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4-HYDROXYQUINOL-2-ONES. 85*. SYNTHESIS OF 2-CHLORO-4-HYDROXYQUINOLINE-3-CARBOXYLIC ACID ETHYL ESTER

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The behavior of 2-chloro-4-hydroxy- and 4-chloro-2-oxoquinoline-3-carboxylic acids under acid catalyzed esterification conditions with methanol has been studied. A method is proposed for obtaining 2-chloro-4-hydroxyquinoline-3-carboxylic acid ethyl ester.

Keywords: quinoline-3-carboxylic acid, chloroquinoline, esterification.

While developing methods for obtaining thio analogs of 1H-3-(2-benzimidazolyl)-4-hydroxy-2-oxoquinoline as one of the possible variants of the synthesis of a 4-hydroxy-2-thio-substituted derivative we suggested the use of 2-chloro-4-hydroxyquinoline-3-carboxylic acid (**1**) [2], readily obtained by alkaline hydrolysis of 2,4-dichloro-3-ethoxycarbonylquinoline (**2**) [3]. The need to esterify acid **1** was noted due to the inclination of such compounds to decarboxylate.

However, our attempts to effect this reaction were not crowned with success. As it turned out esterification of acid **1** with an excess of absolute methyl alcohol in the presence of catalytic amounts of conc. H_2SO_4 leads to the formation of the methyl ester of 1H-4-hydroxy-2-oxoquinoline-3-carboxylic acid (**3**). Probably the total amount of water (separated on esterification of the carboxyl group and the residual moisture in the alcohol) proved to be sufficient to hydrolyze the 2-chloroquinoline to a quinol-2-one, which in general is characteristic for compounds of this class [4]. At the same time, 4-chloro-2-oxoquinoline-3-carboxylic acid (**4**) forms the corresponding 4-chloro-substituted ester **5** under analogous conditions without any difficulty.

Participation of the 4-OH group in the formation of stable intramolecular hydrogen bonds (IMHB) enabled the synthesis of 3-(2-benzimidazolyl)-2-chloro-4-hydroxyquinoline to be effected by direct treatment of the 4-hydroxy-2-oxo derivative with phosphorous oxychloride [2]. It is evident that this principle may also be used to obtain 2-chloro-4-hydroxyquinoline-3-carboxylic acid ethyl ester (**6**), all the more so, since, according to X-ray structural analysis data, the 4-OH group in 1-R-3-ethoxycarbonyl-4-hydroxy-2-oxoquinolines forms stable IMHB with the carbonyl oxygen atoms of the ester groupings, while the C=O group in position 2 of the quinoline ring participates only in the formation of significantly less stable intermolecular hydrogen bonds [5, 6] (Scheme 1).

As was shown by the results of our experiments, the 2-chloro-substituted ester **6** is actually formed in satisfactory yield on short term (no more than 5 min) treatment of 4-hydroxy-2-oxoquinoline **7** with phosphorus oxychloride. It is interesting to note that after such short interaction the initial ester **7** was not detected in the reaction mixture, i.e. the exchange of the 2-hydroxy group by halogen takes place unusually readily.

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* For Part 84 see [1].

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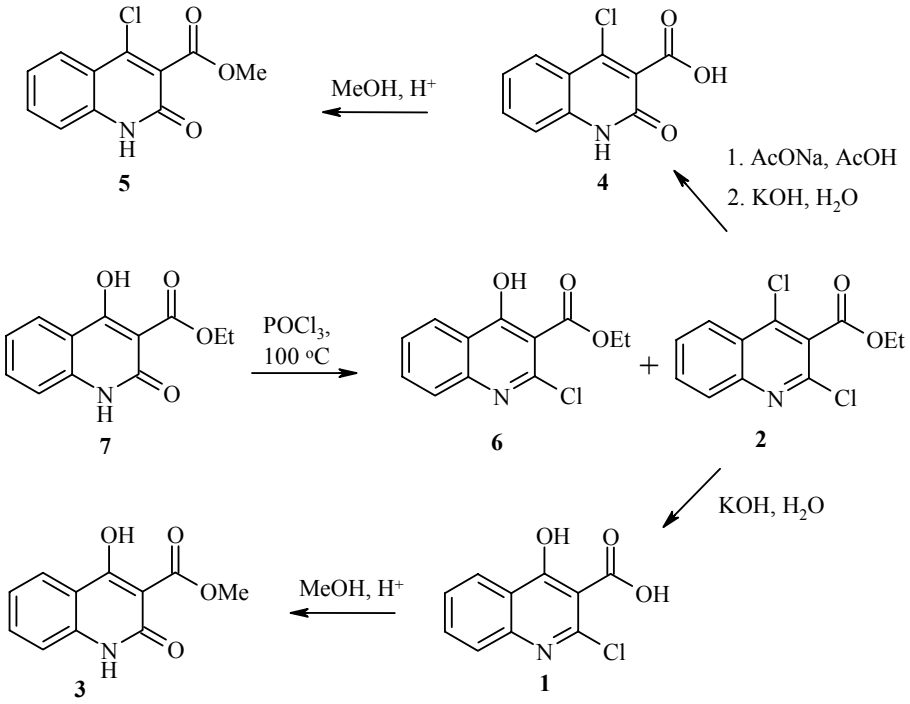
Scheme 1



EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury VX-200 (200 MHz) instrument, solvent was DMSO-d_6, internal standard was TMS. The mass spectrum of ester **6** was recorded on a Finnigan MAT Incos 50 quadrupole spectrometer in the complete scanning mode in the range 33-700 *m/z*, ionization for electron impact was 70 eV, with direct insertion of sample, heating rate was ~5°C/sec.

1H-4-Hydroxy-2-oxoquinoline-3-carboxylic Acid Methyl Ester (3). Conc. H_2SO_4 (3-4 drops) was added to a mixture of 2-chloro-4-hydroxyquinoline-3-carboxylic acid (2.23 g, 0.01 mol) and absolute methyl alcohol (30 ml), and the mixture was boiled with protection from air moisture until complete solution (10 h). The mixture was cooled, and diluted with water. The precipitated solid ester **3** was filtered off, washed with water, and dried. Yield 2.08 g (95%); mp 222-224°C (methanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.41 (1H, s, OH); 11.58 (1H, s, NH); 7.93 (1H, d, *J* = 7.8, H-5); 7.64 (1H, t d, *J* = 7.0 and *J* = 1.5, H-7); 7.12-7.38 (2H, m, H-8, 6); 3.90 (3H, s, CH_3). Found, %: C 60.37; H 4.25; N 6.31. $C_{11}H_9NO_4$. Calculated, %: C 60.28; H 4.14; N 6.39.

1H-4-Chloro-2-oxoquinoline-3-carboxylic Acid Methyl Ester (5) was obtained from acid **4** by the procedure of the previous experiment. Yield 97%; mp 187-189°C (methanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz); 12.48 (1H, s, NH); 7.92 (1H, d, *J* = 8.0, H-5); 7.70 (1H, td, *J* = 8.0 and *J* = 1.8, H-7), 7.27-7.48 (2H, m, H-8, 6); 3.83 (3H, s, CH_3). Found, %: C 55.52; H 3.51; N 5.97. $C_{11}H_8ClNO_3$. Calculated, %: C 55.60; H 3.39; N 5.88.

2-Chloro-4-hydroxyquinoline-3-carboxylic Acid Ethyl Ester (6). A mixture of ester **7** (2.33 g, 0.01 mol) and $POCl_3$ (10 ml) was maintained at 100°C for 5 min, after which the mixture was poured directly onto finely powdered ice. After decomposition of the excess of $POCl_3$, Na_2CO_3 was added with thorough mixing to the reaction mixture to pH 8, and the mixture was filtered. The solid on the filter was washed with water, and dried. The 2,4-dichloro-substituted ester **2** was obtained (0.32 g, 12%), the properties of which were identical to

those described previously in [3]. Acetic acid was added to the filtrate to pH 4.5-5.0. The precipitated solid ester **6** was filtered off, washed with water, and dried. Yield 1.69 g (67%); mp 171-173°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.98 (1H, s, OH); 8.12 (1H, dd, *J* = 8.0 and *J* = 1.8, H-5); 7.78 (1H, td, *J* = 8.1 and *J* = 1.8, H-7); 7.62 (1H, dd, *J* = 8.5 and *J* = 2.0, H-8); 7.46 (1H, td, *J* = 7.0 and *J* = 2.0, H-6); 4 29 (2H, q, *J* = 7.0, $C\underline{H}_2CH_3$); 1.30 (3H, t, *J* = 7.0, $CH_2C\underline{H}_3$). Mass spectrum, *m/z* (I_{rel}, %): 251 (28) $[M]^+$, 205 (100) $[M\text{-}EtOH]^+$, 170 (84), 114 (33). Values of *m/z* are given for the ^{35}Cl isotope. Found, %: C 57.18; H 3.91; N 5.50. $C_{12}H_{10}ClNO_3$. Calculated, %: C 57.27; H 4.00; N 5.58.

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