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4-HYDROXY-2- QUINOLONES

199*. USE OF *N,N'*-DICYCLOHEXYLCARBODIIMIDE IN THE SYNTHESIS OF ETHYL 4-HYDROXY-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLATES

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A novel method has been developed for the synthesis of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids esters based on the use of monoethyl malonate as an acylating agent in the presence of N,N'-dicyclohexylcarbodiimide and characterized by high yields and purity for the final products. Practical recommendations are given for the removal of specific admixtures.

Keywords: 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, acylation, Dieckmann condensation.

4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids esters have intrinsically valuable pharmacological properties [2–4]. However, thanks to their unique structure and high reactivity they are of much greater interest as the basis for the synthesis of a very wide range of biologically active substances with an extremely broad spectrum of activity [5–11].

One of the most widespread, and therefore best studied, synthetic routes to these compounds is the acylation of anthranilic acids esters **1** using ethoxymalonyl chloride and subsequent Dieckmann cyclization of the ethyl 2-alkoxycarbonylmalonates **2** formed.

Despite the simplicity of its carrying out and the satisfactory yields of the final products, this synthetic scheme has, unfortunately, one serious drawback *viz*. using of ethoxycarbonyl chloride. The high cost of this acyl chloride and, no less important, its instability [12] significantly lower the overall efficiency of the method. At the same time, the intermediate synthetic product of the ethoxymalonyl chloride synthesis (the monoethyl ester of malonic acid (**3**)) is an accessible substance, which preparation and storage do not present difficulties [13]. It therefore seems advantageous to activate the carbonyl atom of the acid **3** by methods other than converting it to the acid chloride.

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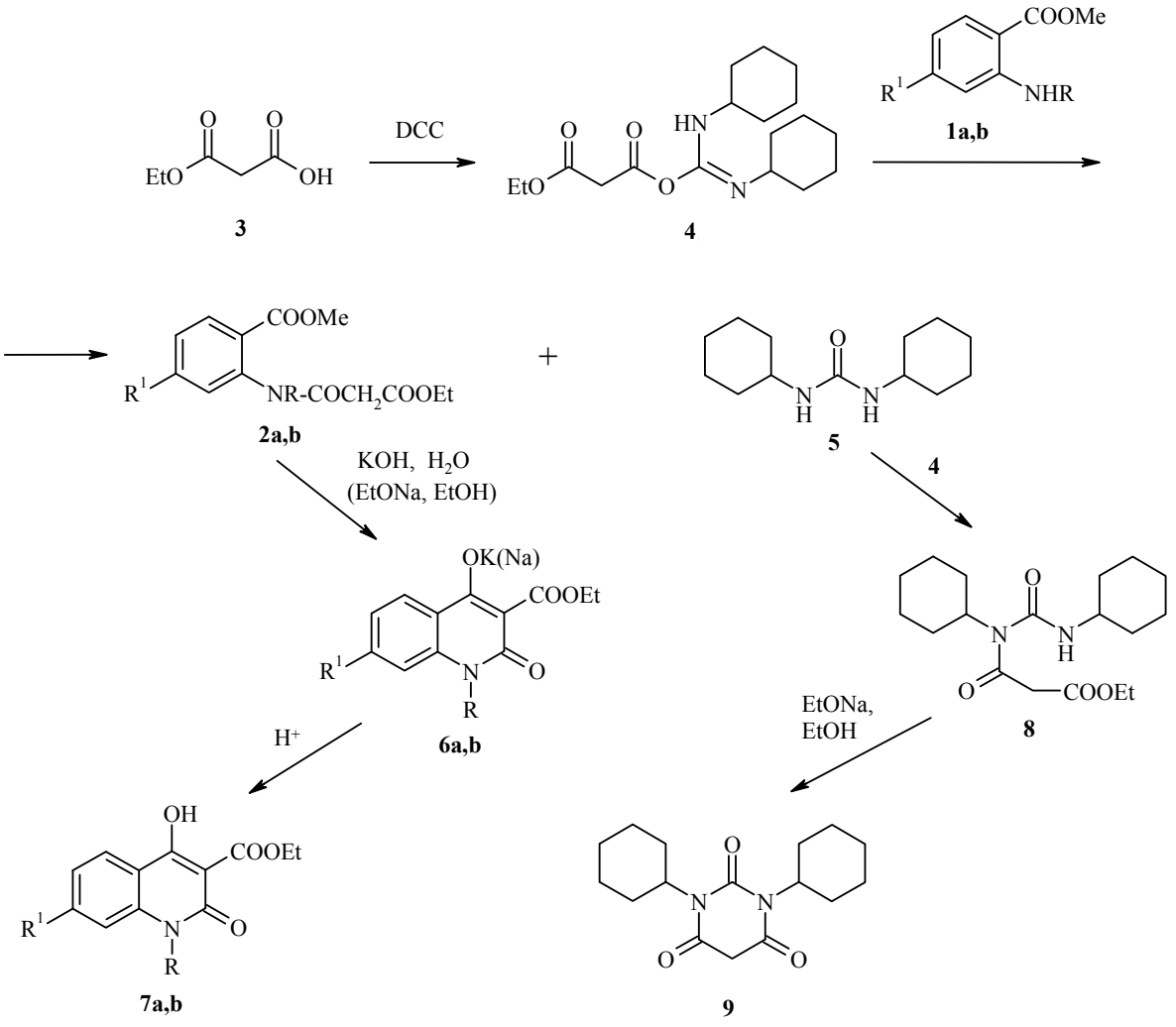

6, **7 a** R = H, R^1 = Cl; **b** R = Me, R^1 = H,
DCC – *N*,*N*′-dicyclohexylcarbodiimide

At the present time the most widespread reagents of this type are *N,N*'-carbonyldiimidazole [14] and *N,N*'-dicyclohexylcarbodiimide [15]. The former *N,N*′-carbonyldiimidazole is a relatively expensive reactant and syntheses using it can only be carried out in strictly anhydrous solvents. For this reason its use in the preparation of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates, although possible, is hardly desirable and is not considered by us in this study.

N,N'-Dicyclohexylcarbodiimide (DCC) is a much more convenient condensing agent, which does not demand special preparation of the solvents, hence its use for activation of the acid **3** appears to be quite promising. As it is known, the reaction of the DCC with acids converts the carboxyl group into an activated ester of type **4** (an *O*-acylisourea), which then reacts with amines under mild conditions to form the corresponding amides in 70-100% yields [15–17].

The experiments carried out by us in the case of the methyl 4-chloro- and *N*-methylanthranilates **1a,b** have shown that in the presence of DCC these aromatic amines are actually acylated readily by the monoethyl malonate **3** in high yields. Moreover, the characteristic drawback of the method (contamination of the reaction mixture with *N,N*'-dicyclohexylurea (**5**), which would be difficult to separate) can, in this case, be successfully removed in subsequent stages. The 4-*O*-potassium or sodium salts of 3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinolines **6a,b**, which are formed after heterocyclization of the anilides **2a,b**, are soluble in water in contrast to the dicyclohexylurea **5**, and this allows separation of the material without any difficulty. Subsequent

acidification of the aqueous solutions of salts **6a**,**b** gives the target ethyl quinoline-3-carboxylates **7a,b** in not less than 90% yield calculated on the starting methyl anthranilates **1a,b**, whereas the use of ethoxymalonyl chloride gives an average yield of about 65% [18]. In addition, a HPLC study of purity of the esters **7a,b** synthesized has been shown that, even without further purification, the concentration of admixtures in them does not exceed 1%.

Hence there is good reason to recommend our modification of the synthesis of the 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids esters as a preparative method. None the less, it should be noted that the use of this malonic acid acylating agent draws attention to the possibility of forming a still further admixture. The activated ester **4** can react not only with the amines, but also with the dicyclohexylurea **5** produced. The *N*-acylurea (**8**) thus formed can cyclize to the *N*,*N*'-dicyclohexylbarbituric acid (**9**) in the presence of sodium alcoholates in anhydrous alcohols. Like the target ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates **7a,b**, this product is readily soluble in aqueous alkalis but insoluble in acids, that is why its removal is even more complex than it is in the case of dicyclohexylurea **5**.

It is clear that formation of the *N*,*N*'-dicyclohexylbarbituric acid **9** needs conditions, which are practically achieved in the synthesis of the chloro-substituted ester **7a** (ester condensation of diesters **2**, prepared on the basis of anthranilic acids substituted in the aromatic ring, possible only in an anhydrous medium). In the preparation of the 1-*N*-methyl-substituted ester **7b,** anhydrous conditions are not mandatory [18]. Hence this side reaction cannot affect the purity of the target product since the N-acylurea **8** is invetably hydrolyzes to the dicyclohexylurea **5** and malonic acid in aqueous KOH solution. None the less, it is sure to affect the final yields negatively and its suppression needs, firstly, the use of a specific order of combining the reagents. In our case, the monoethyl ester of malonic acid **3** is slowly added to the solution of anthranilate **1** and DCC in dichloromethane, thus avoiding a high concentration of the acylating agent. Secondly, with the exothermicity of the reaction in mind, a high temperature of the mixture should be avoided by the use of efficient stirring and appropriate cooling. Thirdly, if the final heterocyclization stage of the synthesis is to be carried out in the anhydrous medium for any reason, then an equimolar amount of the reagents should be used (practically, a 10% excess of the DCC and the acid are used [15, 16]). Observation of these simple and straight forward recommendations allows us to eliminate the formation of an extremely unwanted admixture of dicyclohexylbarbituric acid **9** and to carry out the synthesis of the target ethyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates more efficiently.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury-VX-200 instrument at 200 MHz using DMSO-d_6 and with TMS as an internal standard. HPLC The analysis of the purity of esters **7a,b** was performed on the Waters Alliance 2690 liquid chromatograph with the Waters PAD 996 photodiode array detector. The chromatographic conditions were: Symmetry C8 (Nova Pak C8) column with the size of 3.9×150 mm, the mobile phase flow rate was 1 ml/min, the column temperature was 40ºC, the injection volume 20 μl, and the detection wavelength 232 nm. The composition of the mobile phase was 65% of acetonitrile and 35% of the aqueous solution of ammonium perchlorate (5 ml of 70% perchloric acid and 25% ammonia solution to pH 2.5-3 per litre of the solution).

Commercial dicyclohexylcarbodiimide and methyl 4-chloro- and *N*-methylanthranilates **1a,b** from Fluka were used in the synthesis of the ethyl esters **7a,b**. The monoethyl ester of malonic acid **3** was prepared by a known method [13].

Preparation of the Test Solution. The sample analyzed (0.025 g) was placed to a 25 ml graduated flask, dissolved in acetonitrile (10 ml), diluted to the volume by acetonitrile, and mixed. The suitability of the chromatographic system was monitored by the following parameters: the symmetry of the main peak of the sample analyzed should not exceed 1.5, the relative standard deviation calculated five times from the main peak

area should not exceed 2%, and the efficiency of the analytical column calculated for the main peak of the sample analyzed should not be less than 5000 theoretical plates.

Ethyl 7-Chloro-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (7a). Compound **3** (1.32 g, 10 mmol) was added dropwise with cooling and stirring to the solution of methyl 4-chloroanthranilate **1a** (1.85 g, 0.01 mol) and DCC (2.06 g, 10 mmol) in dichloromethane (30 ml). The product was left at room temperature for 6–8 h. The precipitate of dicyclohexylurea **5** formed was washed on the filter with dichloromethane and the solvent was distilled from the filtrate on the water bath (finally *in vacuo*). The solution of sodium ethylate (prepared from metallic sodium, 0.35 g, 15 mmol and absolute ethanol (25 ml)) was added to the residue, a mixture heated to reflux and left for 4 h at room temperature. The cooled product was treated with cold water (100 ml) and acidified with HCl to pH 4. The precipitated ester **7a** was filtered off, washed with water, and dissolved with heating in 5% aqueous potassium carbonate solution (40 ml). The solution obtained (the dicyclohexylurea **5** admixture remaining in the precipitate) was purified using activated carbon and filtered hot in 30 min. The product was cooled, acidified with HCl to adjust pH 4 and the precipitate of ester **7a** was filtered off, washed with water, and dried. Yield 2.51 g (94%). When heating to about 200ºC, the ester **7a** was decomposed without melting. Its ^{1}H NMR spectrum was identical to that of the known sample [19].

Ethyl 4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (7b). The monoethyl ester of malonic acid (**3**) (1.45 g, 11 mmol) was added dropwise with cooling and stirring to the solution of methyl *N*-methylanthranilate **1b** (1.65 g, 10 mmol) and DCC (2.27 g, 11 mmol) in dichloromethane (30 ml). The product was left at room temperature for 6–8 h. The precipitated dicyclohexylurea **5** was filtered off, washed on the filter with dichloromethane, and the solvent was distilled from the filtrate on the water bath (finally *in vacuo*). The residue was treated with KOH solution (1.12 g, 20 mmol) in water (20 ml) and mixed. In 1 h the reaction mixture was heated to reflux (during which the potassium salt **6b** dissolves in the solution and the admixture of dicyclohexylurea **5** remains in the precipitate). The solution obtained was purified using activated carbon and filtered hot in 30 min. The cooled solution was acidified using HCl to adjust pH 4 and the precipitated ester **7b** was filtered off, washed with cold water, and dried. Yield 2.22 g (90%); mp 105–106ºC (ethanol). Mixing of the sample with the known sample did not cause a depression of the melting point and the ^{1}H NMR spectra of the compounds were identical.

***N*,*N*-Dicyclohexylbarbituric Acid (9)**. Compound **3** (1.32 g, 10 mmol) was added to the solution of DCC (2.06 g, 10 mmol) in dichloromethane (20 ml). In 4–5 h the precipitate of compound **5** was filtered off. The solvent was removed from the filtrate by distillation on the water bath (finally *in vacuo*). The residue of the *N*-acylurea **8** was dissolved in sodium ethylate solution (prepared from metallic sodium (0.5 g, 22 mmol) and absolute ethanol (15 ml)) and refluxed for 1 h. The reaction mixture was cooled, diluted with water, and acidified with HCl to adjust pH 4. The precipitate formed was filtered off, washed with water, and dried. Yield 1.58 g (54%); mp 201–203ºC (DMF) (from data in [20] mp 200–201ºC). ^{1}H NMR spectrum, δ, ppm: 4.45 (2H, m, 2NCH); 3.58 (2H, s, $COCH_2CO$); 2.30–1.12 (20H, m, $2(CH_2)_5$).

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