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Transformation of 3-(3-Arylalkylcarbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanenitriles into Amides and Acids

I. V. Ukrainets, O. V. Gorokhova, and K. V. Andreeva

National University of Pharmacy, ul. Pushkinskaya 53, Kharkiv, 61002 Ukraine
e-mail: uiv-2@mail.ru

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Abstract—A mixture of hydrochloric and acetic acids depleted in water was proposed to effect stepwise transformation of 3-(3-arylalkylcarbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanenitriles into the corresponding amides and then into the acids. The procedure turned out to be efficient with 3-[(2-phenylethyl)-carbamoyl] derivatives, whereas the reactions with benzylcarbamoyl analogs were accompanied by partial or complete debenzylation.

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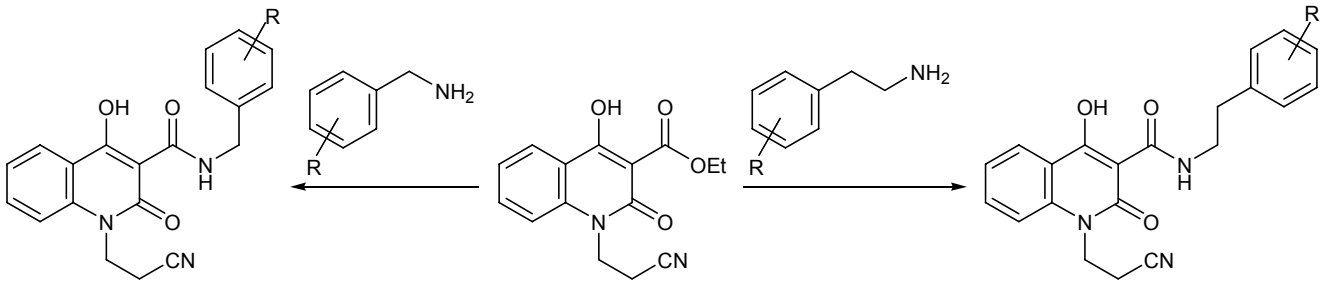
We previously showed that 3-(3-benzylcarbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanoic acids, as well as their synthetic precursors, the corresponding 3-(quinolin-1-yl)propanenitriles, attract interest as base structures for the design of new potential analgesics [1]. However, intermediate 3-(quinolin-1-yl)propanamides that are unavoidably formed in the course of the transformation of nitriles into acids have received almost no attention. Taking into account that metabolism of nitriles *in vivo* can take different pathways, including primary hydration to amides [2], interest in such intermediates exceedingly increases.

Initial 3-(3-arylalkylcarbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanenitriles **I** and **II** were synthesized in two steps, via condensation of 3-anilinopropanenitrile with triethyl methanetricarboxylate [3], followed by aminolysis of heterocyclic ester **III** thus obtained with phenylmethanamine and 2-phenylethanamine, respectively, in boiling ethanol (Scheme 1).

The hydrolysis of nitriles can by no means always be stopped at the stage of formation of the corresponding amide. In fact, this was the case when 3-(quinolin-1-yl)propanenitriles **I** and **II** were treated with aqueous alkali. Up to now, numerous procedures, both chemical [4] and biochemical [5], have been proposed for the transformation of nitriles to amides with fairly high selectivity.

We made an attempt to convert 3-(quinolin-1-yl)-propanenitriles **I** and **II** into amides **IV** and **V** using a solution of hydrogen chloride in acetic acid with low water content. High dissolving ability of this system makes it applicable to various nitriles. The procedure was initially proposed for the hydrolysis of alkyl 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates [6] and is now among the most appropriate methods

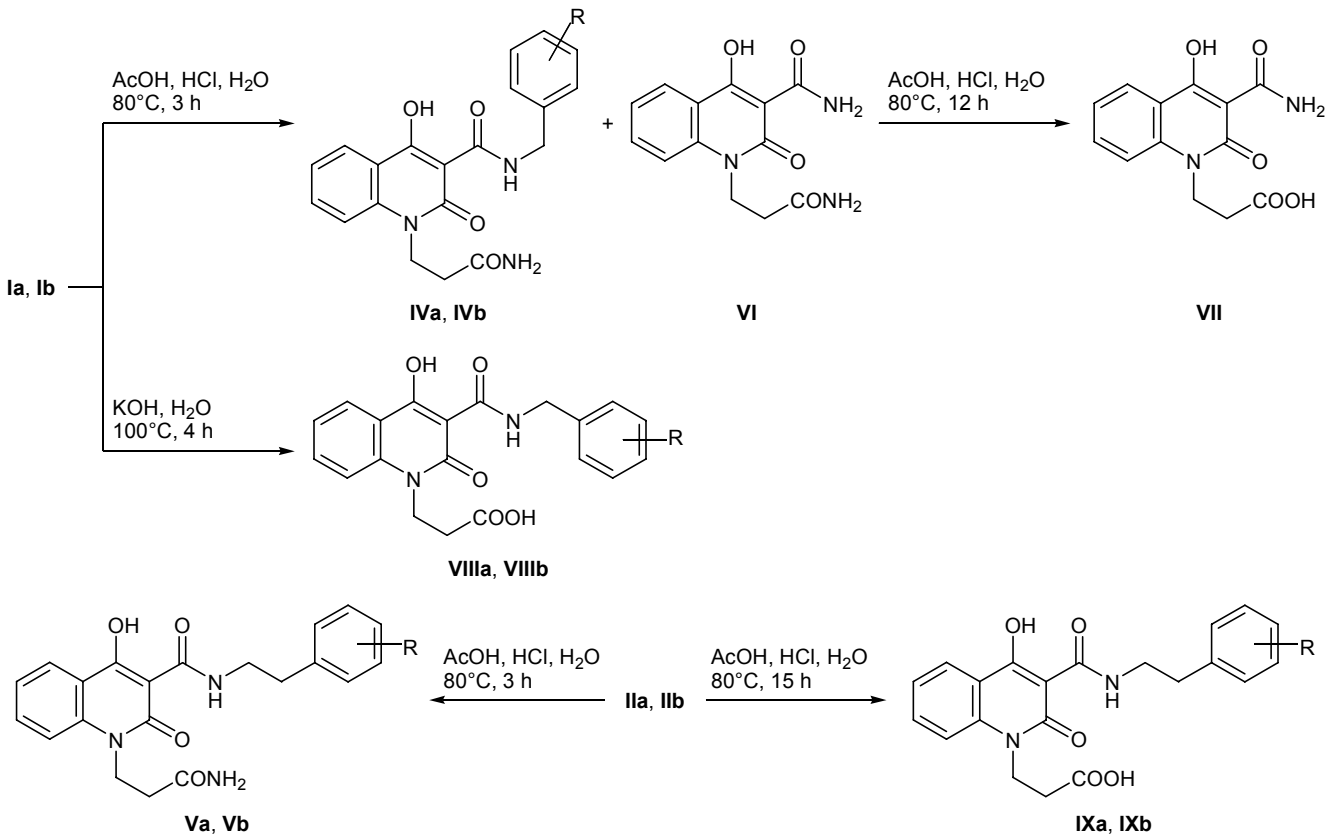
Scheme 1.



Ia, **Ib** **III** **IIa**, **IIb**

R = 4-MeO (**a**), 3,4-$(MeO)_2$ (**b**).

Scheme 2.



R = 4-MeO (**a**), 3,4-(MeO)$_2$ (**b**).

for the preparation of extremely unstable 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, in particular of 4-hydroxy-1-(2-carbamoylethyl)-2-oxo-1,2-dihydroquinoline-3-carboxylic acid possessing strong analgesic properties [7].

Our experiments showed that compounds **I** and **II** readily undergo hydrolysis to amides **IV** and **V**, respectively, on heating for 3 h at 80°C in the system HCl–AcOH–H_2O. However, the reaction smoothly occurred only with phenethylcarbamoyl derivatives **II**. Their benzylcarbamoyl analogs **Ia** and **Ib** turned out to be less stable, and their hydrolysis under similar conditions was accompanied by partial (by 12 and 26%, respectively, according to the ^{1}H NMR spectra of the crude products) debenzylation with formation of 1-(2-carbamoylethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide (**VI**) as an undesirable impurity (Scheme 2).

According to the data of chromatographic monitoring, the rate of elimination of the *N*-benzyl group is determined by substituents present in its benzene ring. In the reaction with 4-methoxybenzyl derivative **Ia**, diamide **VI** appeared in the reaction mixture in ~2 h after the reaction started, whereas in the reaction with 3,4-dimethoxybenzyl derivative **Ib**, diamide **VI** was detected even in 45 min. Chromatographic study also revealed one more important feature, namely target propanamides **IV** were detected almost immediately after dissolution of initial compounds **I** in HCl–AcOH–H_2O. This means that the rate of hydration of the cyano group in **I** is considerably higher than the rate of debenzylation. Taking advantage of the different rates of the main and side reactions we were able to optimize the conditions for the hydrolysis of nitriles **I** to amides **IV** so as to at least minimize the debenzylation process unless avoid it. We succeeded in doing so by shortening the reaction time with 4-methoxybenzyl derivative **Ia** to 2 h. By this time, only traces of **Ia** remained in the reaction mixture.

Selective hydrolysis of benzylcarbamoyl nitriles **I** to carboxylic acids under the same conditions seems to be apparently unfeasible, and increase of the reaction time to 15 h leads to hydrolysis of the aliphatic carbamoyl group with simultaneous complete debenzylation. As a result, 3-(3-carbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanoic acid (**VII**) was isolat-

ed in a good yield. Therefore, benzylcarbamoyl derivatives **I** were hydrolyzed to acids **VIII** with aqueous potassium hydroxide. Unlike compounds **I**, phenethylcarbamoyl nitriles **II** can be converted into the corresponding propanoic acids **IX** in the system HCl–AcOH–H_2O without appreciable decomposition of the *N*-arylalkylamide fragment.

All the synthesized compounds were colorless or off-white crystalline substances which melted in a fairly narrow temperature range. Their structure was confirmed by the analytical data and ^{1}H NMR spectra.

The analgesic activity of nitriles **I** and **II**, amides **IV** and **V**, and acids **VII**–**IX** was studied in 18–23-g white mice using standard acetic acid writhing model [8]. The compounds were tested via peroral administration at a dose of 5 mg/kg as a fine aqueous suspension stabilized by Tween 80. Diclofenac [9] was used as reference at the same dose [10]. The results showed that the acids were generally the least active in the series nitrile > amide > acid. In some cases, amides displayed higher analgesic effect as compared to their synthetic precursors. Therefore, it is reasonable to search for potential analgesics among 1-(2-cyanoethyl) and 1-(2-carbamoylethyl) derivatives within the examined series of compounds. Lower acidity of amides and nitriles as compared to the corresponding carboxylic acids reduces the probability for their ulcerogenic effect which is a serious drawback of many modern analgesics [9].

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Mercury-400 spectrometer at 400 MHz from solutions in DMSO-d_6 with tetramethylsilane as internal reference. Ethyl 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**III**) was synthesized according to the procedure described in [3]. The progress of reactions was monitored by TLC using Sorbfil plates (eluent acetic acid–hexane–diethyl ether, 5:5:7); spots were visualized by treatment with iodine vapor.

1-(2-Cyanoethyl)-4-hydroxy-*N*-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (Ia). 4-Methoxybenzylamine, 1.51 g (0.011 mol), was added to a solution of 2.86 g (0.01 mol) of compound **III** in 20 ml of ethanol, and the mixture was heated for 3 h under reflux. The mixture was cooled, diluted with 100 ml of cold water, and acidified with aqueous HCl to pH 4. The precipitate was filtered off, washed with cold water, and dried. Yield 3.62 g (96%), off-white crystals, mp 149–151°C (from aqueous ethanol), R_f 0.68. ^{1}H NMR spectrum, δ, ppm: 2.88 t (2H, CH_2CN, J = 7.0 Hz), 3.78 s (3H, OCH_3), 4.52 d (2H, NHC**H**$_2$, J = 5.6 Hz), 4.56 t (2H, 1-CH_2, J = 7.0 Hz), 6.89 d (2H, 2′-H, 6′-H, J = 8.8 Hz), 7.30 d (2H, 3′-H, 5′-H, J = 8.8 Hz), 7.36 t (1H, 6-H, J = 6.5 Hz), 7.79–7.75 m (2H, 7-H, 8-H), 8.15 d (1H, 5-H, J = 8.0 Hz), 10.47 t (1H, 3-CONH, J = 5.5 Hz), 17.38 s (1H, 4-OH). Found, %: C 66.74; H 4.96; N 11.05. $C_{21}H_{19}N_3O_4$. Calculated, %: C 66.83; H 5.07; N 11.13.

Compounds **Ib**, **IIa**, and **IIb** were synthesized in a similar way.

1-(2-Cyanoethyl)-*N*-(3,4-dimethoxybenzyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide (Ib). Yield 95%, off-white crystals, mp 154–156°C (from aqueous ethanol), R_f 0.65. ^{1}H NMR spectrum, δ, ppm: 2.88 t (2H, CH_2CN, J = 7.0 Hz), 3.79 s and 3.81 s (3H each, OCH_3), 4.53 d (2H, NHC**H**$_2$, J = 5.7 Hz), 4.57 t (2H, 1-CH_2, J = 7.0 Hz), 6.86 d (1H, 6′-H, J = 8.2 Hz), 6.91 d (1H, 5′-N, J = 8.2 Hz), 6.96 s (1H, 2′-H), 7.37 t (1H, 6-H, J = 6.5 Hz), 7.79–7.76 m (2H, 7-H, 8-H), 8.16 d (1H, 5-H, J = 8.0 Hz), 10.48 t (1H, 3-CONH, J = 5.6 Hz), 17.37 s (1H, 4-OH). Found, %: C 64.75; H 5.12; N 10.22. $C_{22}H_{21}N_3O_5$. Calculated, %: C 64.86; H 5.20; N 10.31.

1-(2-Cyanoethyl)-4-hydroxy-*N*-[2-(4-methoxyphenyl)ethyl]-2-oxo-1,2-dihydroquinoline-3-carboxamide (IIa). Yield 92%, off-white crystals, mp 133–135°C (from aqueous ethanol). ^{1}H NMR spectrum, δ, ppm: 2.81 t (2H, C**H**$_2$Ar, J = 7.2 Hz), 2.89 t (2H, CH_2CN, J = 7.0 Hz), 3.59 q (2H, NHC**H**$_2$, J = 6.7 Hz), 3.75 s (3H, OCH_3), 4.55 t (2H, 1-CH_2, J = 7.0 Hz), 6.82 d (2H, 2′-H, 6′-H, J = 8.6 Hz), 7.16 d (2H, 3′-H, 5′-H, J = 8.6 Hz), 7.34 t (1H, 6-H, J = 6.4 Hz), 7.77–7.73 m (2H, 7-H, 8-H), 8.13 d (1H, 5-H, J = 8.0 Hz), 10.21 t (1H, 3-CONH, J = 5.3 Hz), 17.46 s (1H, 4-OH). Found, %: C 67.43; H 5.34; N 10.85. $C_{22}H_{21}N_3O_4$. Calculated, %: C 67.51; H 5.41; N 10.74.

1-(2-Cyanoethyl)-*N*-[2-(3,4-dimethoxyphenyl)-ethyl]-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide (IIb). Yield 90%, off-white crystals, mp 157–159°C (from aqueous ethanol). ^{1}H NMR spectrum, δ, ppm: 2.89 t (2H, CH_2CN, J = 6.9 Hz), 2.92 t (2H, C**H**$_2$Ar, J = 7.1 Hz), 3.63 q (2H, NHC**H**$_2$, J = 6.4 Hz), 3.77 s and 3.82 s (3H each, OCH_3), 4.57 t (2H, 1-CH_2, J = 6.9 Hz), 6.78 d.d (1H, 6′-H, J = 8.2, 1.7 Hz), 6.82 d (1H, 5′-H, J = 8.2 Hz), 6.85 d (1H, 2′-H, J = 1.7 Hz), 7.36 t (1H, 6-H, J = 6.3 Hz), 7.79–7.76 m (2H, 7-H, 8-H), 8.15 d (1H, 5-H, J = 8.0 Hz), 10.25 t (1H, 3-CONH, J = 5.3 Hz), 17.50 s (1H, 4-OH). Found, %: C 65.65; H 5.59; N 10.06. $C_{23}H_{23}N_3O_5$. Calculated, %: C 65.55; H 5.50; N 9.97.

1-(2-Carbamoylethyl)-4-hydroxy-*N*-(4-methoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (IVa). A mixture of 3.77 g (0.01 mol) of nitrile **Ia** and 20 ml of a ~2.8 M solution of HCl in acetic acid with a low water content (prepared by mixing required amounts of acetic anhydride and concentrated aqueous HCl according to the procedure described in [6]) 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 and washed with water. The crude product was thoroughly ground with 10 ml of ethanol, and the precipitate was filtered off, washed with a small amount of cold ethanol, and dried. Yield 2.81 g (71%), colorless crystals, mp 176–178°C (from ethanol), R_f 0.13 (cf. R_f 0.88 for diamide **VI** in the same solvent system). ^{1}H NMR spectrum, δ, ppm: 2.39 t (2H, CH_2CO, J = 7.4 Hz), 3.72 s (3H, OCH_3), 4.40 t (2H, 1-CH_2, J = 7.4 Hz), 4.50 d (2H, NHC**H**$_2$, J = 5.9 Hz), 6.91 d (2H, 2′-H, 6′-H, J = 8.8 Hz), 7.05 s (1H, $CONH_2$), 7.27 d (2H, 3′-H, 5′-H, J = 8.8 Hz), 7.36 t (1H, 6-H, J = 7.3 Hz), 7.40 s (1H, $CONH_2$), 7.64 d (1H, 8-H, J = 8.4 Hz), 7.79 t (1H, 7-H, J = 7.6 Hz), 8.09 d (1H, 5-H, J = 8.0 Hz), 10.60 t (1H, 3-CONH, J = 5.7 Hz), 17.29 s (1H, 4-OH). Found, %: C 63.87; H 5.42; N 10.52. $C_{21}H_{21}N_3O_5$. Calculated, %: C 63.79; H 5.35; N 10.63.

Compounds **IVb**, **Va**, and **Vb** were synthesized in a similar way.

1-(2-Carbamoylethyl)-4-hydroxy-*N*-(3,4-dimethoxybenzyl)-2-oxo-1,2-dihydroquinoline-3-carboxamide (IVb). Yield 58%, colorless crystals, mp 181–183°C (from ethanol), R_f 0.16. ^{1}H NMR spectrum, δ, ppm: 2.41 t (2H, CH_2CO, J = 7.5 Hz), 3.71 s and 3.73 s (3H each, OCH_3), 4.40 t (2H, 1-CH_2, J = 7.5 Hz), 4.49 d (2H, NHC**H**$_2$, J = 5.7 Hz), 6.87 d (1H, 6′-H, J = 8.3 Hz), 6.91 d (1H, 5′-H, J = 8.3 Hz), 6.99 s (1H, $CONH_2$), 6.95 s (1H, 2′-H), 7.35 t (1H, 6-H, J = 7.4 Hz), 7.42 s (1H, $CONH_2$), 7.65 d (1H, 8-H, J = 8.5 Hz), 7.78 t (1H, 7-H, J = 7.7 Hz), 8.08 d (1H, 5-H, J = 8.0 Hz), 10.59 t (1H, 3-CONH, J = 5.7 Hz), 17.30 s (1H, 4-OH). Found, %: C 62.18; H 5.36; N 9.74. $C_{22}H_{23}N_3O_6$. Calculated, %: C 62.11; H 5.45; N 9.88.

1-(2-Carbamoylethyl)-4-hydroxy-*N*-[2-(4-methoxyphenyl)ethyl]-2-oxo-1,2-dihydroquinoline-3-carboxamide (Va). Reaction time 3 h. No diamide **VI** was formed, and there was no need of grinding the crude product with ethanol. Yield 88%, colorless crystals, mp 139–141°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.40 t (2H, CH_2CO, J = 7.3 Hz), 2.80 t (2H, C**H**$_2$Ar, J = 7.1 Hz), 3.56 q (2H, NHC**H**$_2$, J = 6.3 Hz), 3.70 s (3H, OCH_3), 4.40 t (2H, 1-CH_2, J = 7.3 Hz), 6.84 d (2H, 2′-H, 6′-H, J = 8.5 Hz), 7.18 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 6.95 s (1H, $CONH_2$), 7.34 t (1H, 6-H, J = 7.4 Hz), 7.45 s (1H, $CONH_2$), 7.64 d (1H, 8-H, J = 8.5 Hz), 7.78 t (1H, 7-H, J = 7.6 Hz), 8.08 d (1H, 5-H, J = 8.0 Hz), 10.34 t (1H, 3-CONH, J = 5.2 Hz), 17.42 s (1H, 4-OH). Found, %: C 64.45; H 5.59; N 10.35. $C_{22}H_{23}N_3O_5$. Calculated, %: C 64.54; H 5.66; N 10.26.

1-(2-Carbamoylethyl)-*N*-[2-(3,4-dimethoxyphenyl)ethyl]-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamide (Vb). Reaction time 3 h. No diamide **VI** was formed, and there was no need of grinding the crude product with ethanol. Yield 86%, colorless crystals, mp 145–147°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.40 t (2H, CH_2CO, J = 7.3 Hz), 2.80 t (2H, C**H**$_2$Ar, J = 7.0 Hz), 3.58 q (2H, NHC**H**$_2$, J = 6.2 Hz), 3.69 s and 3.73 s (3H each, OCH_3), 4.39 t (2H, 1-CH_2, J = 7.3 Hz), 6.76 d (1H, 6′-H, J = 8.2 Hz), 6.84 d (1H, 5′-H, J = 8.2 Hz), 6.88 s (1H, 2′-H), 6.96 s (1H, $CONH_2$), 7.34 t (1H, 6-H, J = 7.3 Hz), 7.44 s (1H, $CONH_2$), 7.65 d (1H, 8-H, J = 8.4 Hz), 7.78 t (1H, 7-H, J = 7.6 Hz), 8.08 d (1H, 5-H, J = 8.1 Hz), 10.36 t (1H, 3-CONH, J = 5.3 Hz), 17.43 s (1H, 4-OH). Found, %: C 62.74; H 5.63; N 9.47. $C_{23}H_{25}N_3O_6$. Calculated, %: C 62.86; H 5.73; N 9.56.

3-(3-Carbamoyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl)propanoic acid (VII) was synthesized from compound **Ib** as described above for amides **V**, the reaction time being 15 h. Yield 91%, colorless crystals, mp 230–232°C (from ethanol), R_f 0.60. ^{1}H NMR spectrum, δ, ppm: 2.56 t (2H, CH_2CO, J = 7.6 Hz), 4.43 t (2H, 1-CH_2, J = 7.6 Hz), 7.34 t (1H, 6-H, J = 7.4 Hz), 7.64 d (1H, 8-H, J = 8.6 Hz), 7.78 t (1H, 7-H, J = 7.7 Hz), 8.08 d (1H, 5-H, J = 8.0 Hz), 8.60 s and 9.59 s (1H each, 3-$CONH_2$), 12.45 br.s (1H, COOH), 17.86 s (1H, 4-OH). Found, %: C 56.60; H 4.43; N 10.08. $C_{13}H_{12}N_2O_5$. Calculated, %: C 56.52; H 4.38; N 10.14.

3-[4-Hydroxy-3-(4-methoxybenzylcarbamoyl)-2-oxo-1,2-dihydroquinolin-1-yl]propanoic acid (VIIIa). A mixture of 3.77 g (0.01 mol) of nitrile **Ia** and 20 ml of 20% aqueous potassium hydroxide was heated at the boiling point until ammonia no longer evolved (4 h). The mixture was cooled and filtered, the filtrate was acidified with dilute aqueous HCl to pH 3, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethanol. Yield 3.29 g (83%), colorless crystals, mp 170–172°C. ^{1}H NMR spectrum, δ, ppm: 2.56 t (2H, CH_2CO, J = 7.7 Hz), 3.72 s (3H, OCH_3), 4.42 t (2H, 1-CH_2, J = 7.7 Hz), 4.50 d (2H, NHC**H**$_2$, J = 5.8 Hz), 6.91 d (2H, 2′-H,

6′-H, *J* = 8.5 Hz), 7.26 d (2H, 3′-H, 5′-H, *J* = 8.5 Hz), 7.34 t (1H, 6-H, *J* = 7.6 Hz), 7.64 d (1H, 8-H, *J* = 8.5 Hz), 7.77 t (1H, 7-H, *J* = 7.6 Hz), 8.07 d (1H, 5-H, *J* = 8.0 Hz), 10.56 t (1H, 3-CONH, *J* = 5.7 Hz), 12.43 br.s (1H, COOH), 17.30 s (1H, 4-OH). Found, %: C 63.71; H 4.98; N 7.16. $C_{21}H_{20}N_2O_6$. Calculated, %: C 63.63; H 5.09; N 7.07.

3-[3-(3,4-Dimethoxybenzylcarbamoyl)-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl]propanoic acid (VIIIb) was synthesized in a similar way. Yield 80%, colorless crystals, mp 164–166°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.57 t (2H, CH_2CO, *J* = 7.6 Hz), 3.71 s and 3.76 s (3H each, OCH_3), 4.44 t (2H, 1-CH_2, *J* = 7.6 Hz), 4.51 d (2H, NHC**H**$_2$, *J* = 5.8 Hz), 6.85 d (1H, 6′-H, *J* = 8.1 Hz), 6.90 d (1H, 5′-H, *J* = 8.1 Hz), 6.97 s (1H, 2′-H), 7.33 t (1H, 6-H, *J* = 7.5 Hz), 7.63 d (1H, 8-H, *J* = 8.5 Hz), 7.78 t (1H, 7-H, *J* = 7.7 Hz), 8.06 d (1H, 5-H, *J* = 8.0 Hz), 10.50 t (1H, 3-CONH, *J* = 5.6 Hz), 12.44 br.s (1H, COOH), 17.36 s (1H, 4-OH). Found, %: C 62.08; H 5.30; N 6.65. $C_{22}H_{22}N_2O_7$. Calculated, %: C 61.97; H 5.20; N 6.57.

3-{4-Hydroxy-3-[2-(4-methoxyphenyl)ethylcarbamoyl]-2-oxo-1,2-dihydroquinolin-1-yl}propanoic acid (IXa) was synthesized from nitrile **IIa** as described above for compound **V**, the reaction time being 15 h. Yield 87%, colorless crystals, mp 146–148°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.55 t (2H, CH_2CO, *J* = 7.5 Hz), 2.80 t (2H, C**H**$_2$Ar, *J* = 7.0 Hz), 3.55 q (2H, NHC**H**$_2$, *J* = 6.9 Hz), 3.70 s (3H, OCH_3), 4.42 t (2H, 1-CH_2, *J* = 7.5 Hz), 6.85 d (2H, 2′-H, 6′-H, *J* = 8.6 Hz), 7.17 d (2H, 3′-H, 5′-H, *J* = 8.6 Hz), 7.33 t (1H, 6-H, *J* = 7.4 Hz), 7.63 d (1H, 8-H, *J* = 8.5 Hz), 7.77 t (1H, 7-H, *J* = 7.7 Hz), 8.06 d (1H, 5-H, *J* = 7.9 Hz), 10.30 t (1H, 3-CONH, *J* = 5.6 Hz), 12.41 br.s (1H, COOH), 17.42 s (1H, 4-OH). Found, %: C 64.47; H 5.48; N 6.94. $C_{22}H_{22}N_2O_6$. Calculated, %: C 64.38; H 5.40; N 6.83.

3-{3-[2-(3,4-Dimethoxyphenyl)ethylcarbamoyl]-4-hydroxy-2-oxo-1,2-dihydroquinolin-1-yl}propanoic acid (IXb) was synthesized in a similar way. Yield 84%, colorless crystals, mp 117–119°C (from ethanol). ^{1}H NMR spectrum, δ, ppm: 2.56 t (2H, CH_2CO, *J* = 7.4 Hz), 2.80 t (2H, C**H**$_2$Ar, *J* = 7.0 Hz), 3.58 q (2H, NHC**H**$_2$, *J* = 6.1 Hz), 3.70 s and 3.73 s (3H each, OCH_3), 4.43 t (2H, 1-CH_2, *J* = 7.4 Hz), 6.75 d (1H, 6′-H, *J* = 8.1 Hz), 6.85 d (1H, 5′-H, *J* = 8.1 Hz), 6.88 s (1H, 2′-H), 7.34 t (1H, 6-H, *J* = 7.4 Hz), 7.65 d (1H, 8-H, *J* = 8.5 Hz), 7.78 t (1H, 7-H, *J* = 7.7 Hz), 8.08 d (1H, 5-H, *J* = 8.0 Hz), 10.35 t (1H, 3-CONH, *J* = 5.6 Hz), 12.43 br.s (1H, COOH), 17.44 s (1H, 4-OH). Found, %: C 62.63; H 5.54; N 6.25. $C_{23}H_{24}N_2O_7$. Calculated, %: C 62.72; H 5.49; N 6.36.

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