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3-Hydroxymethyl-1,4-dihydro-4-oxoquinoline like compound with promising biological and complexing activity

Viktor Milata, Maroš Bella, Robert Kurinec

Department of Organic Chemistry, Institute of Organic Chemistry, Catalysis and Petrochemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, 812 37 Bratislava, Radlinského 9, Slovakia
viktor.milata@stuba.sk

Introduction

Hydroxymethyl group is present in many useful and biologically potent substances like sugars, kojic acid (Bajpai, 1982), ronicol (3-hydroxymethylpyridine) (Moncol, 2006; Broghammer, 1967) or hydroxymethylphenol — intermediate for bakelite (Baekeland, 1909).

On the other hand, 4-quinolones are a group of antibacterials with various biological activities if substituted in position 3- and they are anti-CNS and similar diseases agents if substituted in position 2- (kynurenic acid derivatives) (Turski, 2013; Szalardy, 2012; Fulop, 2009). Considering this, we were interested in the synthesis of 3-hydroxymethyl-1,4-dihydro-4-oxoquinoline.

4-Quinolones are a well-known group of chemotherapeutics with a broad spectrum of activities (Andriole, 2000; Milata, 2000) based on inhibition of the enzyme of bacterial topoisomerase II (DNA gyrase) and topoisomerase IV in Gram-positive species, thus inhibiting tertiary negative supercoiling of bacterial DNA (Gellert, 1976; Wang, 1985; Gootz, 1996) mostly bound to oxygen atoms in positions 3- and 4- of the fused pyrid-4-one-3-carboxylic acid moiety (Andriole, 2000). Therefore, it should be interesting to prepare and evaluate the corresponding structural motif, namely 3-hydroxymethylquinol-4-one.

Substructural search in database SciFinder® provided only various applications of formaldehyde with 4-quinolones or their precursors (Goldsworthy, 1982) but no true synthesis has been reported. Therefore, this compound with promising binding and complexing activity has been prepared.

Materials and Methods

Spectrometer INOVA 300 (300 MHz, Varian Inc., Palo Alto, CA, USA) was used to measure ^{1}H NMR spectra, at their RT frequencies. Chemical shifts in (δ)—[ppm] (parts per million) were referenced to the residual signal of the solvent. Coupling constants (J) are given in [Hz] with multiplicity: s (singlet), d (doublet), dd (doublet of the doublet), t (triplet), q (quartet), q (quintet) and m (multiplet). Tetramethylsilane was used for the calculation of ^{1}H chemical shift scales and correctly referenced using the (residual) solvent signals (2.50 and 39.52 ppm for DMSO).

All reagents and solvents were purchased from Sigma-Aldrich® (Darmstadt, Germany), Alfa-Aesar® (Ward Hill, MA, USA), Fluka® (Buchs, Switzerland) and Mikrochem® (Pezinok, Slovakia). Solvents were purified and/or dried using standard laboratory methods and stored over molecular sieves (4 Å). Column chromatography was performed using silica gel Nomasil—40—63 m (VWR®, Randor, PA, USA) and a suitable eluent according to TLC. Reaction progress was monitored by thin layer chromatography on Silufol or Alufol plates (Merck®, Darmstadt, Germany) with a UV indicator for λ = 254 nm.

Melting points (m. p.) of the prepared compounds were determined on a Boetius micro hot stage using digital thermometer TD 121 (VWR®, Randor, PA, USA) and are uncorrected.

Experimental

3-Hydroxymethyl-4-oxo-1,4-dihydroquinoline 7

A sample of 0,5 g (2,3 mmol) of ethyl 1,4-dihydro-4-oxoquinoline-3-carboxylate (**4**) was added to a 100 mL flask and solved in dry THF (20 mL) equipped with a $CaCl_2$ drying stopper under argon at LT. To this solution, small portions of powdered $LiAlH_4$ (0.5 g) were added and the mixture was stirred at LT for 24 hours. Then, it was poured into a water solution of NH_4Cl (50 mL, 10 %) which was afterwards filtered and the filter was washed with ethyl acetate. The filtrate was also extracted with ethyl acetate. Both parts were collected and evaporated to dryness. Yield 0.3 g (74,4 %) of 3-hydroxymethyl-4-oxo-1,4-dihydroquinoline, almost pure raw product. M. p. 183—184 °C.

Elemental analysis (calc./found): %C: 68,57/68,69, %H: 5,14/4,96 and %N: 8,00/7,69.

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^{1}H NMR (DMSO-d_6): 4.42 d (CH_2, 2H, 4,8 Hz), 4.94 t (OH, 1H, 4,8 Hz), 7.30 t (H-8, 1H, 7,8 Hz), 7.53 d (H-6, 1H, 7,8 Hz), 7,63 t (H-7, 1H, 7,8 Hz), 7,88 bs (H-2, 1H), 8.11 d (H-5, 1H, 7,8 Hz).

Results and Discussion

3-Hydroxymethyl derivative **7** represents an interesting tautomeric system (Scheme 1).
4-Oxoform B, compared to tautomer A, includes an intramolecular hydrogen bond between oxygen of the carbonyl group of the 4-pyridone system and hydrogen of the hydroxyl group. Another possible tautomer is aromatic 4-hydroxyquinoline with intramolecular hydrogen bond between hydrogen of the hydroxy group of 4-hydroxyquinoline and oxygen of the hydroxymethyl group (C) (Scheme 1).
Our first attempt was focused on the exploitation of formaldehyde as a hydroxymethylation agent considering that unsubstituted 4-quinolone (**6,** prepared from **4** *via* **5,** Scheme 2) reacts under the conditions of electrophilic substitution to position 3-, which has the highest electron density in the enaminone system, in agreement with previous results (Zubkov, 2003). Variation of reaction conditions (time, temperature, solvent) resulted in unsatisfactory yields, reactions produced mixtures of deeply colored and hardly separable by-products.
The second strategy was based on the reduction of corresponding 3-ethoxycarbonylderivative, easily accessible through the Gould-Jacobs reaction (Nicolson 1989). Heating of the starting equimolar mixture of aniline and diethyl ethoxymethylene malonate (EMME) to 120—130 °C for three hours (instead of 2 h at 130 °C) gave only an 83 % yield after cooling to LT (Nicolson, 1989: 96 % after cooling to –78 °C). Thermal cyclisation of diethyl anilinomethylene malonate (**3)** in diphenyl ether to reflux, including cooling of the reaction mixture, filtering off of the separated raw solid (**4)** and washing with chloroform to remove traces of **3** yielded 60 % of ethyl 4-oxo-1,4-dihydroquinoline-3-carboxylate (**4)** (Nicolson, 1989: after cyclisation in Dowtherm, an eutectic mixture of biphenyl and diphenyl ether offered a 73 % yield after recrystallisation from acetic acid). Dilution of **3** in solvent was 2,63 g/20 ml while Nicolson (1989) used the dilution of 10 g/50 ml both for 30 min.

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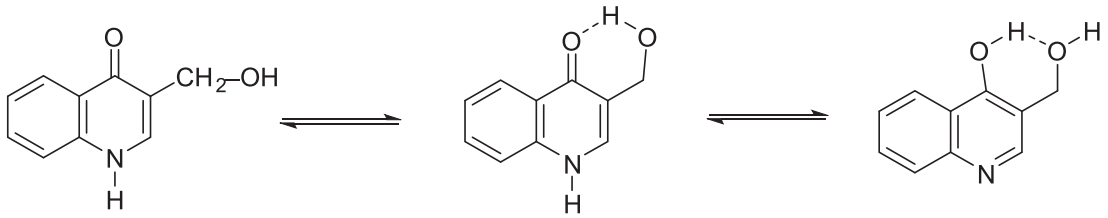
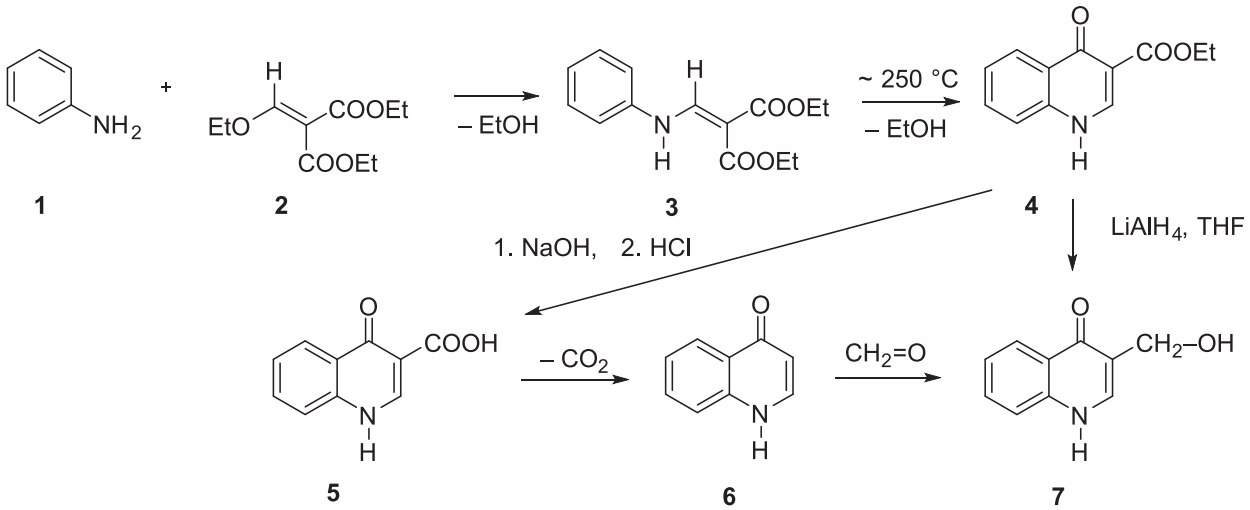


Scheme 1. Tautomerism of 3-hydroxymethyl-1,4-dihydro-4-oxoquinoline **7**.



Scheme 2: Preparation of 3-hydroxymethyl-1,4-dihydro-4-oxoquinoline **7**.

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