

4-HYDROXY-2-QUINOLONES.

17.* DIECKMANN CONDENSATION AS A THERMALLY ACTIVATED PROCESS

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The thermolysis of ethyl 2-ethoxycarbonylmalonanilate in boiling diphenyl oxide gave the 2-ethoxycarbonylanilide of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid, which is also formed from the N,N'-di-2-ethoxycarbonylaniline of malonic acid in the conditions of the Dieckmann reaction. The mechanism of the chemical conversions indicated is presented and discussed.

The Dieckmann reaction, which is well known in organic chemistry as the intramolecular alternative to the Claisen ester condensation [2, 3], finds wide application in the synthesis of numerous cyclic and, especially, heterocyclic compounds.

The successful course of this reaction is possible both in different organic solvents (alcohol [4], ether [3], etc.) and in water [5, 6], whereby the presence of two ester groupings is not always obligatory [7, 8]. However, the utilization of some base catalysts is a required condition in all cases.

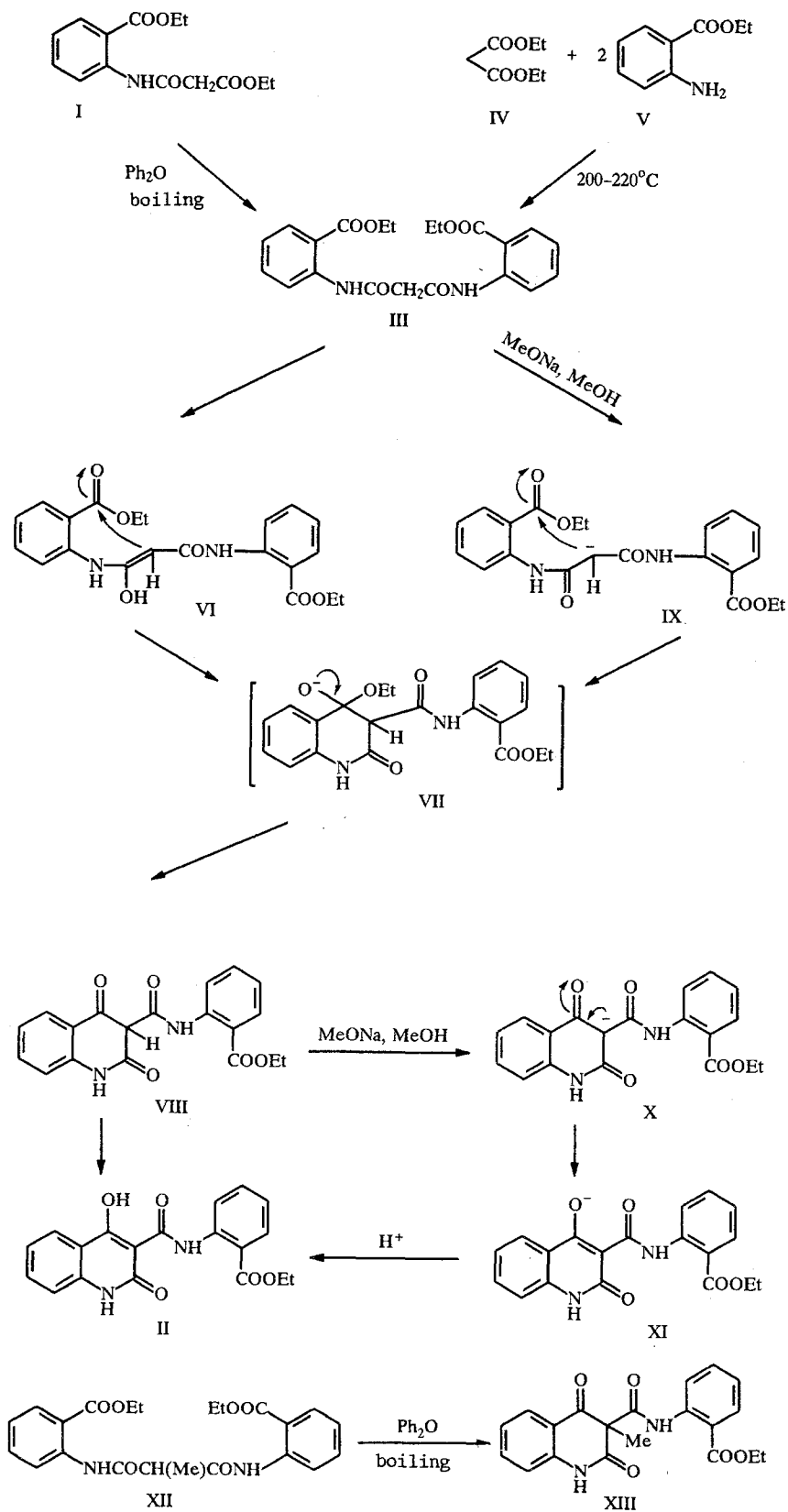
The present investigation also indicates the possible accomplishment of the Dieckmann condensation in the absence of bases; this allows this reaction to be regarded from another viewpoint, different from its classical presentation.

The boiling of ethyl 2-ethoxycarbonylmalonanilate (I) in diphenyl oxide led to the isolation of the 2-ethoxycarbonylanilide of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid (II). It is known that the pyrolysis of ethyl esters of malonanilic acids or their boiling in DMF leads to high yields of the symmetrical dianilides of malonic acids [9]. It is evident that the formation of the dianilide (III) is the first stage in the given case. It is hardly possible to explain the cyclization of this compound to the quinolone (II) under conditions of thermolysis by the ability of malonic acid derivatives to form stable carbanions since, first, the initial diester (I) would be cyclized to 1H-2-oxo-3-ethoxycarbonyl-4-hydroxyquinoline [5] and, second, the boiling of diethyl malonate (IV) with excess of ethyl anthranilate (V) only leads to the formation of the dianilide (III). In other words, there is clearly an insufficiency in the basic properties of the amino group of ethyl anthranilate, which is probably formed by the thermolysis of the diester (I), to accomplish the cyclization by the Dieckmann type of reaction.

All that has been stated leads one to believe that the given reaction includes a stage of the intramolecular interaction in the enol form (VI), in which the carbonyl carbon atom of the ester grouping emerges as the electrophile, and the enol emerges as the nucleophile. The resulting closing of the quinolone ring in (VII) leads to the 2,4-dioxo derivative (VIII) and, in the end, to the quinolone (II) (see scheme on following page).

The intermediate formation of the 2,4-dioxoquinoline (VIII) can be confirmed by taking the example of the thermolysis of the N,N'-di-2-ethoxycarbonylanilide of methylmalonic acid:

*For Communication 16, see [1].



Under the classical conditions of the Dieckmann condensation, the 2,4-dioxo derivative (VIII) is also one of the intermediate compounds. However, in this case, the possibility of the formation of the anion of the compound (X) is necessary for the reaction to proceed in the required direction [2]. Such a conversion is accompanied by the elimination of a proton (and not by its transfer, as in the case of thermolysis) and leads to the anion (XI); the acidification of (XI) leads to the isolation of the quinolone (II).

EXPERIMENTAL

The PMR spectra of the compounds synthesized were recorded on the Bruker WP-100 SY instrument (100 MHz); the solvent was DMSO-D₆, and the internal standard was TMS. The mass spectra were obtained on the Finnegan MAT 461 B instrument with the ionizing voltage of 70 eV and the ballistic heating of the sample.

The data of the elemental analysis for C, H, and N correspond with the calculated data.

Ethyl 2-ethoxycarbonylmalonanilate (I) was obtained by the method which we described previously [5].

2-Ethoxycarbonylanilide of 1H-2-Oxo-4-hydroxyquinoline-3-carboxylic Acid (II) (C₁₉H₁₆N₂O₅). A. The mixture of 2.79 g (0.01 mole) of the diester (I) in 20 ml of diphenyl oxide is maintained on a metallic bath at 260°C for 10 h. The reaction mixture is cooled prior to the addition of 50 ml of diethyl ether and careful trituration. The residue of the quinolone (II) is filtered off, washed with diethyl ether, and dried. Yield 1.12 g (64%); mp 242-244°C (dioxane). PMR spectrum (ppm): 16.42 (1H, s, OH), 13.01 (1H, s, NH anilide), 11.97 (1H, s, NH quinolone), 8.23-7.20 (8H, m, H_{arom}), 4.35 (2H, q, CH₂), 1.31 (3H, t, CH₃). Mass spectrum, m/z: 352 (M⁺).

B. To the solution of 3.98 g (0.01 mole) of the dianilide (III) in 10 ml of absolute methanol is added the solution of sodium methoxide [from 0.69 g (0.03 mole) of metallic sodium and 10 ml of methanol], and the mixture is boiled using a reflux condenser for 4 h. To the reaction mixture are added 50 ml of water prior to the acidification with HCl to the pH 3-4. The residue of the quinolone (II), which was separated out, was filtered off, washed with water, and dried. Yield 3.27 g (93%).

The mixed test with the quinolone (II), obtained by method A, does not give a depression of the melting temperature.

2-Ethoxycarbonylanilide of 1H-3-Methyl-2,4-dioxoquinoline-3-carboxylic Acid (XIII) (C₂₀H₁₈N₂O₅). This compound was obtained from the dianilide (XII) by method A of the preceding experiment. Yield 85%; mp 223-224°C (ethanol). PMR spectrum (ppm): 12.93 (1H, s, NH), 11.14 (1H, s, NH quinolone), 8.21-7.14 (8H, m, H_{arom}), 4.36 (2H, q, CH₂), 2.01 (3H, s, CH₃), 1.35 (3H, t, CH₂CH₃).

N,N'-Di-2-ethoxycarbonylanilide of Malonic Acid (III) (C₂₁H₂₂N₂O₆). The mixture of 4.13 g (0.025 mole) of ethyl anthranilate and 1.60 g (0.01 mole) of malonic ester is maintained on a metallic bath at 200-220°C with the simultaneous distillation of the released ethanol in the course of 2 h. The mixture is cooled and the residue is carefully triturated with 20 ml of hexane. The residue of the dianilide (III) is filtered off, washed on the funnel with hexane, and dried. Yield 3.82 g (96%); mp 139-140°C (ethanol). PMR spectrum (ppm): 10.86 (2H, s, NH), 8.26 (2H, d, J = 8.0 Hz, 3,3'-H), 7.93 (2H, dd, J = 7.5 and 2.0 Hz, 6,6'-H), 7.64 (2H, td, J = 7.0 and 2.0 Hz, 5,5'-H), 7.22 (2H, td, J = 7.1 and 1.2 Hz, 4,4'-H), 4.32 (4H, q, J = 7.0 Hz, CH₂CH₃), 3.69 (2H, s, COCH₂CO), 1.32 (6H, t, J = 7.0 Hz, CH₃). Mass spectrum, m/z: 398 (M⁺).

N,N'-Di-2-ethoxycarbonylanilide of Methylmalonic Acid (XII) (C₂₂H₂₄N₂O₆). This compound was obtained analogously. Yield 92%; mp 99-101°C (ethanol). PMR spectrum (ppm): 10.97 (2H, s, NH), 8.32 (2H, d, J = 8.0 Hz, 3,3'-H), 7.93 (2H, dd, J = 8.0 and 2.0 Hz, 6,6'-H), 7.62 (2H, td, J = 8.2 and 2.0 Hz, 5,5'-H), 7.21 (2H, td, J = 8.0 and 1.2 Hz, 4,4'-H), 4.32 (4H, q, J = 7.0 Hz, CH₂CH₃), 3.74 (1H, q, J = 7.0 Hz, COCHCO), 1.50 (3H, d, J = 7.0 Hz, CH₃), 1.30 ppm (6H, t, J = 7.0 Hz, CH₂CH₃).

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