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4-HYDROXY-2-QUINOLONES. 112*. REACTION OF 2-ETHOXYCARBONYLMETHYL-4H-3,1-BENZOXAZIN-4-ONE WITH ACTIVE METHYLENE COMPOUNDS

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The reaction of 2-ethoxycarbonylmethyl-4H-3,1-benzoxazin-4-one with malononitrile in dry pyridine leads to 1-hydroxy-3,6-dioxo-4,6-dihydro-3H-pyrimido[1,2-a]quinoline-5-carbonitrile. Acetoacetic and cyanoacetic esters under analogous conditions form anilides of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid while diethyl malonate gives N,N′-di-2-carboxyanilides of malonic acid.

Keywords: 4H-3,1-benzoxazin-4-one, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides, active methylene compounds.

Under the action of active methylene compounds (acetoacetic, cyanoacetic, or malonic esters) in dry pyridine 2-substituted 4H-3,1-benzoxazin-4-ones (acylanthranils) usually recyclize into 2-R-4-oxo-3,4-dihydroquinoline-3-carboxylates [2]. Occasionally the reaction stops at the acyclic esters of 3-(2-acylaminophenyl)-3-oxopropionic acid [3].

Proceeding from this, it seemed of interest to study the behavior of 2-ethoxycarbonylmethyl-4H-3,1-benzoxazin-4-one (**1**) under the described reaction conditions. Interest in such a family of investigations is caused, primarily, by the fact that the given acylanthranil itself contains an active methylene group, affording the possibility of the occurrence of more profound, occasionally unexpected, heterocyclizations [4-7].

With the highly nucleophilic carbanion generated from malononitrile, benzoxazinone **1** reacts similarly with isatoic anhydride [8], i.e. the acylmalononitrile **2** formed initially is cyclized into the aminoquinolone **3**. However, to isolate it was unsuccessful since under the conditions of the synthesis, boiling pyridine, the amino group is subject to intramolcular acylation with the formation of 1-hydroxy-3,6-dioxo-4,6-dihydro-3H-pyrimido[1,2-*a*]quinoline-5-carbonitrile (**4**).

A completely different picture is observed on using acetoacetic, cyanoacetic, and malonic esters. In the first two cases the reaction products unexpectedly proved to be 2-ethoxycarbonyl- (**5**) and the 2-carboxy- (**6**) anilides of 1H-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid, and in the latter case the N,N'-di-2-carboxyanilide of malonic acid (**7**). The structures of the obtained compounds were confirmed by ^{1}H NMR and mass spectra, and also by a contrary synthesis, by amidation of 1H-3-ethoxycarbonyl-4-hydroxy-2-oxoquinoline (**8**) with ethyl anthranilate and anthranilic acid respectively or thermolysis of ethyl ester of 2-carboxymalonanilic acid (**9**).

* For Part 111 see [1].

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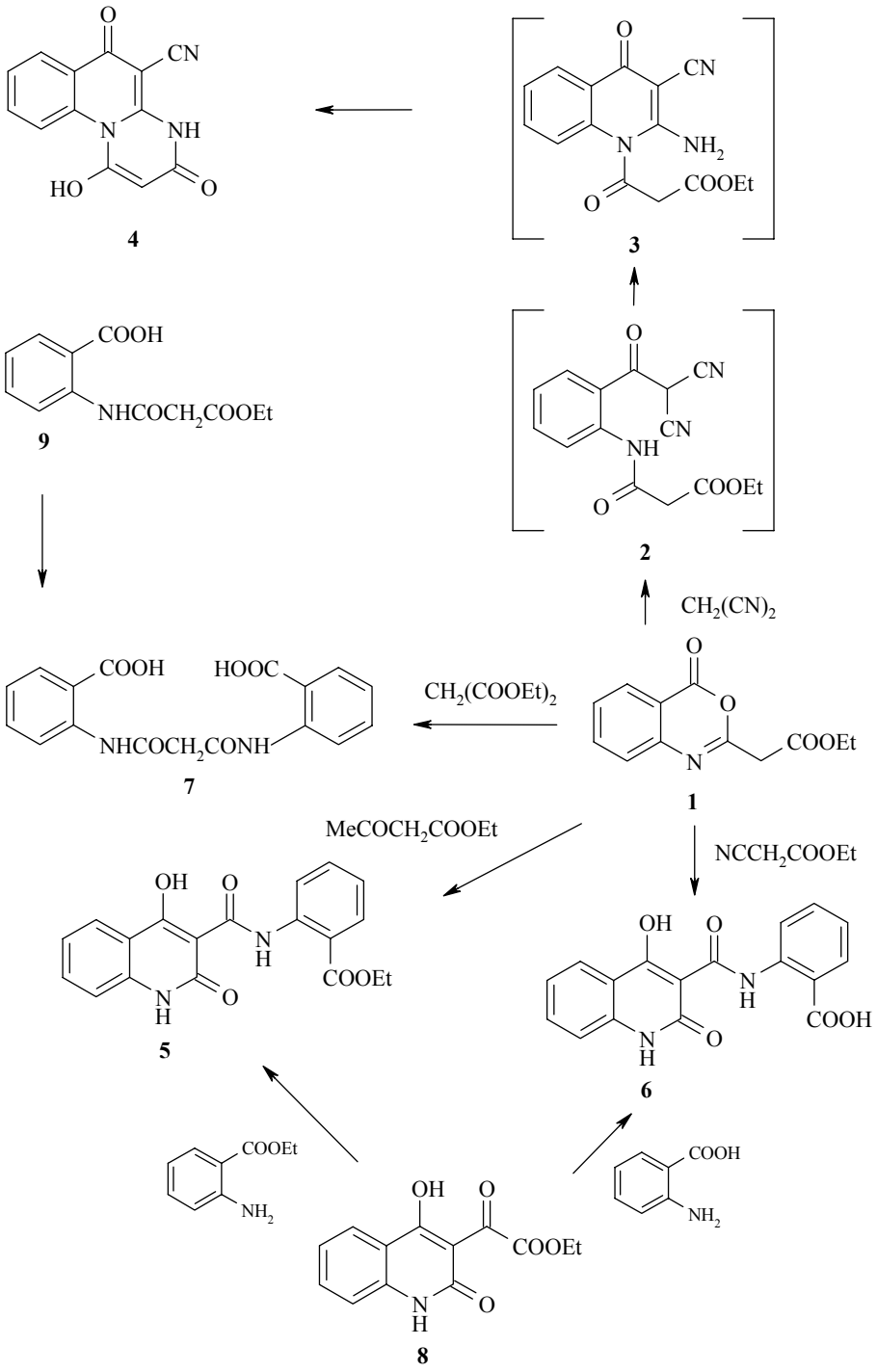

It is difficult to give an unequivocal explanation of the mechanism for these chemical processes. Nonetheless the fact of the participation of two molcules of benzoxazinone **1** in the formation of anilides **5-7** is indisputable. If it is assumed that benzoxazinone **1** reacts with the active methylene substrate, then the variant with the formation initially of a compound analogous to the structure of acylmalonitrile **2** is completely logical at first sight. Later the final anilides **5** or **6** are given. In principle such a route should lead to a single type of final product, but this contradicts the experimental data and is not in agreement with the formation of dianilide **7** on reaction with malonic ester.

Consequently the intermolcular interaction of two molcules not of benzoxazinone **1** itself but of its acyclic derivatives seems more probable. Allowing for the fact that acylation of dicarbonyl compounds in pyridine leads to the formation of products of O-acylation [9], such an intermediate derivative may, for example, be an ester of 2-ethoxymalonylaminobenzoic acid with the enol of acetoacetic ester. Further progress of the reaction occurs by a mechanism like the transformation of ethyl esters of malonanilic acids into symmetrical dianilides of malonic acid [10], after which the usual closure of the quinolone ring follows. For malonic ester, as is known from [11], an extremely small content of the enolic form is a characteristic. Possibly itdoes not participate in the reaction in general, but the intramolcular N-acylpyridinium salt formed initially from benzoxazinone **1** and pyridine is subject to conversion into a symmetrical dianilide. Confirmation of such a conclusion is served by the fact that free diethyl malonate is always isolated on forming dianilides of malonic acid from the ethyl esters of malonanilic acid [10]. Nonetheless its presence in the reaction mixture in no way influenced the result of the reaction of benzoxazinone **1** with acetoacetic or cyanoacetic esters.

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury VX-200 instrument (200 MHz), solvent was DMSO-d_6, internal standard TMS. The mass spectra were recorded on Finnigan MAT Incos 50 quadrupole spectrometer in the full scanning mode over the range 33-700 *m/z*, with electron impact ionization at 70 eV anddirect insertion of samples, rate of heating ~5^{o}C/sec. The IR spectrum of carbonitrile **4** was recorded on a Specord M 80 spectrometer, substance concentration 1%. 2-Ethoxy-carbonylmethyl-4H-3,1-benzoxazin-4-one (**1**) was obtained by the known procedure of [12]. Commercial anhydrous pyridine (Fluka) was used in the experiments.

1-Hydroxy-3,6-dioxo-4,6-dihydro-3H-pyrimido[1,2-*a*]quinoline-5-carbonitrile (4). Malononitrile (1.98 g: 0.03 mol) was added to a solution of compound **1** (2.33 g: 0.01 mol) in anhydrous pyridine (20 ml) and the mixture was boiled for 10 h. The reaction mixture was cooled, diluted with cold water, and acidified with HCl to pH 3. The solid which separated was filtered off, washed with water, then with alcohol, anddried. Yield was 1.92 g (76%). Mp 283-285°C (from DMF). Mass spectrum, *m/z*, (I_{rel}, %): 253 (100) $[M]^+$, 236 (20) $[M-OH]^+$, 226 (3) $[M-HCN]^+$, 170 (19), 127 (12). IR spectrum (nujol), ν, cm^{-1}: 2220 (C≡N), 1688 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.77 (1H, s, OH); 11.11 (1H, s, NH); 7.95 (1H, dd, *J* = 8.0 and *J* = 1.8, H-7); 7.59 (1H, td, *J* = 7.8 and *J* = 1.8, H-9); 7.36 (1H, d, *J* = 7.2, H-10); 7.24 (1H, td, *J* = 7.9 and *J* = 1.7, H-8); 7.08 (1H, s, H-2). Found, %: C 61.78; H 2.87; N 16.44. $C_{13}H_7N_3O_3$. Calculated, %: C 61.66; H 2.79; N 16.59.

2-Ethoxycarbonylanilide of 1H-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (5). A. Compound **5** was obtained from benzoxazinone **1** and acetoacetic ester by the method of the previous experiment. Yield 65%. Mp 242-244°C (from dioxane). Mass spectrum, *m/z* (I_{rel}, %): 352 (63) $[M]^+$, 307 (12) $[M-OEt]^+$, 279 (10) $[M-OEt-CO]^+$, 188 (20), 165 (100), 119 (81), 92 (34). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.40 (1H, s, OH); 13.00 (1H, s, NH); 11.97 (1H, s, NH); 7.23-8.25 (8H, m, H_{arom}); 4.34 (2H, q, *J* = 7.0, OCH_2); 1.32 (3H, t, *J* = 7.0, CH_3).

B. A mixture of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid ethyl ester (**8**) (2.33 g: 0.01 mol), ethyl anthranilate (1.48 ml: 0.01 mol), anddMF (1 ml) was maintained at 170°C for 5 min. The mixture was cooled, diluted with alcohol (30 ml), and mixed thoroughly. The solid anilide **5** was filtered off, washed with alcohol, anddried. Yield was 83%.

A mixing test with a sample of anilide **5** obtained by method A, and also by boiling the ethyl ester of 2-carbethoxymalonanilic acid in diphenyl oxide [13], gave no depression of melting point. The ^{1}H NMR spectra of these compounds were identical.

2-Carboxyanilide of 1H-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (6). A. Compound **6** was obtained from benzoxazinone **1** and cyanoacetic ester by the method of synthesis of carbonitrile **4**. Yield was 61%. Mp 234-236°C (from DMF, decomp.). Mass spectrum, *m/z* (I_{rel}, %): 324 (29) $[M]^+$, 188 (27),

137 (100), 119 (89), 92 (26). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.54 (1H, s, OH); 13.14 (1H, s, NH); 11.99 (1H, s, NH); 7.19-8.30 (8H, m, H_{arom}). Found, %: C 62.82; H 3.85; N 8.55. $C_{17}H_{12}N_2O_5$. Calculated, %: C 62.96; H 3.73; N 8.64.

B. A mixture of compound **8** (2.33 g, 0.01 mol), anthranilic acid (1.37 g: 0.01 mol), and DMF (2 ml) was maintained at 170°C for 5 min. The mixture was cooled, diluted with alcohol (30 ml), and thoroughly mixed. The solid anilide **6** was filtered off, washed with alcohol, anddried. Yield was 86%.

A mixing test with a sample of anilide **6** obtained by method A gave no depression of melting point. The ^{1}H NMR spectra of these compounds were identical.

N,N'-Di-2-carboxyanilide of Malonic Acid (7). Compound **7** was obtained from benzoxazinone **1** and malonic ester by the method of synthesis of carbonitrile **4**. Yield was 73%. Mp 242-244°C (from dioxane). Mass spectrum, *m/z* (I_{rel}, %): 342 (4) $[M]^+$, 324 (6) $[M-H_2O]^+$, 161 (53), 137 (69), 119 (100), 92 (32). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 13.68 (2H, br s, 2COOH); 11.33 (2H, s, 2NH); 8.45 (2H, d, *J* = 8.0, H-3, 3'); 7.98 (2H, dd, *J* = 8.0 and *J* = 1.8, H-6, 6'); 7.62 (2H, td, J = 8.0 and J = 1.8, H-5, 5'); 7.18 (2H, td, *J* = 8.0 and *J* = 1.2, H-4, 4'); 3.68 (3H, s, CH_3).

A mixing test with a sample of dianilide **7** obtained by the thermolysis of the ethyl ester of 2-carboxymalonanilic acid (**9**) by the method of [10] gave no depression of melting point. The ^{1}H NMR spectra of these compounds were identical.

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