Journal of Organic and Pharmaceutical Chemistry

Original Research

OPEN ACCESS
Freely available online on
http://ophcj.nuph.edu.ua

UDC 547.831

Yu. V. Ishkov[1], V. V. Veduta[1], N. F. Fed'ko[1], N. M. Bogdan[2]

[1] I. I. Mechnikov Odessa National University, 2 Dvoryanskaya str., 65082 Odessa, Ukraine
[2] Institute of Organic Chemistry of the National Academy of Sciences of Ukraine, 5 Academician Kukhar str., 02098 Kyiv, Ukraine

A Simple Preparative Synthesis of Isomeric 2-Chloroquinolinecarboxylic Esters

Abstract

A simple two-stage method for the synthesis of isomeric esters of 2-chloroquinoline-5-, 6-, 7-carboxylic acids by successive oxidation and chlorination reactions of methyl quinoline-5-, 6-, 7-carboxylates has been developed. The target compounds have been obtained in acceptable yields using readily available reagents, simple transformations, and purification methods. Quinoline-8-carboxylic acid ester is unreactive under these conditions. The ester of 2-chloroquinoline-8-carboxylic acid has been obtained with an overall yield of 55 %, starting from 8-methylquinoline. The multi-stage process is paid off by the fact that several transformations occur in one reaction cycle. All the methods developed can be used for the synthesis of target compounds on a multigram scale. Intermediate 2(1*H*)-oxoquinoline carboxylates are promising compounds in the synthesis of functionalized and condensed heterocycles.

Keywords: 2-chloroquinoline; esters; oxidation; quinolone-2; chlorination

Ю. В. Ішков[1], В. В. Ведута[1], Н. А. Федько[1], Н. М. Богдан[2]

[1] Одеський національний університет ім. І. І. Мечнікова, вул. Дворянська, 2, м. Одеса, 65082, Україна
[2] Інститут органічної хімії Національної академії наук України, вул. Академіка Кухаря, 5, м. Київ, 02660, Україна

Простий препаративний синтез ізомерних 2-хлорхінолінкарбонових естерів

Анотація

Розроблено простий двостадійний метод синтезу ізомерних естерів 2-хлорохінолін-5-, 6-, 7-карбонових кислот за допомогою послідовних реакцій окиснення і хлорування метилхінолін-5-, 6-, 7-карбоксилатів. Цільові сполуки було одержано з прийнятними виходами з використанням доступних реагентів, простих перетворень і методів очищення. Естер хінолін-8-карбонової кислоти в цих умовах є нереакційноздатним. Естер 2-хлорхінолін-8-карбонової кислоти було одержано із 8-метилхіноліну з загальним виходом 55 %. Багатостадійність процесу окупається тим, що в одному реакційному циклі відбувається кілька перетворень. Усі розроблені методи можна використовувати для синтезу цільових сполук у мультиграмовому масштабі. Проміжні 2(1*H*)-оксохінолінкарбоксилати є перспективними сполуками в синтезі функціоналізованих та конденсованих гетероциклів.

Ключові слова: 2-хлорхінолін; естер; окиснення; хінолон-2; хлорування

Citation: Ishkov, Yu. V.; Veduta, V. V.; Fed'ko, N. F.; Bogdan, N. M. A Simple Preparative Synthesis of Isomeric 2-Chloroquinolinecarboxylic Esters. *Journal of Organic and Pharmaceutical Chemistry* **2023**, *21* (4), 11–17.
https://doi.org/10.24959/ophcj.23.298574
Received: *2 September 2023*; **Revised:** *18 November 2023*; **Accepted:** *25 November 2023*

Funding: The authors received no specific funding for this work.
Conflict of interests: The authors have no conflict of interests to declare.

■ Introduction

2-Chloroquinolines with a carboxyl/ester substituted ring are attractive compounds with a great potential for transformation of the quinoline core [1]. A chlorine atom in position 2 can be easily substituted by N-, O- and S-nucleophiles [2], and this ability is widely used in organic and pharmaceutical chemistry. 2-Chloroquinoline derivatives with carboxyl substituents have a wide range of activities, including antimicrobial [3], anti-inflammatory [4], antitumor [5] and antiparasitic ones [6, 7]. There are several methods of introducing halogen into position 2 of the quinoline molecule, but most of them relate to 2-chloroquinoline derivatives with a carboxyl/ester group in the pyridine nucleus [8, 9].

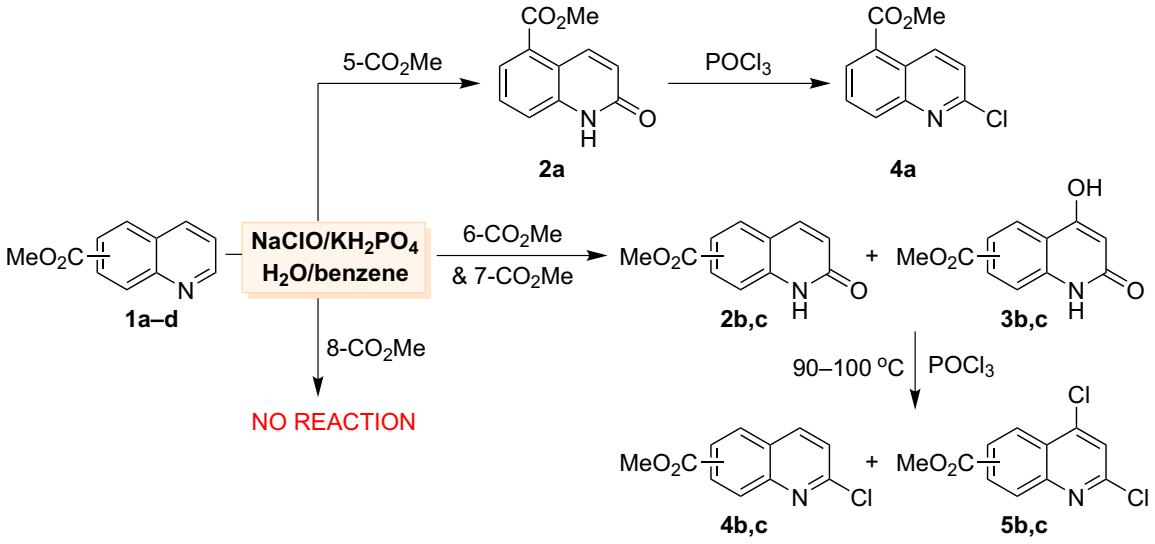
Modern synthetic approaches to 2-chloroquinolines with an ester function in the benzene ring use metal complex catalysts based on ruthenium or iridium [11, 12], which are not always cost effective. Unfortunately, the reaction of C-2 chlorination of N-oxides for quinoline esters in our hands did not give satisfactory results [13, 14]. The aim of this work is to develop simple preparative methods for the 2-chloroquinolines synthesis with ester substituents in positions 5, 6, 7, and 8 of quinoline. Amazingly, all 2-chloroquinolinecarboxylic acids have been known for a long time, but their physical and spectral properties are given in fragments. And we provide known data when it is available.

■ Results and discussion

We studied the possibilities of optimization for the known classical reactions. The easiest way to obtain the desired compounds is the oxidation of the quinoline 2-position to quinolone-2 followed by the replacement of an oxygen atom with chlorine according to the Friedlander method [15]. Therefore, it seemed attractive to optimize the oxidation reaction of quinolines into quinolone-2 with sodium hypochlorite, an effective low-cost reagent [16]. A series of experiments on the oxidation of 5-, 6-, 7-, and 8-quinoline carboxylate esters **1a–d** with sodium hypochlorite in a two-phase benzene-water system was performed.

In an alkaline solution of hypochlorite (pH ≈ 11), the oxidation of esters **1a–d** did not proceed; therefore, the pH of the solution was adjusted by adding an acidifier potassium dihydrogen phosphate (**Scheme 1**). We obtained the best results with such ratio of $NaClO/KH_2PO_4$ reagents as 2:1.07, while the initial solution had a pH value of 11. After the addition of potassium dihydrogen phosphate and esters **1**, the solution had a pH of 7.5, at the end of the reaction the pH was 5. A fivefold hypochlorite excess was used for the oxidation. The reaction was monitored by the presence of sodium hypochlorite in the reaction mixture. The reaction was not carried out for complete ether **1** conversion since during a prolonged contact the excess hypochlorite also oxidized the target reaction products **2**. The conversion of starting esters **1a–c** reached 80%, and methyl quinoline-8-carboxylate **1d** was unreactive under the reaction conditions.

For better yields of products **2a–c**, sodium thiosulfate $Na_2S_2O_3$ was added to the reaction mixture immediately after exhausting the oxidizing agent. Quinolones-2 **2a,b** precipitated from the reaction mixture, then they were filtered, and impurities were removed by the extraction with



Scheme 1. The synthesis of methyl 2-chloroquinoline carboxylates **4** and 2,4-dichloroquinoline carboxylates **5**

ISSN 2308-8303 (Print) / 2518-1548 (Online)

boiling ethanol. In contrast to compound **1a**, upon the oxidation of esters **1b,c** together with quinolones **2b,c**, minor products were formed – 2,4-dihydroxy derivatives **3b,c**, which were also poorly soluble.

Quinolones **2a–c** under short-term heating with $POCl_3$ [15] were transformed into 2-chloroquinoline esters **4a–c**, in the case of esters **4b,c** – with an impurity of 2,4-dichloro derivatives **5b**,**c**. Monochlorinated **4b** and dechlorinated **5b** quinolines were separated by column chromatography and recrystallized from benzene.

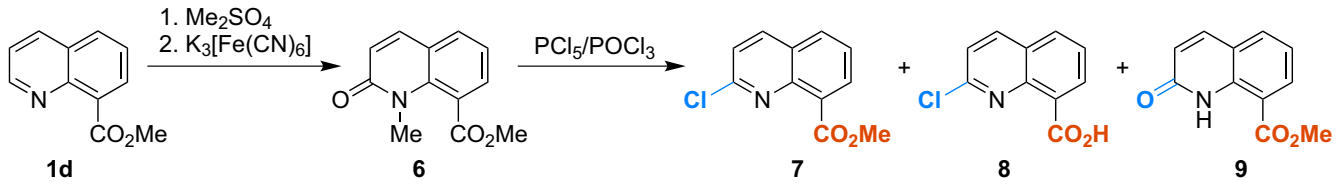
Methyl ester of quinoline-8-carboxylic acid (**1d**) was inert to the $NaClO/KH_2PO_4$ oxidizing system. According to the Dekker's method [17], it was converted into methyl 1-methyl-2-oxoquinoline-8-carboxylate (**6**) with a 42% yield by heating with dimethyl sulfate $(CH_3O)_2SO_2$ at 185 °C for 2.5 h and further oxidation of the quaternary salt with an alkaline solution of potassium hexacyanoferrate(III) at 60 °C (**Scheme 2**). Compound **6** was then converted to methyl 2-chloroquinoline carboxylate **7** according to the Fischer approach [18] by heating it in a mixture of $POCl_3/PCl_5$ at 140 °C with a 40% yield. 2-Chloroquinoline-8-carboxylic acid (**8**) (6%) and 2-oxoquinoline-8-carboxylic acid methyl ester (**9**) (21%) were also isolated along with product **7**.

The low yield of ester **7** and the presence of minor products forced us to develop an alternative route based on 8-methylquinoline (**10**). The alkylation of **10** with dimethyl sulfate and the subsequent oxidation by potassium hexacyanoferrate(III) yielded 1,8-dimethylquinolone-2 (**11**) in one reaction cycle (**Scheme 3**).

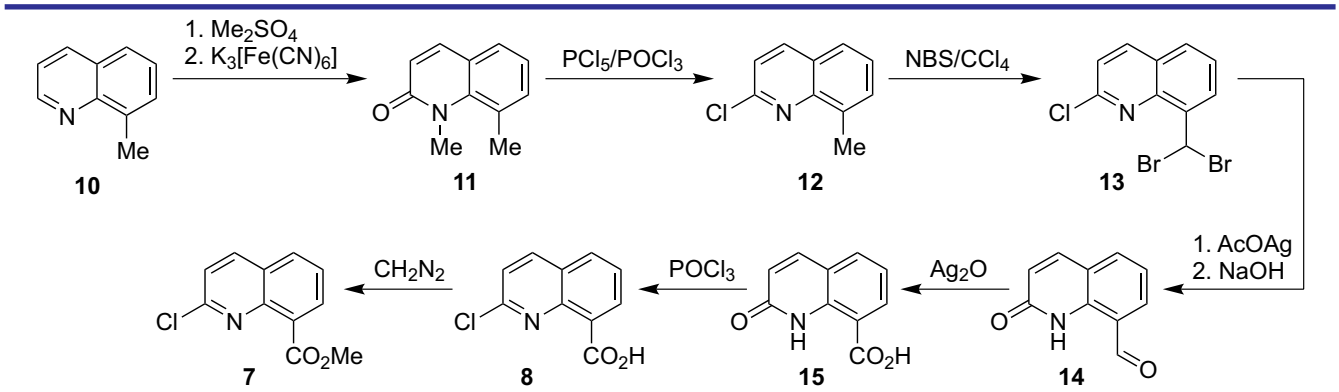
The chlorination of quinolone **11** with a mixture of $PCl_5/POCl_3$ gave 8-methyl-2-chloroquinoline (**12**) [18], which was converted into the corresponding dibromomethyl derivative **13** with N-bromosuccinimide in CCl_4. The hydrolysis of the dibromomethyl group with silver acetate into aldehyde **14** and its oxidation with silver oxide yielded 2-oxoquinoline-8-carboxylic acid (**15**). After the chlorination of acid **15** in $POCl_3$ and the esterification of 2-chloro-8-carboxyquinoline (**8**) with diazomethane in ether, the target ester **7** was obtained. Despite the multistep process, the overall yield of the target product was 55% based on 8-methylquinoline.

■ Conclusions

Simple methods for the synthesis of isomeric esters of 2-chloroquinoline-5-, 6- and 7-carboxylic acids have been developed with acceptable yields using available reagents, simple transformations, and methods of purifying target compounds. A convenient *r*oute for the synthesis of methyl 2-chloroquinoline-8-carboxylate with the total yield of 55% starting from 8-methylquinoline has been developed. The multi-stage process for obtaining this compound is paid off by the fact that several transformations occurred as a telescopic process. All the methods developed can be used for the synthesis of target compounds on a multigram scale. In addition, this



Scheme 2. The synthesis of methyl 2-chloroquinoline-8-carboxylate 7 from methyl quinoline-8-carboxylate



Scheme 3. An optimized reaction set for the methyl 2-chloroquinoline-8-carboxylate synthesis

reaction set provides easy access to useful intermediates with a carboxyl group in a functionalized quinolone core.

■ Experimental part

Control over the course of the reactions, purity and identity of the products obtained was carried out by thin-layer chromatography on Merck 60 F254 plates. ^{1}H and ^{13}C NMR spectra were measured in DMSO-d_6 solution on a Bruker 170 Avance 500 spectrometer (400 MHz on protons and 100 MHz on carbon atoms, respectively), the internal standard was TMS. Chemical shifts were reported in δ (ppm). Data were presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet), coupling constants (Hz) and integration. The elemental analysis data corresponded to the calculated data. The melting points were determined on a Fisher-Johns apparatus. A commercial aqueous solution of sodium hypochlorite in 0.305 mol L^{-1} concentration was used. The consumption of the oxidizer was monitored using iodine-starch paper. Melting points of known substances were given if they were found in the literature. Intermediates and non-target substances **5c**, **6**, **9**, **13**, **15** were characterized only by melting points and ^{1}H NMR spectroscopy. The elemental analysis was performed in the Analytical Laboratory of the Institute of Organic Chemistry of the National Academy of Sciences of Ukraine.

Methyl 2-oxoquinoline-5-carboxylate (2a)

Potassium dihydrogen phosphate (15.2 g, 0.112 mol) under vigorous stirring was added to a mixture of the solution of methyl quinoline-5-carboxylate (**1a**) (10 g, 0.053 mol) in 150 mL of benzene and 850 mL (0.255 mol) of the sodium hypochlorite solution at room temperature, and the resulting mixture was stirred for 5 h. Then sodium thiosulfate (53 g, 0.212 mol) was added and stirred for another 3 h. The resulting precipitate was filtered, washed with benzene, water and air-dried. From the benzene mother liquor, 4.8 g of the starting ester **1a** was recovered.

A white powder. Yield – 4.5 g (42%). M. p. ~290 °C. Anal. Calcd for $C_{11}H_9NO_3$, %: C 65.0, H 4.46, N 6.89. Found, %: C 65.1, H 4.40, N 6.94. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.90 (3H, s, MeO), 6.60 (1H, d, J = 10.0 Hz), 7.52 (1H, d, J = 7.2 Hz), 7.63 (1H, t, J = 7.2 Hz), 7.75 (1H, d, J = 7.2 Hz), 8.60 (1H, d, J = 10.0 Hz), 12.0 (1H, br. s, NH). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 52.0 (MeO), 120.0, 124.1, 124.5, 129.5, 137.0, 117.0, 127.8, 140.1, 161.4 (C=O), 167.7 (C=O).

Methyl 2-chloroquinoline-5-carboxylate (4a)

Quinolone **2a** (6.4 g, 0.0315 mol) and 12 mL (0.128 mol) of phosphoryl chloride were heated on a water bath (100 °C) for 20 min. The reaction mass was cooled to room temperature, 25 mL of acetic acid was added, and the mixture was poured onto 500 g of ice. The mixture was made alkaline with NaOH solution (36 g, 0.8 mol) in 75 mL of water, the precipitate was filtered off, washed with water, and dried. The solution of the reaction product in 100 mL of benzene was passed through a layer of Al_2O_3 (5 cm), evaporated to 15 ml, and ~60 mL of heptane was then added. The precipitated crystals were filtered yielding methyl 2-chloroquinoline-5-carboxylate (**4a**).

A yellowish solid. Yield – 5.94 g (87%). M. p. 122–124 °C. Anal. Calcd for $C_{11}H_8ClNO_2$, %: C 59.6, H 3.64, Cl 16.0, N 6.32. Found, %: C 60.0, H 3.55, Cl 16.10, N 6.30. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.93 (3H, s, CH_3), 7.73 (1H, d, J = 9 Hz, 8-H), 7.89 (1H, t, J = 6 Hz, 7-H), 8.18 (1H, d, J = 6 Hz, 6-H), 8.25 (1H, d, J= 6 Hz, 3-H), 9.18 (1H, d, J = 9 Hz, 4-H). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 52.9, 124.2, 125.3, 127.2, 130.3, 131.2, 133.6, 137.9, 147.8, 150.7, 166.4.

Methyl 2-chloroquinoline-6-carboxylate (4b) and methyl 2,4-dichloroquinoline-6-carboxylate (5b)

The mixture was obtained according to the method described for compound **4a**. 6.6 g of a mixture of quinolones **2b** and **3b** was obtained from 9.5 g (0.051 mol) of ester **1b**, and 1.4 g of the original ester **1b** was recovered. After the reaction of mixture **2b** and **3b** with $POCl_3$, 5.33 g of mixture **4b** and **5b** was obtained, and the components were separated in a column (45×2.5 cm) with silica gel, benzene as an eluent. Methyl 2,4-dichloro-6-carboxylate (**5b**) was eluted first and recrystallized from a mixture of benzene/heptane (1:3). Next, methyl 2-chloro-6-carboxylate (**4b**) was eluted and recrystallized from a mixture of benzene/heptane (1:3).

Methyl 2-chloroquinoline-6-carboxylate (**4b**)

White crystals. Yield – 4.06 g (45%). M. p. 134 °C (lit. M. p. 134–136 °C [13]), R_f = 0.52 (benzene). Anal. Calcd for $C_{11}H_8ClNO_2$, %: C 59.60, H 3.64, Cl 16.00, N 6.32. Found, %: 59.93, H 3.61, Cl 16.00, N 6.28. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.92 (3H, s, OMe), 7.70 (1H, d, J = 9 Hz), 8.03 (1H, d, J = 9 Hz), 8.25 (1H, d, J = 9 Hz), 8.66 (1H, d, J = 9 Hz), 8.74 (1H, s). ^{13}C NMR

ISSN 2308-8303 (Print) / 2518-1548 (Online)

(100 MHz, DMSO-d_6), δ, ppm: 52.9 (MeO), 123.8, 126.5, 128.3, 128.9, 130.2, 130.7, 131.2, 141.7, 149.37, 152.0, 152.7, 165.9 (C=O).

Methyl 2,4-dichloroquinoline-6-carboxylate (**5b**)

Yellowish crystals. Yield – 1.1 g (10%). M. p. 132 °C, R_f = 0.72 (benzene). Anal. Calcd for $C_{11}H_7Cl_2NO_2$, %: C 51.59, H 2.76, Cl 27.69, N 5.47. Found, %: C 51.72, H 2.65, Cl 27.80, N 5.40. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.91 (3H, s, OMe), 7.99 (1H, d, J = 9 Hz), 8.19 (1H, d, J = 9 Hz), 8.61 (1H, s), 8.91 (1H, s). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 52.9 (MeO), 123.8, 126.5, 128.3, 128.9, 130.2, 130.7, 131.2, 141.7, 149.3, 152.0, 152.7, 165.9 (C=O).

Methyl 2-chloroquinoline-7-carboxylate (4c) and methyl 2,4-dichloroquinoline-7-carboxylate (5c)

The mixture was synthesized according to the method for compound **4b** from 9.0 g (0.048 mol) of ester **1c**. 5.2 g of a mixture of substances **4c** and **5c** were obtained. 2.1 g of the starting ester was isolated from the benzene mother liquor. 5.15 g of a mixture of **4c** and **5c** was dissolved in 400 mL of hot benzene, filtered through a silica gel layer (5 cm) and evaporated to 30 mL. 2,4-Dichloro-7-carboxylate (**5c**), which precipitated after cooling, was filtered off. The mother solution was evaporated to 10 mL, 20 mL of heptane was added, and the precipitate was filtered off giving **4c**.

Methyl 2-chloroquinoline-7-carboxylate (**4c**)

Yellowish crystals. Yield – 4.18 g (49%). M. p. 112–113 °C, R_f = 0.51 ($CHCl_3$). Anal. Calcd for $C_{11}H_8ClNO_2$, %: C 59.6, H 3.64, Cl 16.00, N 6.32. Found, %: C 59.95, H 3.60, Cl 16.00, N 6.30. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.94 (3H, s, MeO), 7.35 (1H, d, J = 10 Hz), 7.70 (1H, d, J = 10 Hz), 8.02-8.07 (2H, m), 8.54 (1H, d, J = 5 Hz). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 52.7 (MeO), 123.5, 126.6, 128.0, 129.9, 130.2, 130.8, 140.0, 149.2, 153.5, 166.6 (C=O).

Methyl 2,4-dichloroquinoline-7-carboxylate (**5c**)

A yellowish powder. Yield – 0.65 g (6.4%). M. p. 118–120 °C, R_f = 0.67 ($CHCl_3$). Anal. Calcd for $C_{11}H_7Cl_2NO_2$, %: C 51.59, H 2.76, Cl 27.69, N 5.47. Found, %: C 51.65, H 2.68, Cl 27.72, N 5.36. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.91 (3H, s, MeO), 8.11 (1H, s), 8.56 (1H, d, J = 9 Hz), 8.59 (1H, s), 8.78 (1H, d, J = 9 Hz).

Methyl 2-chloroquinoline-8-carboxylate (7). Method 1

Step 1. *Methyl 1-methyl-2(1H)-oxoquinoline-8-carboxylate* (**6**)

Ester **1d** (15.15 g, 0.081 mol) and 26 mL (0.278 mol) of freshly distilled dimethyl sulfate were stirred at 180–185 °C for 2.5 h. After cooling, 50 mL of water was added to the reaction mixture and then poured into the solution of 75 g (0.2278 mol) of potassium hexacyanoferrate(III) in 220 mL of water at 60 °C. Then the solution of NaOH (32 g, 0.8 mol) in 64 mL of water was added to the mixture while stirring for 2-3 min. After cooling, it was extracted with benzene (2×200 mL). The benzene extract was evaporated to 20 mL, and 60 mL of heptane was added. The precipitate was filtered, dried, and compound **6** was thus obtained.

White crystals. Yield – 7.38 g (42%). M. p. 95–96 °C. Anal. Calcd for $C_{12}H_{11}NO_3$, %: C 66.35, H 5.10, N 6.45. Found, %: C 66.40, H 5.05, N 6.40. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.36 (3H, s, N-Me), 3.89 (3H, s, MeO), 6.68 (1H, d, J = 9 Hz), 7.31 (1H, t, J = 9 Hz), 7.75 (1H, d, J = 9 Hz), 7.88 (1H, d, J = 9 Hz), 7.97 (1H, d, J = 12 Hz).

Step 2. *Methyl 2-chloroquinoline-8-carboxylate* (**7**), *2-chloroquinoline-8-carboxylic acid* (**8**), *methyl 2(1H)-2-oxoquinoline-8- carboxylate* (**9**)

Ester **6** (9.7 g, 0.0447 mol) was mixed with phosphorus pentachloride (12.6 g, 0.0605 mol) and phosphorus oxychloride (4.2 mL, 0.0447 mol), and stirred at 140 °C for 1 h. Water and ice were added to the reaction mass, the mixture was neutralized with 20% NaOH to pH 5–6 and extracted with chloroform 3×150 mL. The extract was passed through the aluminum oxide layer (6–7 cm) and evaporated. The residue was dissolved in benzene (~20–25 mL) and introduced into a column with silica gel (2.5×50 cm). Ester **7** was obtained with benzene as an eluent. By changing the eluent to benzene/acetone 50:1, 2-chloroquinoline-8-carboxylate (**8**) and methyl 2(*1H*)-oxoquinoline-8-carboxylate (**9**) were isolated.

Methyl 2-chloroquinoline-8-carboxylate (**7**)

A yellowish oil. Yield – 4 g (40.4%). Anal. Calcd for $C_{11}H_8ClNO_2$, %: C 59.60, H 3.64, Cl 16.00, N 6.32. Found, %: C 59.90, H 3.60, Cl 16.10, N 6.33. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.90 (3H, s, MeO), 7.69 (1H, d, J = 8 Hz), 7.73 (1H, t, J = 8 Hz), 8.05 (1H, d, J = 8 Hz), 8.22 (1H, d, J = 8), 8.54 (1H, d, J = 8 Hz). ^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 53.3, 121.4, 121.8, 122.0, 130.2, 132.3, 138.5, 140.1, 162.5, 169.0.

2-Chloroquinoline-8-carboxylic acid (**8**)

A yellowish solid. Yield – 0.55 g (5.9%). M. p. 212–215 °C. Anal. Calcd for $C_{10}H_6ClNO_2$, %: C 57.85, H 2.91, Cl 17.08, N 6.75. Found, %: C 57.90, H 2.87, Cl 17.10, N 6.65. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.52–7.76 (2H, m), 8.20–8.28 (2H, m), 8.62 (1H, d, J = 9 Hz), 13.82 (1H, s, COOH).

^{13}C NMR (100 MHz, DMSO-d_6), δ, ppm: 123.55, 127.16, 127.34, 127.48, 132.26, 132.43, 132.78, 133.08, 141.69, 150.55.

Methyl 2(1H)-2-oxoquinoline-8-carboxylate (**9**)

A white solid. Yield – 1.92 g (21%). M. p. 134–136 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.91 (3H, s, MeO), 6.61 (1H, d, J = 9 Hz), 7.28 (1H, t, J = 9 Hz), 7.99-8.04 (2H, m), 8.15 (1H, d, J = 9 Hz), 11.38 (1H, br. s, NH).

Methyl 2-chloroquinoline-8-carboxylate (7). Method 2

Step 1. *2-Chloro-8-dibromomethylquinoline* (**13**)

A mixture of 2-chloro-8-methylquinoline (**12**) (15 g, 0.0845 mol) [16], N-bromosuccinimide (32 g, 0.1798 mol), 150 mL of carbon tetrachloride, and 0.25 g of azo-*bis*-isobutyronitrile was refluxed for 2 h. The reaction was diluted with 150 mL of boiling CCl_4 and quickly filtered, the filter was washed with 50 mL of carbon tetrachloride. The solvent was evaporated to the volume of 120 mL, 150 mL of hot ethanol was added and evaporated to the volume of 110-120 mL. After 12 h, compound **13** was filtered, washed with ethanol (~60 mL) and dried.

A yellow powder. Yield – 21.8 g (76.9%). M. p. 165–170 °C. Dibromo derivative **13** was used without further purification.

Step 2. *2(1H)-Oxoquinoline-8-carboxylic acid* (**15**)

A mixture of 21.8 g (0.065 mol) of dibromide **13** and 53.93 g (0.325 mol) of silver acetate in 150 ml of ethanol was heated to 55 °C and, with stirring, 50 mL of hot (50 °C) water was added. Then the solution of 18.2 g (0.455 mol) of NaOH in 50 mL of water was added dropwise over 20 min. Next, 50 mL portion of hot water was added and stirred for 10 min. The reaction mixture was heated to 60–65 °C, and the stirring was continued for another 40 min, and the heating was removed. After 30 min, the solution was filtered from silver compounds, and the residue on the filter was washed with 200 mL of hot water (60–65 °C). The solution obtained was extracted with benzene (2×200 mL) and neutralized with the solution of 35 mL (0.132 mol) of 10% hydrochloric acid. The precipitate of acid **15** was filtered off and dried.

A white powder. Yield – 9.46 g (77%). M. p. 139–140 °C (lit. M. p. 140–142 °C [19]). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.62 (1H, d, J = 10 Hz), 7.31 (1H, d, J = 7.8 Hz), 7.99 (1H, d, J = 7.8 Hz), 8.04 (1H, d, J = 10 Hz), 8.20 (1H, d, J = 7.8 Hz), 11.8 (1H, br. s, NH).

Step 3. *2-Chloroquinoline-8-carboxylic acid* (**8**)

A mixture of oxoacid **15** (14.7 g, 0.078 mol) and phosphorus oxychloride (17 mL, 0.182 mol) was heated for 20 min under reflux. Then the mixture was cooled to 40–45 °C, 80 mL of glacial acetic acid was added and poured onto crushed ice (~200 g), mineral acids were neutralized with a dry sodium carbonate to pH 5. The precipitate was filtered off, washed with water, dried in air giving 15.2 g (93%) of acid **8**. M. p. 216–219 °C. ^{1}H and ^{13}C NMR spectra were consistent with compound **8** obtained by the **Method 1** and the literature data [20].

Step 4. *Methyl 2-chloroquinoline-8-carboxylate* (**7**)

Acid **8** (14.7 g, 0.0705 mol) was heated to boiling in 650 mL of chloroform and 50 mL of methanol and cooled to 25 °C. The solution of diazomethane (5.6 g, 0.133 mol) in 200 mL of a mixture of benzene/diethyl ether (1:1) was poured into the solution for 10 min. After the release of nitrogen, the excess of diazomethane was decomposed by glacial acetic acid. The resulting solution was washed with water, 300 mL of 3% sodium bicarbonate solution was passed through the aluminum oxide layer (10 cm), the solvent was evaporated in vacuum.

Yield of ester **7** – 15 g (95.6%) as a yellow oil. ^{1}H and ^{13}C NMR spectra were consistent with those for compound **7** obtained by **Method 1** and the literature data [20].

References

1. Hamama, W. S.; Ibrahim, M. E.; Gooda, A. A.; Zoorob, H. H. Recent advances in the chemistry of 2-chloroquinoline-3-carbaldehyde and related analogs. *RSC Adv.* **2018,** *8* (16), 8484–8515. https://doi.org/10.1039/C7RA11537G.
2. Lee, B. S.; Lee, J. H.; Chi, D. Y. Novel Synthesis of 2-Chloroquinolines from 2-Vinylanilines in Nitrile Solvent. *J. Org. Chem.* **2002,** *67* (22), 7884–7886. https://doi.org/10.1021/jo016196i.
3. El-Sayed, O. A.; Al-Bassam, B. A.; Hussein, M. E. Synthesis of Some Novel Quinoline-3-carboxylic Acids and Pyrimidoquinoline Derivatives as Potential Antimicrobial Agents. *Arch. Pharm.* **2002,** *335* (9), 403–410. https://doi.org/10.1002/1521-4184(200212)335:9<403::AID-ARDP403>3.0.CO;2-9.
4. Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. Quinolines and structurally related heterocycles as antimalarials. *Eur. J. Med. Chem.* **2010,** *45* (8), 3245–3264. https://doi.org/10.1016/j.ejmech.2010.04.011.
5. Abdou, W. M.; Khidre, R. E.; Shaddy, A. A. Synthesis of Tetrazoloquinoline-Based Mono- and Bisphosphonate Esters as Potent Anti-Inflammatory Agents. *J. Heterocycl. Chem.* **2013,** *50* (1), 33–41. https://doi.org/10.1002/jhet.968.
6. Abdou, W. M.; Khidre, R. E.; Kamel, A. A. Elaborating on Efficient Anti-Proliferation Agents of Cancer Cells and Anti-Inflammatory-Based N-Bisphosphonic Acids. *Arch. Pharm.* **2012,** *345* (2), 123–136. https://doi.org/10.1002/ardp.201100080.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

7. Selvi, S. T.; Nadaraj, V.; Mohan, S.; Sasi, R.; Hema, M. Solvent free microwave synthesis and evaluation of antimicrobial activity of pyrimido[4,5-b]- and pyrazolo[3,4-b]quinolines. *Bioorg. Med. Chem.* **2006,** *14* (11), 3896–3903. https://doi.org/10.1016/j.bmc.2006.01.048.
8. Dine, I.; Mulugeta, E.; Melaku, Y.; Belete, M. Recent advances in the synthesis of pharmaceutically active 4-quinolone and its analogues: a review. *RSC Adv.* **2023,** *13* (13), 8657–8682. https://doi.org/10.1039/D3RA00749A.
9. Kumar, G.; Saroha, B.; Kumar, R.; Kumari, M.; Kumar, S. Recent Advances in Synthesis and Biological Assessment of Quinoline-Oxygen Heterocycle Hybrids. *ChemistrySelect* **2021,** *6* (20), 5148–5165. https://doi.org/10.1002/slct.202100906.
10. Shvekhgeimer, M. G. A. The Pfitzinger Reaction. (Review). *Chem. Heterocycl. Comp.* **2004,** *40* (3), 257–294. https://doi.org/10.1023/B:COHC.0000028623.41308.e5.
11. Mandal, S.; Bhuyan, S.; Jana, S.; Hossain, J.; Chhetri, K.; Roy, B. G. Efficient visible light mediated synthesis of quinolin-2(1H)-ones from quinoline N-oxides. *Green Chem.* **2021,** *23* (14), 5049–5055. https://doi.org/10.1039/D1GC01460A.
12. Pachupate, N. J.; Vaidya, P. D. Catalytic wet oxidation of quinoline over Ru/C catalyst. *Journal of Environmental Chemical Engineering* **2018,** *6* (1), 883–889. https://doi.org/10.1016/j.jece.2017.12.014.
13. Abe, H.; Sato, A.; Tokishita, Sh.-i.; Ohta, T.; Ito, H. Synthesis of Fluorescence Pyriproxyfen Analogues as Juvenile Hormone Agonists. *Heterocycles* **2011**, *83* (7), 1649–1658. https://doi.org/10.3987/COM-11-12232.
14. Qiao, K.; Wan, L.; Sun, X.; Zhang, K.; Zhu, N.; Li, X.; Guo, K. Regioselective Chlorination of Quinoline N-Oxides and Isoquinoline N-Oxides Using PPh3/Cl3CCN. *Eur. J. Org. Chem.* **2016,** *2016* (8), 1606–1611. https://doi.org/10.1002/ejoc.201501567.
15. Friedlaender, P.; Ostermaier, H. Ueber das Carbostyril. II. *Chem. Ber.* **1882,** *15* (1), 332–338. https://doi.org/10.1002/cber.18820150179.
16. Chakrabartty, S. K.; Kretschmer, H. O. Sodium hypochlorite as a selective oxidant for organic compounds. *J. Chem. Soc., Perkin Trans. 1* **1974,** 0, 222–228. https://doi.org/10.1039/P19740000222.
17. Decker, H. Ueber die Einwirkung von Alkalien auf Jodalkylate der Chinolin- und Acridinreihe. *Journal für Praktische Chemie* **1892,** *45* (1), 161–200. https://doi.org/10.1002/prac.18920450120.
18. Fischer, O. Einwirkung von Phosphorpentachlorid auf N- Alkyl-Pyridone und-Chinolone. *Chem. Ber.* **1898,** *31* (1), 609–612. https://doi.org/10.1002/cber.189803101127.
19. Yang, J.; Gustavsson, A.-L.; Haraldsson, M.; Karlsson, G.; Norberg, T.; Baltzer, L. High-affinity recognition of the human C-reactive protein independent of phosphocholine. *Org. Biomol. Chem.* **2017,** *15* (21), 4644–4654. https://doi.org/10.1039/C7OB00684E.
20. Xu, W.; Nagata, Y.; Kumagai, N. TetraQuinolines: A Missing Link in the Family of Porphyrinoid Macrocycles. *J. Am. Chem. Soc.* **2023,** *145* (4), 2609–2618. https://doi.org/10.1021/jacs.2c12582.

Information about the authors:
Yurii V. Ishkov, D.Sci. in Chemistry, Professor of the Organic and Pharmaceutical Chemistry Department, I. I. Mechnikov Odesa National University; https://orcid.org/0000-0003-1228-3880.
Vira V. Veduta, Ph.D. in Chemistry, Associate Professor of the Organic and Pharmaceutical Chemistry Department, I. I. Mechnikov Odesa National University; https://orcid.org/0000-0002-1151-650X.
Nadia F. Fedko, Ph.D. in Chemistry, Associate Professor of the Organic and Pharmaceutical Chemistry Department, I. I. Mechnikov Odesa National University; https://orcid.org/0000-0003-1222-9817.
Natalia M. Bohdan (*corresponding author*), Ph.D. in Chemistry, Senior Researcher, Laboratory of Condensed Heterocyclic Systems, Institute of Organic Chemistry of the National Academy of Sciences of Ukraine; https://orcid.org/0000-0003-1222-9817;
e-mail for correspondence: n_bogdan@email.ua.