin-1-ium chloride **10**, 8-hydroxyquinoline hydrochloride **11**, and the acylated product 8-(2-chloroacetoxy)quinolin-1-ium chloride **12**. A certain influence of the catalyst and the used solvent was observed, and feasible explanations for product formations were furnished. The structure of the compounds was proved by using ^{1}H- and ^{13}C-NMR spectra as well as single-crystal X-ray diffraction studies for compounds **12** and **11**. According to X-ray crystallography, compounds **11** and **12** have a planar structure and exhibit an ionic crystal structure crystallized as a hydrochloride salt of the corresponding organic base. The crystal structures of both compounds are stabilized by intermolecular hydrogen bonds and π-π stacking interactions. In the crystals of compounds **11** and **12**, the structural components are interconnected by a system of intermolecular hydrogen bonding, and a similar one-dimensional array is formed via hydrogen bonding and π-π stacking. The further assembling of the structure for **12** and **11** occurs with the formation of a three-dimensional supramolecular network.

Keywords: 8-hydroxychinoline hydrochloride; 1-(2-chloro-2-oxoethyl)pyridin-1-ium chloride; 8-(2-chloroacetoxy)quinolin-1-ium chloride; acylation; X-ray studies; supramolecular interactions

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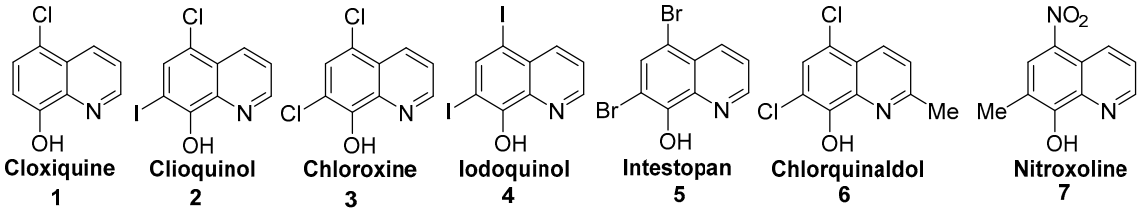
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1. Introduction

Over the past few decades, 8-hydroxyquinoline (8-HQ) has attracted many researchers because of its unique biological, physical, and chemical properties. Structurally, 8-HQ is a bicyclic fused pyridine with a phenolic hydroxyl attached at the eighth position. The pyridine ring in 8-HQ maintains its characteristics as an electron-deficient six-membered ring with a slightly basic nitrogen, enabling acid–base reactions, alkylations, oxidations, and more. The phenolic hydroxyl group at the eighth position of the quinoline ring is

highly reactive and versatile, enabling a variety of chemical reactions, such as substitutions, complexation with various metals, diazonium coupling, and others [1–5].

On the other hand, 8-hydroxyquinoline and its derivatives are excellent scaffolds in medicinal chemistry, with a wide variety of biological and pharmacological applications, including anticancer, antibacterial, antifungal, antileishmanial, antitubercular, anti-HIV, antioxidant, anti-inflammatory, and anti-Alzheimer's [4–23]. In fact, 8-HQ is a core scaffold in many drugs, such as Cloxiquine **1**, Clioquinol **2**, Chloroxine **3**, Iodoquinol **4**, Intestopan **5**, Chlorquinaldol **6**, and Nitroxoline **7** [24–26], as shown in Scheme 1.



Scheme 1. 8-hydroxyquinoline scaffold in diverse drugs.

Taking into account the above considerations, our expertise in the field of biologically active quinoline [27–30], and aiming to obtain new chemical entities derived from 8-HQ of potential interest in medicinal chemistry, we present herein a detailed study related to the acylation reaction product of 8-hydroxyquinoline with 2-chloroacyl chloride, with new insights and clarifications related to the structure of compounds brought by the NMR and the X-ray studies.

2. Materials and Methods

2.1. Materials

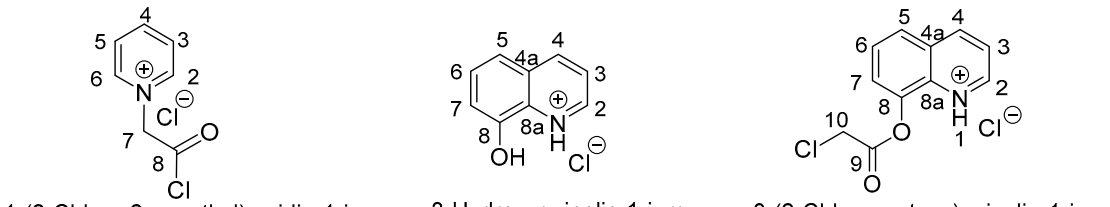
Reagents and solvents were acquired from Merck and Sigma-Aldrich and used as received. The melting points were measured with an A. Krüss Optronic Melting Point Meter KSPI. The thin-layer chromatography plates (60 F254, Merck Darmstadt, Darmstadt, Germany) were used to monitor the reactions under UV light (max = 254 or 365 nm). The NMR spectra were recorded with a Bruker Avance III 500 MHz spectrometer (Bruker, Vienna, Austria), operating at 125 MHz for 13C and 500 MHz for 1H. Chemical shifts (δ units) are reported in parts per million (ppm), with coupling constants (J) in Hz. Single-crystal X-ray diffraction data were collected on a Rigaku XtaLAB Synergy Dualflex HyPix diffractometer (Wilmington, MA, USA) using Cu Kα radiation. Unit cell calculation and data integration were performed with the CrysAlisPro package from Oxford Diffraction [31]. Structure solutions were acquired using the SHELXT program with intrinsic phasing, followed by refinement with SHELXL through least-squares minimization [32]. Olex2 served as the graphical interface for the SHELX programs [33]. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms attached to carbon were added in idealized positions and refined using a riding model. The H atoms of OH and NH groups were located from Fourier maps, and their positions were verified by the geometric parameters of the corresponding hydrogen bonds. Selected crystallographic data and structure refinement details are provided in Table 1 and the relevant CIF files [see also Supplementary Materials, CCDC no. 2536830 (for compound **12**) and 2536831 (for compound **11**)]. The supplementary crystallographic data are available free of charge from the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe via https://www.ccdc.cam.ac.uk/services/structures (accessed on 28 March 2026) or deposit@ccdc.cam.ac.uk.

Table 1. Crystal data and details of structure refinement of the X-ray analysis for compounds **12** and **11**.

Compound	**12**	**11**
Emp. formula	$C_{11}H_{11}Cl_2NO_3$	$C_9H_{10}ClNO_2$
Fw	276.11	199.63
T [K]	100	100
Space group	$P2_1/n$	*P*-1
a [Å]	14.2286(4)	7.2622(3)
b [Å]	5.02309(14)	8.2725(3)
c [Å]	17.7425(5)	8.4646(3)
α [°]	90	78.166(3)
β [°]	106.435(3)	86.011(3)
γ [°]	90	66.573(3)
V [Å^3]	1216.27(6)	456.65(3)
Z	4	2
ρ_{calcd} [g cm^{-3}]	1.508	1.452
μ [mm^{-1}]	4.789	3.432
Crystal size [mm]	0.10 × 0.07 × 0.02	0.30 × 0.20 × 0.15
2Θ range	7.064 to 153.864	10.68 to 133.188
Refls. collected	6675	4042
Indep. Refls., R_{int}	2312, 0.0255	1603, 0.0140
Data/rests./params.	2312/0/160	1603/0/122
GOF	1.056	1.124
R_1, wR_2(all data)	0.0272, 0.0736	0.0256, 0.0709

2.2. Methods

In Scheme 2, the chemical structure with atom numbering for the obtained compounds is shown.



Scheme 2. Atom numbering for obtained compounds.

1-(2-Chloro-2-oxoethyl)pyridin-1-ium chloride **10**.

The experimental reaction setup was repeated according to the literature procedure described in former papers [34,35]: in a two-necked round-bottomed flask (250 mL), 0.04 mol of 8-hydroxyquinoline was dissolved in 100 mL of dry pyridine. Then 0.022 mol of freshly distilled 2-chloroacyl chloride was added dropwise and then stirred for 2 h at room temperature. The pyridinium salt **10** was obtained as beige crystals, η = 92%, m.p. = 152–154 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 5.39 (2H, s, methylene protons from 7-th position), 8.16 (2H: H3 and H5, dd, J = 6.0 Hz, J = 8.0 Hz), 8.62 (1H: H4, t, J = 8.0 Hz, J = Hz), 9.04 (2H: H2 and H6, d, J = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 62.05 (carbon from methylene group from 7-th position), 127.42 (C3 and C5), 145.59 (C4), 145.93 (C2 and C6), 166.93 (C from ester C=O from 8th position).

General procedure to obtain salts **11** and **12**.

In total, 1 mmol (0.145 g) of 8-hydroxyquinoline was dissolved in 15 mL of acetone in a 25 mL round-bottom flask. Then, 2 mmol (0.27 mL) of triethylamine was added. To

the stirred solution, 5 mmol (0.4 mL) of 2-chloroacyl chloride was added dropwise. When salts **11** are to be obtained, the reaction mixture is stirred at room temperature overnight. If salts **12** are to be obtained, the reaction mixture was refluxed for 24 h. In either case, the mixture formed a white precipitate, which was separated by filtration and washed twice with diethyl ether to remove unreacted chloride.

8-Hydroxyquinolin-1-ium chloride **11**.

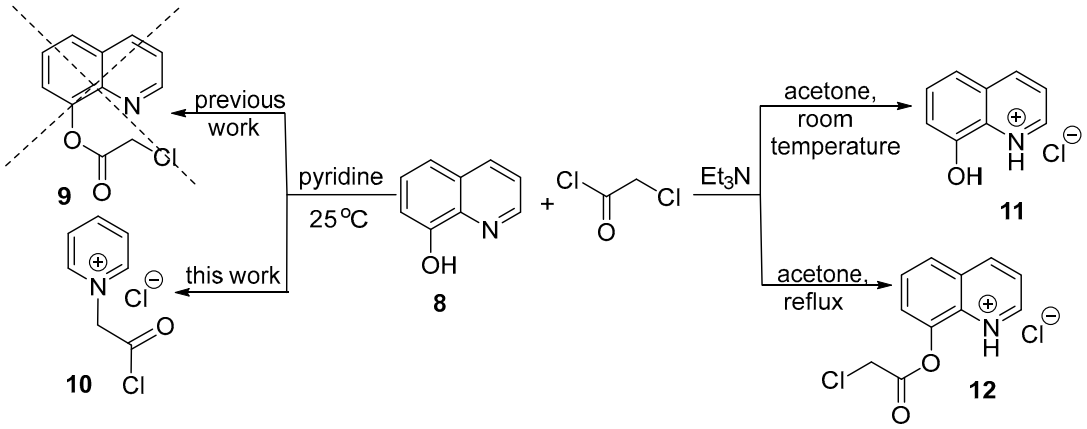
The quinolinium chloride **11** was obtained as yellow crystals, ɳ= 98%, m.p. = 217–218 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 7.60 (1H: H7, dd, J = 3.0 Hz, J = 6.0 Hz), 7.74 (2H: H3, H6, m), 8.02 (1H: H5, q, J = 3.0 Hz, J = 8.5.0 Hz), 9.09 (2H: H2, H4, m), 12.18 [1H, broad singlet, proton from OH1-st position]; ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 115.75 (C7), 118.32 (C5), 122.36 (C6), 129.63 (C4a), 129.74 (C8), 130.25 (C3), 144.62 (C4), 145.55 (C8a), 149.00 (C2).

8-(2-Chloroacetoxy)quinolin-1-ium chloride **12**.

The quinolinium salt **12** was obtained as white crystals, ɳ= 94%, m.p.= 107–110 °C. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm): 4.94 (2H, s, methylene protons from 10-th position), 5.91 [1H, broad singlet, proton from NH1-st position], 7.72 (2H: H6 and H7), 7.75 (1H: H3, d, J = 3.5 Hz), 8.04 (1H: H5, d, J = 8.0 Hz), 8.65 (1H: H4, d, J = 8.0 Hz), 9.01 (1H: H2, d, J = 3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 41.34 (carbon from methylene group from 10-th position), 122.41 (C7), 122.45 (C5), 126.75 (C6), 127.05 (C3), 129.25 (C4), 130.90 (C4a), 138.27 (C8), 145.35 (C8a), 150.01 (C2), 166.31 (C from ester C=O from 9-th position).

3. Results and Discussions

Our initial goal was to obtain the quinoline compound quinolin-8-yl 2-chloroacetate **9**, a key intermediate for further synthesis of hybrid biologically active quinoline derivatives. In this respect, we accurately repeated an experimental literature procedure [34,35], where the authors claim that in the reaction of 8-hydroxyquinoline **8** with 2-chloroacyl chloride and using pyridine as a catalyst, they obtained compound **9**; Scheme 3.



Scheme 3. Reaction pathway between 8-hydroxyquinoline and 2-chlorocetyl chloride.

The above authors claim that they obtained the acylated product, quinolin-8-yl 2-chloroacetate **9**, and attempted to confirm its structure using melting point and elemental analysis. Because melting point and elemental analysis are not enough to prove the structure of a compound, we performed the NMR (^{1}H- and ^{13}C-) spectra of the product obtained by using the literature procedure. The ^{1}H- and ^{13}C-NMR spectra of this compound reveal that the real product of synthesis is the salt 1-(2-chloro-2-oxoethyl)pyridin-1-ium chloride **10**, and not the acylated product quinolin-8-yl 2-chloroacetate **9**, as the literature authors claim. Table 2 lists the signals from the ^{1}H- and ^{13}C-NMR spectra of salt **10** (see also the Supplementary Materials for copies of ^{1}H- and ^{13}C-NMR spectra).

Table 2. Crystal ^{1}H- NMR (up) and ^{13}C-NMR spectra (down) of salt 1-(2-chloro-2-oxoethyl)pyridin-1-ium chloride **10**.

	H_2 and H_6	H_3 and H_5	H_4	H_7 (from CH_2)	-
	C_2 and C_6	C_3 and C_5	C_4	C_7 (from CH_2)	C_8, of C=O
10	9.04	8.16	8.62	5.39	-
	145.93	127.42	145.59	62.05	166.93

The protons from the α-position of the pyridine ring (H_2 and H_6) appear at 9.04 ppm as two equivalent protons, having a coupling constant of 6.0 Hz with protons $H_{3/5}$ (d, J = 6.0 Hz). The protons from the β-position of the pyridine ring (H_3 and H_5) appear at 8.16 ppm, also as two equivalent protons, coupled with $H_{2/6}$ and H_4 (dd, J = 6.0 Hz, J = 8.0 Hz). The H_4 proton from the γ-position of the pyridine ring appears at 8.62 ppm as a triplet (t, J = 8.0 Hz, J = Hz). These protons from the pyridine ring appear at such a high chemical shift because of the powerful unshielded effect exerted by the positive nitrogen from the pyridine ring: the most unshielded protons are H_2 and H_6 (α-position to the positive nitrogen), followed by H_4 protons (γ-position to the positive nitrogen), and H_3 and H_5 (β-position to the positive nitrogen). The two H_7 methylene protons appear at 5.39 ppm (s). This very unusual high chemical shift for these aliphatic methylene protons could be explained by the powerful unshielded effect exerted by the positive nitrogen (from the pyridine ring) and carbonyl ketone group from the vicinity. The carbons from the α-position of the pyridine ring (C_2 and C_6) appear at 145.93 ppm, those from the β-position of the pyridine ring (C_3 and C_5) appear at 127.42 ppm, and the C_4 carbons from the γ-position appear at 145.59 ppm. The carbon from the methylene group appears at 62.05 ppm, while the carbon from the carbonyl group moiety appears at 166.93 ppm.

The formation of salt 1-(2-chloro-2-oxoethyl)pyridin-1-ium chloride **10** could be explained by the difference in basicity between the two heterocycles, pyridine and 8-hydroxyquinoline. Pyridine (pka = 5.2) is a stronger base compared with 8-hydroxyquinoline (pka = 9.9), and in the reaction conditions employed (room temperature), 2-chloroacyl chloride reagent realizes an alkylation reaction to the more basic nitrogen from pyridine, leading to salt **10**.

Having in view that the above literature setup procedure does not lead to the desired compound, we were searching for another experimental procedure to obtain the quinolin-8-yl 2-chloroacetate **9**. By using different reaction setups (different catalysts, solvents, molar ratios of reagents, reaction time, and temperature), we found that triethylamine as a catalyst and acetone as a solvent are suitable for this reaction (Scheme 2). Thus, if the reaction took place at room temperature, quinoline hydrochloride **11** is obtained, while using acetone on reflux leads to the 8-(2-chloroacetoxy)quinolin-1-ium chloride **12**; Scheme 2. The structure of the obtained compounds was proven by elemental (C, H, N) and spectral analysis: ^{1}H- and ^{13}C-NMR spectra and single-crystal X-ray diffraction spectra (see also Supplementary Materials for copies of ^{1}H- and ^{13}C- NMR spectra and X-ray diffraction spectra of compounds **11** and **12**).

The formation of quinoline hydrochloride **11** and salt 8-(2-chloroacetoxy)quinolin-1-ium chloride **12** could be explained by taking into consideration the basicity of heterocycles, the reactivity of 2-chloroacyl chloride, and the reaction conditions. If the reaction took place at room temperature, the system does not have enough energy to accomplish the acylation reaction of the hydroxyl functionality from 8-HQ. Instead, the existing hydrochloric acid from the 2-chloroacyl chloride reagent will achieve a protonation reaction of the nitrogen atom of the pyridine ring of 8-HQ, with the formation of quinoline hydrochloride **11**. If the reaction took place at reflux, the system has enough energy to accomplish the acylation reaction of the hydroxyl functionality from 8-HQ, and simultaneously, the hydrochloric

acid existing in the 2-chloroacyl chloride reagent will achieve a protonation reaction of the nitrogen atom of the pyridine ring of 8-HQ, with the formation of salt **12**.

The X-ray diffraction analysis on monocrystal proved the structure of compounds **12** and **11** unambiguously. The obtained results of the X-ray diffraction studies are illustrated in Figures 1 and 2. The bond distances and angles are summarized in Table S1 (see also Supplementary Materials).

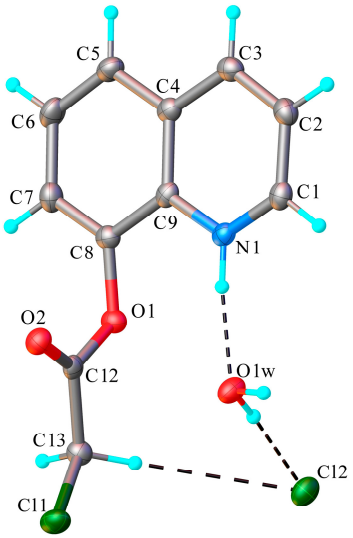


Figure 1. View of the asymmetric part in crystal structure **12** with atom labeling and thermal ellipsoids at a 50% probability level. H-bonds are shown as black-dashed lines.

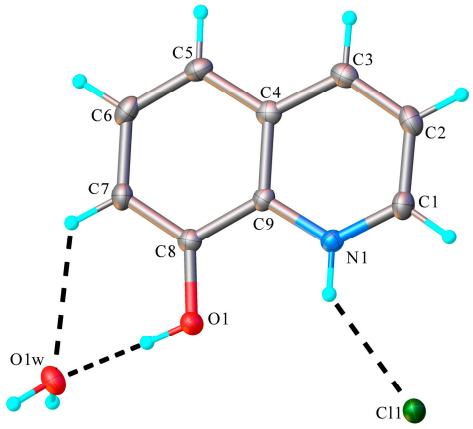


Figure 2. View of the asymmetric part in crystal structure **11** with atom labeling and thermal ellipsoids at a 50% probability level. H-bonds are shown as black-dashed lines.

As it turned out, both compounds have a planar structure, and in the case of salt **12,** the chloroacetyl group from the eighth position of the quinoline ring is slightly out of plane. In the solid state, each of the two compounds **11** and **12** exhibits an ionic crystal structure crystallized as a hydrochloride salt of the corresponding organic base. There is also an interstitial water molecule in the asymmetric part of both crystals, and all the components of the structure are interconnected through a system of intermolecular hydrogen bonding (Figures 1 and 2). In the case of salt **11,** the water molecule is connected via hydrogen bonds with the hydrogen atom from hydroxyl group 8-HQ and the hydrogen atom from the seventh position of the 8-HQ moiety. In the case of acylated salt **12,** the water molecule is connected via hydrogen bonds with the basic nitrogen atom N1 from the quinoline ring and the chorine atom. The H-bond characteristics are displayed in Table 3.

Table 3. Hydrogen bond parameters.

Compound **12**				
D-H···A	d_{D-H}/Å	d_{H-A}/Å	d_{D-A}/Å	∠D-H-A/°
N1-H···O1*w*	0.89	1.76	2.643(2)	170
C2-H···Cl2	0.95	2.78	3.549(2)	139
C3-H···Cl2	0.95	2.75	3.642(2)	156
C7-H···Cl1	0.95	2.79	3.654(2)	152
C13-H···Cl2	0.99	2.89	3.858(2)	168
C13-H···O2	0.99	2.50	3.434(2)	157
O1*w*-H···Cl2	0.89	2.17	3.044(1)	168(2)
O1w-H···Cl2	0.82	2.23	3.042(1)	176(2)
Compound **11**				
D-H···A	d_{D-H}/Å	d_{H-A}/Å	d_{D-A}/Å	∠D-H-A/°
O1-H···O1w	0.84	1.80	2.6382(13)	174.3
N1-H···Cl1	0.88	2.37	3.0965(11)	139.7
C1-H···Cl1	0.95	2.70	3.4729(14)	139.1
C7-H···O1w	0.95	2.63	3.2674(17)	125.2
O1*w*-H···Cl1	0.87	2.26	3.1243(11)	172.9

The crystal structures of both compounds **12** and **11** are stabilized by intermolecular hydrogen bonds and π-π stacking interactions. Analyzing the structure of compounds **12** and **11** from the point of view of short intermolecular contacts, it should be noticed that in both cases, besides the classical hydrogen bonding (*C-H···O* and *C-H···Cl*), the π-π stacking interactions involving aromatic rings have been identified to influence the crystal packing. Thus, in both crystal structures of **12** and **11,** a similar one-dimensional supramolecular array formed via π-π stacking interactions has been observed, as shown in Figures 3 and 4, respectively. Also, numerous hydrogen bonds are present in crystal structures (Table 3, Figures 3 and 4), consolidating the supramolecular structures.

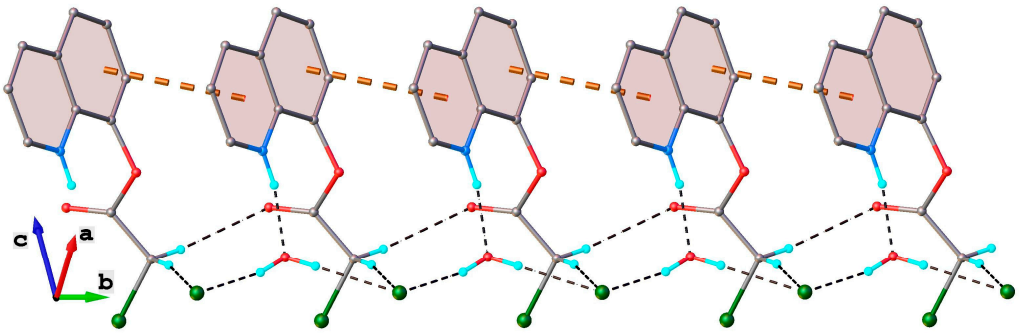


Figure 3. A view of the one-dimensional supramolecular module showing the role of π-π stacking and hydrogen bonding in the crystal structure of **12**. Hydrogen bonds and centroid-to-centroid distances (3.884 Å) are shown as black- and brown-dashed lines, respectively.

In turn, the intermolecular *C-H···Cl* hydrogen bonds (Table 3) in the case of crystal **12**, and *O-H···O*, *O-H···Cl*, *N-H···Cl* in the case of **11**, assemble the 1D chains into two-dimensional supramolecular layers, illustrated in Figure 5.

The further analysis has revealed that both structures represent a three-dimensional supramolecular module. In the crystal of **12,** the assembly of 2D layers occurs through C3-H···Cl2 hydrogen bond (Table 3) and short interlayer Cl1···Cl1′ contacts at 3.316 Å (symmetry code: −*x*. 2—*y*, 1—*z*), as shown in Figure 6 (left side). In the crystal of compound **11,** the 3D network is formed due to O1*w*-H···Cl1 interlayer H-bonds. A fragment of the 3D supramolecular structure in the crystal of compound **11** is shown in Figure 6 (right side).

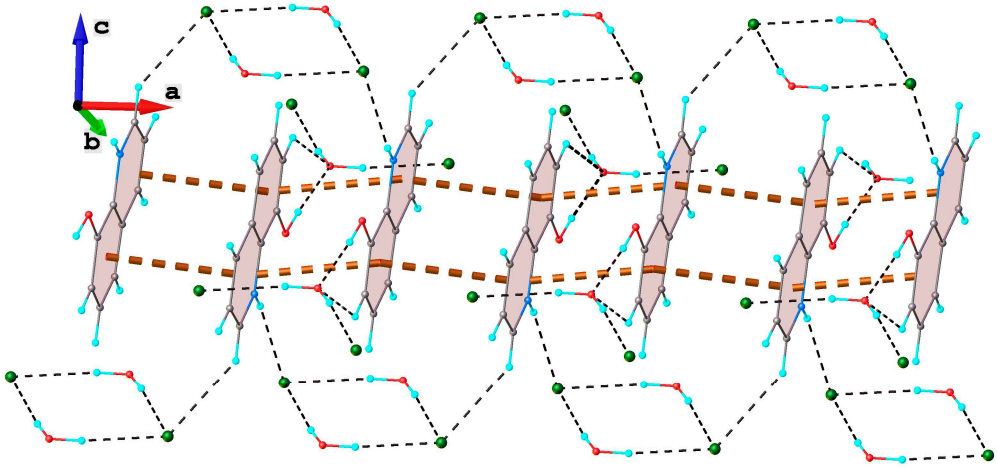


Figure 4. A view of the one-dimensional supramolecular module showing the role of π-π stacking and hydrogen bonding in the crystal structure of **11**. Hydrogen bonds and centroid-to-centroid distances (3.812 and 3.554 Å) are shown as black- and brown-dashed lines, respectively.

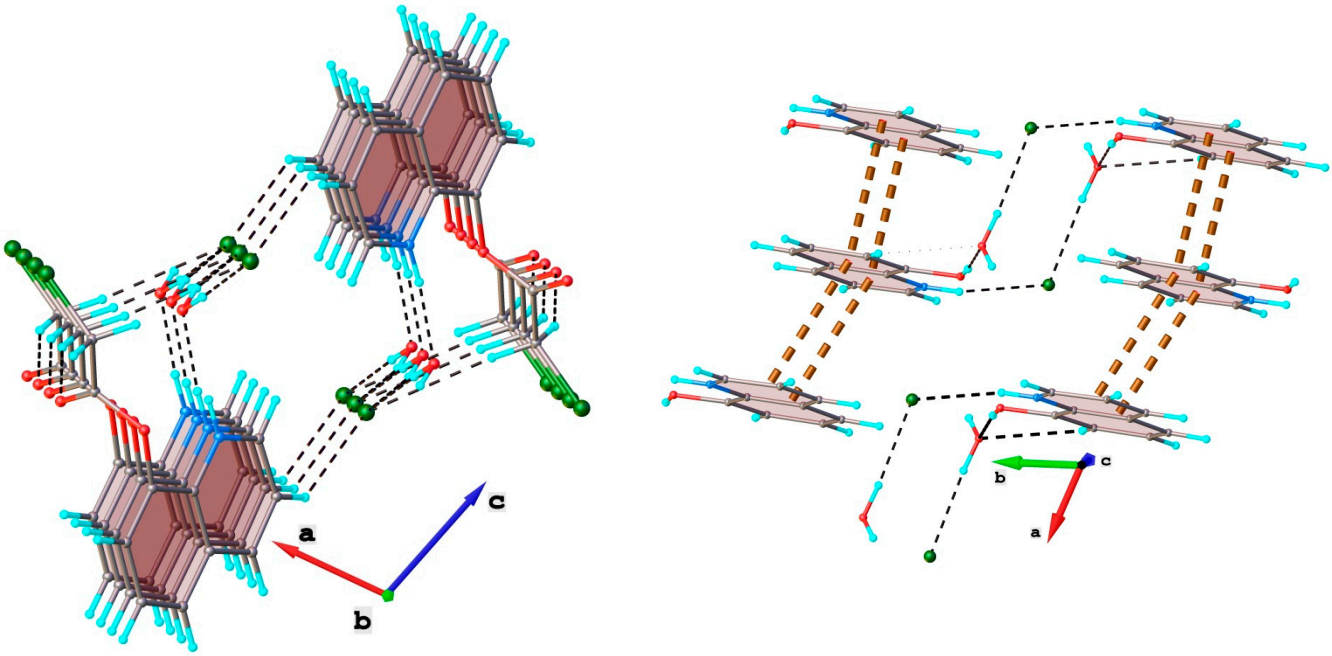


Figure 5. Partial view of the crystal packing showing the formation of a two-dimensional supramolecular layer in the crystal of **12** (**left**); partial view of the crystal packing showing the formation of a two-dimensional supramolecular layer in the crystal of **11**. Hydrogen bonds and centroid-to-centroid distances are shown as black- and brown-dashed lines, respectively (**right**).

The water-soluble salt 8-(2-chloroacetoxy)quinolin-1-ium chloride **12** will be used in further synthesis in an aqueous solution, which is an important asset from a medicinal and green chemistry point of view.

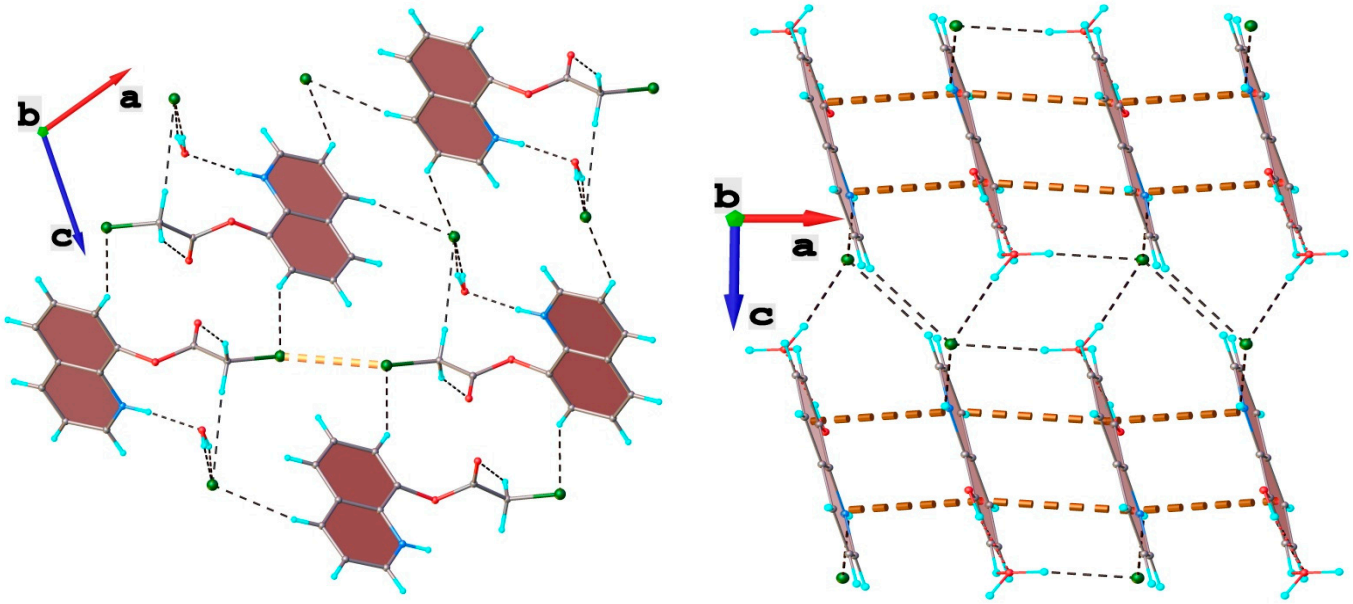


Figure 6. Partial view of the 3D network in the crystal of **12**. Cl···Cl contacts are shown in dashed-orange lines (left side); partial view of the 3D network in the crystal of **11** (right side).

4. Conclusions

This paper presents a detailed study of the acylation reaction products of 8-hydroxyquinoline with 2-chloroacyl chloride, providing new insights and clarifications based on NMR and X-ray analyses. The products formed mainly depend on the catalyst used. When pyridine is employed as the catalyst, the reaction yields salt 1-(2-chloro-2-oxoethyl)pyridin-1-ium chloride **10**. The formation of salt **10** could be explained by an alkylation reaction of the more basic nitrogen from pyridine (compared with 8-HQ). Using triethylamine as the catalyst results either in 8-hydroxyquinoline hydrochloride **11** at room temperature or in 8-(2-chloroacetoxy)quinolin-1-ium chloride **12** under reflux conditions. The formation of compounds **11** and **12** could be explained by taking into consideration, in addition to the catalysts, the basicity of heterocycles, the reactivity of 2-chloroacyl chloride, and the reaction conditions. The structures of these compounds were confirmed through ^{1}H- and ^{13}C-NMR spectra, as well as single-crystal X-ray diffraction studies of compounds **12** and **11**. The X-ray analyses show that compounds **11** and **12** have a planar structure, and in the case of salt **12**, the chloroacetyl group from the eighth position of the quinoline ring is slightly out of plane. Also, both compounds form ionic crystal structures as hydrochloride salts of the respective organic bases. Compound **12** crystallizes in the monoclinic P2_1/n space group, while compound **11** crystallizes in the P-1 space group, each with an interstitial water molecule in the asymmetric unit. The crystal structures are stabilized by intermolecular hydrogen bonds. In their crystal packing, compounds **12** and **11** form similar one-dimensional supramolecular chains through hydrogen bonds (C-H···O and C-H···Cl) and π-stacking interactions (involving aromatic rings), which reinforce the supramolecular architecture. The 1D chains assemble into two-dimensional layers via intermolecular C-H···Cl hydrogen bonds in compound **12**, and O-H···O, O-H···Cl, and N-H···Cl hydrogen bonds in compound **11**. The 3D supramolecular structure of compound **12** forms through C3-H···Cl2 hydrogen bonds and short interlayer Cl1···Cl1′ contacts, while that of compound **11** is stabilized by O1w-H···Cl1 interlayer hydrogen bonds.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/cryst16040259/s1.

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