ISSN 1070-4280, Russian Journal of Organic Chemistry, 2014, Vol. 50, No. 1, pp. 63–65. © Pleiades Publishing, Ltd., 2014.
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Synthesis and Structure of 3-(3-Acetoxyalkylcarbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanoic Acids

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Received July 17, 2013

Abstract—Treatment of 1-(2-cyanoethyl)-4-hydroxy-*N*-(hydroxyalkyl)-2-oxo-1,2-dihydroquinoline-3-carboxamides with a solution of hydrogen chloride in aqueous acetic acid ensures selective transformation of the cyano group into amide or carboxy with simultaneous acetylation of the hydroxyalkyl fragments.

DOI: 10.1134/S1070428014010126

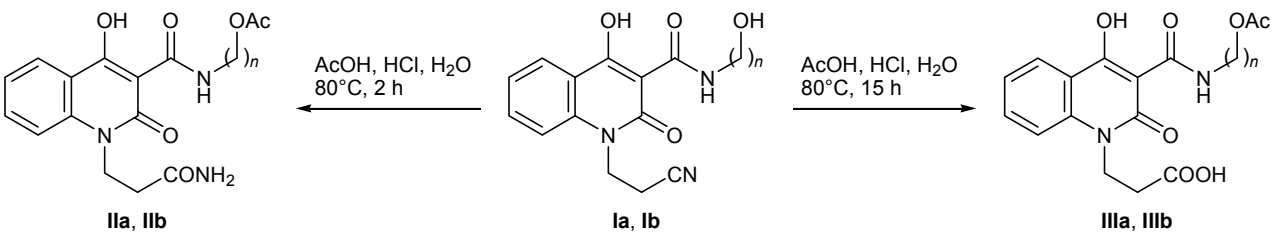
We previously proposed a procedure for selective hydration of 3-(3-R-carbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanenitriles into the corresponding propanamides by treatment with a solution of HCl in acetic acid with a low concentration of water, which may be useful in the search for new non-narcotic analgesics [1]. If necessary, prolonged reaction time makes it possible to accomplish profound transformations, in particular hydrolysis of the initially formed propanamides to 3-(quinolin-1-yl)propanoic acids which may be interesting as models for structural biological studies [1, 2] and substrates for various subsequent modifications.

3-(3-R-Carbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanenitriles behaved similarly in the examined reaction, and all steps of their successive transformations into propanamides and then propanoic acids gave reproducibly good results. However, some deviations from the general pattern were possible if the reaction involved other molecular fragments in addition to the cyano group. For example, 3-benzylcarbamoyl derivatives in the system HCl–AcOH–H_2O underwent *N*-debenzylation whose extent depended on the substituent in the benzyl fragment and ranged from negligible to almost complete [1].

1-(2-Cyanoethyl)-4-hydroxy-*N*-(hydroxyalkyl)-2-oxo-1,2-dihydroquinoline-3-carboxamides **Ia** and **Ib** also showed some specificity in the reaction with HCl–AcOH–H_2O. The ^{1}H NMR spectra of the isolated products clearly showed stepwise transformation of the cyano group in these compounds first into amide and then into carboxy. On the other hand, in all cases the ^{1}H NMR spectra lacked signal assignable to alcoholic hydroxy proton; instead, an additional three-proton singlet appeared in a strong field. These findings led us to presume that the hydration (hydrolysis) of cyano group in hydroxyalkylamides **Ia** and **Ib** in the system HCl–AcOH–H_2O is accompanied by *O*-acetylation to produce acetoxyalkylcarbamoyl derivatives **IIa** and **IIb** (propanamides) or **IIIa** and **IIIb** (propanoic acids; Scheme 1).

In fact, our assumption was unambiguously confirmed by X-ray analysis of acid **IIIb** (see figure). It is interesting that the described reactions combine, as it may seem, two mutually exclusive processes under the same conditions, hydrolysis of the amide (cyano) group

Scheme 1.



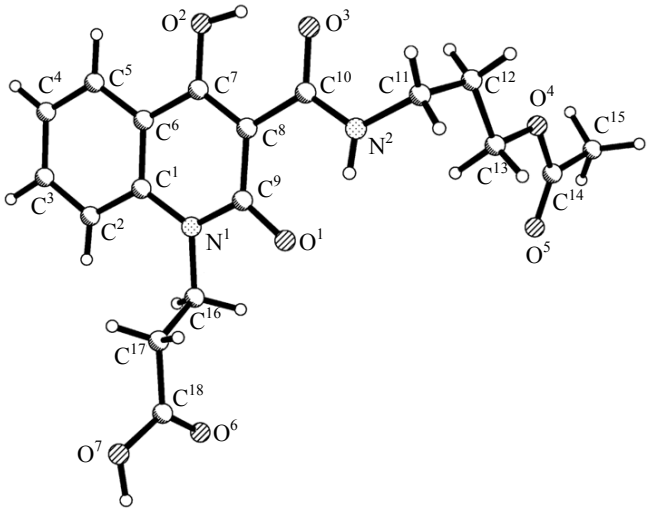
IIa, **IIb** **Ia**, **Ib** **IIIa**, **IIIb**

n = 2 (**a**), 3 (**b**).

and esterification. Moreover, it is surprising that the acetoxyalkyl fragment in **II** and **III** remains intact in the system HCl–AcOH–H_2O which was originally proposed [3, 4] just for hydrolysis of esters.

Let us note some structural features of molecule **IIIb** (for atom numbering, see figure). The dihydropyridine ring slightly deviates from planarity [endocyclic torsion angles $C^9N^1C^1C^6$ 5.7(2)°, $C^1N^1C^9C^8$ –6.7(2)°], which may be due to fairly strong steric repulsion between the carboxyethyl group, neighboring atoms of the aromatic ring, and carbonyl group in the vicinal position [shortened intramolecular contacts $H^2\cdots C^{16}$ 2.58 Å (the sum of the van der Waals radii 2.87 Å [5]), $H^2\cdots H^{16a}$ 2.11 (2.34), $H^{16a}\cdots C^2$ 2.58 (2.87), $H^{16b}\cdots O^1$ 2.35 Å (2.46 Å)]. The same steric repulsions are responsible for extension of the N^1–C^{16} [1.478(2)], N^1–C^9 [1.376(2)], and N^1–C^1 bonds [1.394(1) Å] relative to the corresponding standard bonds (1.469, 1.353, and 1.371 Å, respectively [6]).

The terminal carboxymethylene fragment in the substituent on N^1 is oriented orthogonally to the pyridine ring plane [torsion angle $C^9N^1C^{16}C^{17}$ 89.7(1)°], and the carboxy group appears in the antiperiplanar orientation with respect to the N^1–C^{16} bond and is slightly turned about the C^{16}–C^{17} bond [torsion angles $N^1C^{16}C^{17}C^{18}$ –179.6(1)° and $C^{16}C^{17}C^{18}O^6$ 14.6(2)°]. The amide fragment in the substituent on C^8 is almost coplanar to the dihydropyridine ring plane due to formation of strong intramolecular hydrogen bonds N^2–$H^{2N}\cdots O^1$ ($H\cdots O$ 1.99 Å, ∠NHO 137°) and O^2–$H^{2O}\cdots O^3$ ($H\cdots O$ 1.54 Å, ∠OHO 155°). These H-bonds also induce elongation of the O^1–C^9 [1.251(1) Å] and O^3–C^{10} bonds [1.266(2) Å] relative to the standard C=O bond (1.210 Å [5]), whereas the O^2–C^7 [1.318(1) Å], N^2–C^{10} [1.322(2) Å], and C^8–C^9 bonds [1.436(2) Å] are shortened (standard values 1.362, 1.334, and 1.455 Å, respectively). The C^7–C^8 bond is extended to 1.384(2) Å (against 1.326 Å), which is typical of 4-hydroxyquinolin-2-ones.



Structure of the molecule of 3-[3-(3-acetoxypropylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl]propanoic acid (**IIIb**) according to the X-ray diffraction data.

The substituent on the amide nitrogen atom occupies antiperiplanar position with respect to the C^8–C^{10} bond [torsion angle $C^8C^{10}N^2C^{11}$ 178.7(1)°] and adopts *–sc/–sc* conformation [torsion angles $C^{10}N^2C^{11}C^{12}$ –82.1(2)° and $N^2C^{11}C^{12}C^{13}$ –64.2(2)°]. The acetoxy group is antiperiplanar with respect to the C^{11}–C^{12} bond and is almost coplanar to the C^{12}–C^{13} bond [torsion angles $C^{11}C^{12}C^{13}O^4$ 177.6(1)° and $C^{14}O^4C^{13}C^{12}$ –171.5(1)°]. Attractive $H^5\cdots O^2$ interaction (2.40 Å) should also be noted (the sum of the van der Waals radii 2.46 Å).

Molecules **IIIb** in crystal are linked through fairly strong intermolecular H-bonds O^7–$H^{7O}\cdots O^{1'}$ (0.5 – *x*, –0.5 + *y*, 1.5 – *z*; $H\cdots O$ 1.66 Å, ∠OHO 177°) to form infinite chains along the [010] crystallographic axis. Correspondingly, the O^7–C^{18} bond [1.316(2) Å] is appreciably shorter than the reference value (1.362 Å).

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury-VX-200 spectrometer (200 MHz) from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The elemental compositions were determined on a EuroVector EA-3000 micro analyzer. The melting points were measured in capillaries on a Stuart SMP10 digital melting point apparatus and were not corrected. The synthesis and properties of initial 1-(2-cyanoethyl)-4-hydroxy-*N*-(hydroxyalkyl)-2-oxo-1,2-dihydroquinoline-3-carboxamides **Ia** and **Ib** were reported in [7].

2-[4-Hydroxy-1-(2-carbamoylethyl)-2-oxo-1,2-dihydroquinolin-3-ylcarboxamido]ethyl acetate (IIa). A mixture of 3.01 g (0.01 mol) of nitrile **Ia** and 20 mL of a ~2.8 M solution of HCl in acetic acid with low water content (prepared by mixing required amounts of acetic anhydride and concentrated aqueous HCl according to the procedure described in [3]) was heated for 2 h at 80°C. The mixture was cooled and diluted with 50 mL of cold water, and the precipitate was filtered off, washed with water, and dried. Yield 2.82 g (78%), colorless crystals, mp 179–181°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.02 s (3H, CH_3), 2.43 t (2H, $N^1CH_2CH_2$, *J* = 7.4 Hz), 3.62 q (2H, $NHCH_2CH_2O$, *J* = 5.6 Hz), 4.17 t (2H, $NHCH_2CH_2O$,

J = 5.4 Hz), 4.42 t (2H, $N^1CH_2CH_2$, J = 7.5 Hz), 6.95 s (1H, CH_2CONH_2), 7.36 t (1H, 6-H, J = 7.5 Hz), 7.45 s (1H, CH_2CONH_2), 7.67 d (1H, 8-H, J = 8.8 Hz), 7.80 t (1H, 7-H, J = 7.7 Hz), 8.10 d (1H, 5-H, J = 7.9 Hz), 10.42 t (1H, 3-CONH, J = 5.9 Hz), 17.20 s (1H, OH). Found, %: C 56.60; H 5.41; N 11.54. $C_{17}H_{19}N_3O_6$. Calculated, %: C 56.51; H 5.30; N 11.63.

Compounds **IIb**, **IIIa**, and **IIIb** were synthesized in a similar way, but in the synthesis of **IIIa** and **IIIb** the reaction mixture was heated for 15 h.

3-[1-(2-Carbamoylethyl)-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-ylcarboxamido]propyl acetate (IIb). Yield 2.74 g (73%), colorless crystals, mp 182–184°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.88 q (2H, $NHCH_2CH_2CH_2O$, J = 6.4 Hz), 2.02 s (3H, CH_3), 2.42 t (2H, $N^1CH_2CH_2$, J = 7.2 Hz), 3.45 q (2H, $NHCH_2CH_2CH_2O$, J = 6.2 Hz), 4.07 t (2H, $NHCH_2CH_2CH_2O$, J = 6.1 Hz), 4.41 t (2H, $N^1CH_2CH_2$, J = 7.2 Hz), 6.94 s (1H, CH_2CONH_2), 7.35 t (1H, 6-H, J = 7.5 Hz), 7.44 s (1H, CH_2CONH_2), 7.65 d (1H, 8-H, J = 8.7 Hz), 7.79 t (1H, 7-H, J = 7.6 Hz), 8.08 d (1H, 5-H, J = 8.0 Hz), 10.37 t (1H, 3-CONH, J = 5.7 Hz), 17.38 s (1H, OH). Found, %: C 57.72; H 5.55; N 11.07. $C_{18}H_{21}N_3O_6$. Calculated, %: C 57.59; H 5.64; N 11.19.

3-[3-(2-Acetoxyethylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl]propanoic acid (IIIa). Yield 3.04 g (84%), colorless crystals, mp 171–173°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 2.01 s (3H, CH_3), 2.56 t (2H, $N^1CH_2CH_2$, J = 7.5 Hz), 3.61 q (2H, $NHCH_2CH_2O$, J = 5.5 Hz), 4.18 t (2H, $NHCH_2CH_2O$, J 5.5 Hz), 4.45 t (2H, $N^1CH_2CH_2$, J = 7.5 Hz), 7.35 t (1H, 6-H, J = 7.4 Hz), 7.65 d (1H, 8-H, J = 8.6 Hz), 7.79 t (1H, 7-H, J = 7.6 Hz), 8.08 d (1H, 5-H, J = 8.1 Hz), 10.37 t (1H, CONH, J = 6.1 Hz), 12.45 br.s (1H, COOH), 17.22 s (1H, 4-OH). Found, %: C 56.28; H 4.93; N 7.81. $C_{17}H_{18}N_2O_7$. Calculated, %: C 56.35; H 5.01; N 7.73.

3-[3-(3-Acetoxypropylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl]propanoic acid (IIIb). Yield 3.01 g (80%), colorless crystals, mp 164–166°C (from EtOH). ^{1}H NMR spectrum, δ, ppm: 1.87 q (2H, $NHCH_2CH_2CH_2O$, J = 6.3 Hz), 2.01 s (3H, CH_3), 2.57 t (2H, $N^1CH_2CH_2$, J = 7.5 Hz), 3.45 q (2H, $NHCH_2CH_2CH_2O$, J = 6.1 Hz), 4.08 t (2H, $NHCH_2CH_2CH_2O$, J = 6.1 Hz), 4.45 t (2H, $N^1CH_2CH_2$, J = 7.5 Hz), 7.37 t (1H, 6-H, J = 7.4 Hz), 7.66 d (1H, 8-H, J = 8.6 Hz), 7.80 t (1H, 7-H, J = 7.8 Hz), 8.10 d (1H, 5-H, J = 8.1 Hz), 10.34 t (1H, CONH, J = 5.9 Hz), 12.43 br.s (1H, COOH), 17.42 s (1H, 4-OH). Found, %: C 57.57; H 5.43; N 7.50. $C_{18}H_{20}N_2O_7$. Calculated, %: C 57.44; H 5.36; N 7.44.

X-Ray diffraction data for compound IIIb. Monoclinic crystals (from EtOH) with the following unit cell parameters (20°C): a = 7.4313(3), b = 11.7269(5), c = 20.2090(7) Å; β = 94.660(3)°; V = 1755.3(1) Å^3; M 376.36; Z = 4; space group $P2_1/n$; d_{calc} = 1.424 g/cm^3; μ(MoK_α) = 0.111 mm^{-1}; F(000) = 792. The unit cell parameters and intensities of 20111 reflections (5126 independent reflections, R_{int} = 0.025) were measured on an Xcalibur-3 diffractometer (MoK_α radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 60°). The structure was solved by the direct method using SHELXTL software package [8]. The positions of hydrogen atoms were determined by difference synthesis of electron density and were refined in isotropic approximation. The structure was refined against F^2 by the full-matrix least-squares method in anisotropic approximation for non-hydrogen atoms; wR_2 = 0.141 for 5057 reflections [R_1 = 0.047 for 3411 reflections with $F > 4\sigma(F)$]; goodness of fit S = 1.015. The complete set of crystallographic data for compound **IIIb** was deposited to the Cambridge Crystallographic Data Centre (entry no. CCDC 940243).

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