Chemistry of Heterocyclic Compounds, Vol. 42, No. 7, 2006

4-HYDROXY-2-QUINOLONES. 97*. SIMPLE SYNTHESIS OF THE ESTERS OF 4-HALO-SUBSTITUTED 2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACIDS

I. V. Ukrainets[1], L. V. Sidorenko[1], O. V. Gorokhova[1], S. V. Slobodzyan[2]

Short term treatment of 3-ethoxycarbonyl-4-morpholino-2-oxo-1,2-dihydroquinoline with aqueous solutions of hydrohalogen acids leads to the formation of the ethyl esters of 4-halo-substituted 2-oxo-1,2-dihydroquinoline-3-carboxylic acids. Hydrolysis in HF is possible on extended boiling only to the 4-hydroxy derivative.

Keywords: 4-amino-2-oxo-1,2-dihydroquinolines, enamines, ethyl esters of 4-halo-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, hydrolysis, decarboxylation.

The ability of enamines to form carbonyl compounds under acid-catalyzed hydrolysis conditions has been known for a long time and is used widely in organic chemistry as a method of indirect C-alkylation or acylation of aldehydes and ketones inclined to selfcondense in the presence of strong bases [2].

We previously studied the acid hydrolysis of 4-benzylamino-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolines. In this was noted the ease of N-debenzylation and the relative stability of the ester grouping. As a result the investigation proved to be a convenient method of obtaining ethyl esters of 1-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids with a primary amino group in position 4 of the quinoline nucleus [3].

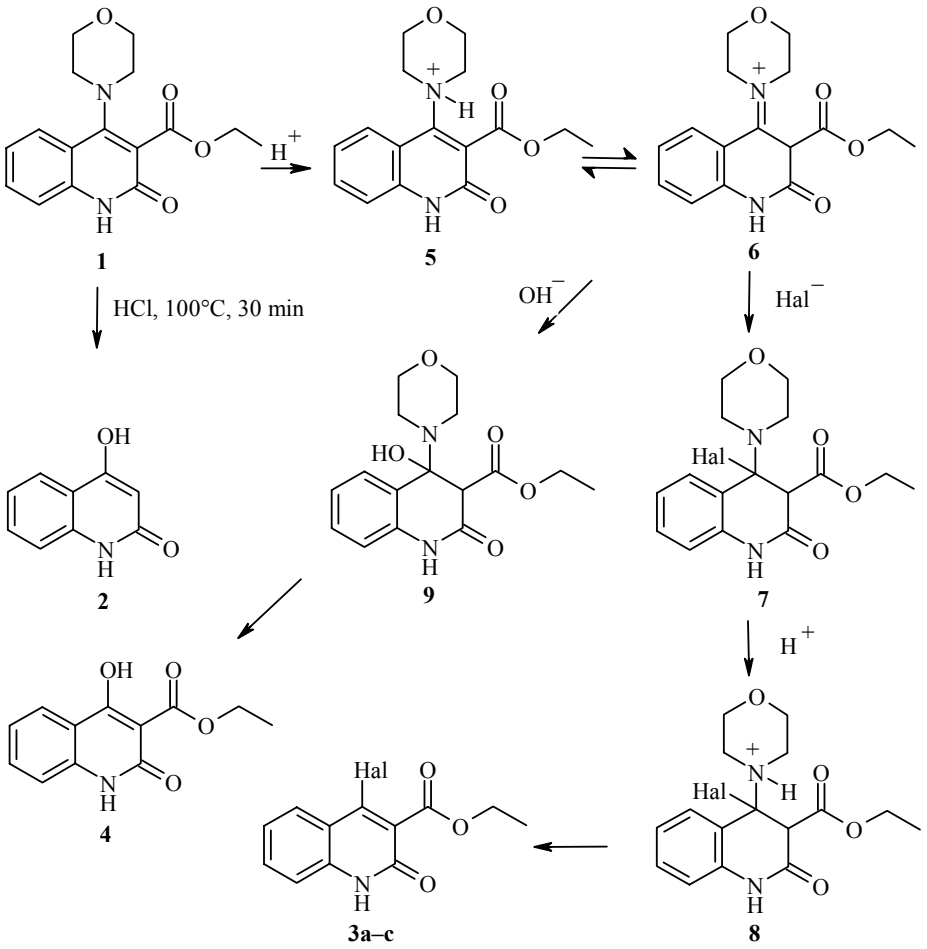
On going over to tertiary enamines, which are similar in structure, different hydrolysis products must be expected, and typical for this type of reaction are the initial carbonyl compounds and amines. In reality short term (30 min) boiling of the ethyl ester of 4-morpholino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**) in concentrated hydrochloric acid causes breakdown of this enamine to morpholine and 3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinoline, which under the experimental conditions is also hydrolyzed, decarboxylated, and converted finally into 4-hydroxy-1H-quinolin-2-one (**2**). Reducing the time of treatment to 1-2 min we unexpectedly discovered that, with retention of the ester grouping, the residue of morpholine has time to be substituted not by a hydroxyl group, as the mechanism of the hydrolysis reaction of enamines requires [4], but by a chlorine atom. This reaction occurs analogously with hydrobromic and hydriodic acids and leads to the ethyl ester of the corresponding 4-halo-substituted 2-oxo-1,2-dihydroquinoline-3-carboxylic acids **3a-c** in

* For Part 96 see [1].

[1] National Pharmaceutical University, Kharkiv 61002, Ukraine; e-mail: uiv@kharkov.ua. [2] Ohio Northern University, Ada, Ohio 45810, USA; e-mail: s-slobodzian@onu.edu. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1022-1025, July, 2006. Original article submitted November 8, 2004.

 0009-3122/06/4207-0882

practically quantitative yield. However, to carry out a similar replacement by fluorine was unsuccessful. Morpholinoquinoline **1** in boiling hydrofluoric acid for 1 h 30 min is hydrolyzed by the scheme typical for enamines to the 4-hydroxy derivative **4** while the ester group is not affected.



3 a Hal = Cl, **b** Hal = Br, **c** Hal = I

By correlating the results of the investigations carried out it is possible to draw the conclusion that in all the examples the conversion of enamine **1** occurs in one way under the influence of hydrogen halide acids. The ammonium salt **5** is formed initially, the immonium tautomer of which **6** is also subject at the following stage to nucleophilic S_N2_{Ar} attack at the $C_{(4)}$ atom of the quinolone nucleus. In the case of HCl, HBr, or HI the attacking particles proved to be chloride, bromide, or iodide ions. After the formation of the $C_{(4)}$-Hal bond the strongly acidic medium assists a second N-protonation of morpholine thereby converting it into a good leaving group. Fluoride ion in hydroxyl-containing solvents, as a rule [5], is far less nucleophilic than the other halogens. Water builds up a significant competition to S_N2_{Ar} substitution and, as follows from the experimental results, wins leading to the hydroxyester **4**. Hydrogen fluoride is also superseded in acidic properties significantly by the other hydrogen halides which evidently take only the morpholine nitrogen atom for protonation in the 4-hydroxy intermediate **9**, but not the ester carbonyl. This may explain the observed stability to hydrolysis in boiling hydrofluoric acid of the ethoxycarbonyl grouping, which must also be protonated according to the mechanism of this reaction in [5].

The ^{1}H NMR spectra of the 4-halo-substituted esters **3a-c** proved to be very similar, consequently we used chromato-mass spectrometry as well to establish the structures of these compounds. Fragmentation of the molecular ions of esters **3a-c** under the action of electron impact occurs by one pathway and begins with breakdown of the ester grouping. The formed fragment ions $[M\text{-}OEt]^+$ preferentially lose CO, after which removal of halogen follows. Less characteristic, but observed in all cases, was the fission of hydrogen halide from the $[M\text{-}OEt]^+$ fragment. Only in the case of the 4-iodo derivative **3c** was a low intensity peak recorded corresponding to loss of HI directly from the molecular ion. This route of fragmentation was not a characteristic of the chloro and bromo substituted esters **3a,b**.

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were obtained on a Varian Mercury VX 200 (200 MHz) instrument, solvent was DMSO-d_6, internal standard was TMS. Chromato-mass spectra were recorded on a Finnigan MAT Incos 50 quadrupole spectrometer in full scanning mode over the range 33-700 *m/z*, ionization was by electron impact at 70 eV on direct insertion of samples, heating rate was ~5°C/sec. The ethyl ester of 4-morpholino-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**) was obtained by the known procedure of [6]. Commercial hydrohalogen acids were used in the experiments: HF 70%, HCl 37%, HBr 48%, and HI 55%.

4-Hydroxy-1H-quinolin-2-one (2). A solution of compound **1** (3.02 g, 0.01 mol) in conc. HCl (30 ml) was boiled for 30 min then poured into cold water. The separated crystals were filtered off, washed with water, and dried. Yield 1.38 g (86%); mp 338-340°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.90 (1H, s, OH); 11.18 (1H, s, NH); 7.83 (1H, dd, *J* = 8.0 and *J* = 1.9, H-5); 7.51 (1H, td, *J* = 7.5 and *J* = 1.8, H-7); 7.30 (1H, d, *J* = 8.2, H-8); 7.16 (1H, t, *J* = 7.8, H-6); 5.77 (1H, s, H-3).

A mixed test sample with a specimen of 4-hydroxy-1H-quinolin-2-one (**2**) obtained by the deacetylation of 3-acetyl-4-hydroxy-2-oxo-1,2-dihydroquinoline [7] gave no depression of melting point, the ^{1}H NMR spectra of these compounds were identical.

Ethyl Ester of 4-Chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (3a). A solution of compound **1** (3.02 g, 0.01 mol) in conc. HCl (20 ml) was heated to boiling, maintained for 1-2 min, and poured into cold water. The separated solid ester **3a** was filtered off, washed with water, and dried. Yield 2.43 g (97%); mp 194-196°C (ethanol). Mass spectrum, *m/z* (I_{rel}, %): 251 (13) $[M]^+$, 206 (23) $[M\text{-}OEt]^+$, 179 (100) $[M\text{-}OEt\text{-}CO]^+$, 170 (3) $[M\text{-}OEt\text{-}HCl]^+$, 144 (2) $[M\text{-}OEt\text{-}CO\text{-}Cl]^+$, values of *m/z* are given only for the ^{35}Cl isotope. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.45 (1H, s, NH); 7.88 (1H, dd, *J* = 8.0 and *J* = 2.0, H-5); 7.70 (1H, td, *J* = 7.5 and *J* = 1.3, H-7); 7.37 (2H, m, H-6,8); 4,35 (2H, q, *J* = 7.0, OCH_2); 1.30 (3H, t, *J* = 7.0, CH_3).

A mixed test sample with a specimen of ester **3a** obtained by the reaction of the ethyl ester of 2,4-dichloroquinoline-3-carboxylic acid with sodium acetate [8] gave no depression of melting point, the ^{1}H NMR and chromato-mass spectra of these compounds were identical.

Compounds **3b,c** were obtained by an analogous procedure.

Ethyl Ester of 4-Bromo-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (3b). Yield 98%; mp 210-212°C (ethanol). Mass spectrum, *m/z* (I_{rel}, %): 295 (23) $[M]^+$, 250 (47) $[M\text{-}OEt]^+$, 223 (100) $[M\text{-}OEt\text{-}CO]^+$, 170 (13) $[M\text{-}OEt\text{-}HBr]^+$, 144 (30) $[M\text{-}OEt\text{-}CO\text{-}Br]^+$, values of *m/z* are given only for the ^{79}Br isotope. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.42 (1H, s, NH); 7.89 (1H, dd, *J* = 8.0 and *J* = 2.0, H-5); 7.68 (1H, td, *J* = 7.5 and *J* = 1.7, H-7); 7.39 (2H, m, H-6,8); 4.34 (2H, q, *J* = 7.0, OCH_2); 1.32 (3H, t, *J* = 7.0, CH_3). Found, C 48.80; H 3.49; N 4.62. $C_{12}H_{10}BrNO_3$. Calculated, %: C 48.67; H 3.40; N 4.73.

Ethyl Ester of 4-Iodo-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (3c). Yield 95%; mp 183-185°C (ethanol). Mass spectrum, *m/z* (I_{rel}, %): 343 (96) $[M]^+$, 298 (88) $[M\text{-}OEt]^+$, 271 (81) $[M\text{-}OEt\text{-}CO]^+$, 215 (5) $[M\text{-}HI]^+$, 170 (30) $[M\text{-}OEt\text{-}HI]^+$, 144 (100) $[M\text{-}OEt\text{-}CO\text{-}I]^+$. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.33 (1H, s,

NH); 7.77 (1H, dd, J = 8.3 and J = 1.9, H-5); 7.62 (1H, td, J = 7.5 and J = 1.2, H-7); 7.33 (2H, m, H-6,8); 4.34 (2H, q, J = 7.0, OCH_2); 1.33 (3H, t, J = 7.0, CH_3). Found, %: C 42.14; H 2.99; N 4.12. $C_{12}H_{10}INO_3$. Calculated, %: C 42.01; H 2.94; N 4.08.

Ethyl Ester of 4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (4). A solution of compound **1** (3.02 g, 0.01 mol) in 70% HF (20 ml) was boiled in a platinum beaker for 1 h 30 min, adding fresh portions of HF according to the extent of evaporation. The reaction mixture was cooled, and diluted with cold water. The solid ester **4** was filtered off, washed with water, and dried. Yield 2.14 g (92%); mp 203-204°C (ethanol). Mass spectrum, m/z (I_{rel}, %): 233 (23) $[M]^+$, 187 (100) $[M\text{-}EtOH]^+$, 161 (35), 119 (82). ^{1}H NMR spectrum, δ, ppm (J, Hz); 13.44 (1H, s, OH); 11.45 (1H, s, NH); 7.92 (1H, dd, J = 8.0 and J = 1.7, H-5); 7.62 (1H, td, J = 8.0 and J = 1.8, H-7); 7.29 (1H, d, J = 8.1, H-8); 7.20 (1H, t, J = 7.9, H-6); 4.34 (2H, q, J = 7.0, OCH_2); 1.32 (3H, t, J = 7.0, CH_3).

A mixed test sample with an authentic specimen of ester **4** [9] gave no depression of melting point, the ^{1}H NMR and chromato-mass spectra of these compounds were identical.

REFERENCES

1. I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, and S. V. Shishkina, *Khim. Geterotsikl. Soedin.*, 887 (2006). [*Chem. Heterocycl. Comp.*, **42**, 776 (2006)].
2. R. Mackie and D. Smith, *Handbook of Organic Synthesis* [Russian translation], Mir, Moscow (1985).
3. I. V. Ukrainets, L. V. Sidorenko, and O. V. Gorokhova, *Khim. Geterotsikl. Soedin.*, 1355 (2005). [*Chem. Heterocycl. Comp.*, **41**, 1155 (2005)].
4. E. J. Stamhuis, in A. G. Cook (editor) *Enamines: Synthesis, Structure and Reactions*, Marcel Dekker, New York (1969), p. 101.
5. P. Sykes, *A Guidebook to Mechanism in Organic Chemistry*, 6th Edit., Longman, Harlow (1986), 416 pp.
6. P. A. Bezugly, I. V. Ukrainets, N. Skaif, O. V. Gorokhova, and L. V. Sidorenko, *Farmakom*, No. 3, 23 (2003).
7. C. M. Sarangi and Y. R. Rao, *Res. and Ind.*, **37**, 113 (1992).
8. I. V. Ukrainets, S. G. Taran, O. V. Gorokhova, N. A. Marusenko, S. N. Kovalenko, A. V. Turov, N. I. Filimonova, and S. M. Ivkov, *Khim. Geterotsikl. Soedin.*, 195 (1995). [*Chem. Heterocycl. Comp.*, **31**, 167 (1995)].
9. I. V. Ukrainets, P. A. Bezugly, V. I. Treskach, A. V. Turov, and S. V. Slobodzyan, *Khim. Geterotsikl. Soedin.*, 636 (1992). [*Chem. Heterocycl. Comp.*, **28**, 534 (1992)].