4-Hydroxy-2-Quinolones. 233*. Synthesis and Diuretic Activity of 9-Bromo-7-Hydroxy-5-Oxo-2,3-Dihydro-1H,5H-Pyrido[3,2,1-ij]Quinoline-6-Carboxylic Acid Anilides

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4-HYDROXY-2-QUINOLONES. 233*. SYNTHESIS AND DIURETIC ACTIVITY OF 9-BROMO-7-HYDROXY-5-OXO-2,3-DIHYDRO-1*H*,5*H*-PYRIDO[3,2,1-*ij*]QUINOLINE-6-CARBOXYLIC ACID ANILIDES

I.V. Ukrainets[1], N. Yu. Golik[1], and I. N. Chernenok[1]**

The ethyl ester of 7-hydroxy-5-oxo-2,3-dihydro-1H,5H-pyrido[3,2,1-ij]quinoline-6-carboxylic acid reaction with bromine in anhydrous acetic acid producing a mixture of the 9-bromo-substituted product and 6-ethoxycarbonyl-5,7-dihydroxy-2,3-dihydro-1H-pyrido[3,2,1-ij]quinolinium tribromide in a 1:1 ratio. It has been established experimentally that the diuretic activity of 9-bromo-7-hydroxy-5-oxo-2,3-dihydro-1H,5H-pyrido[3,2,1-ij]quinoline-6-carboxanilides increases substantially in comparison with their non-brominated analogs.

Keywords: 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, pyrido[3,2,1-*ij*]quinolines, bromination, diuretic activity.

As shown previously, tricyclic 1-R-4-hydroxyquinolin-2-ones vary significantly in chemical properties from their bicyclic analogs. For example, the reaction of the 7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido-[3,2,1-*ij*]quinoline-6-carboxylic acid ethyl ester (**1**) with molecular bromine in aqueous acetic acid proceeds with bromination of not only the pyridine moiety of the molecule (which is common), but also the benzene moieties of the molecule as well [2].

The reaction of the tricyclic ester **1** with bromine in non-aqueous conditions also is not usual. In the case of the bicyclic 1-R-4-hydroxyquinolin-2-ones this method is a fairly simple and convenient route for the synthesis of 6-bromo-substituted derivatives [3]. However, attempts to apply it for the purpose-directed bromination of ester **1** in position 9 ended ambiguously. Thus, on adding dry molecular bromine to a solution of ester **1** in anhydrous acetic acid a yellow-orange substance was precipitated practically at once. The analysis proved it to be 6-ethoxycarbonyl-5,7-dihydroxy-2,3-dihydro-1*H*-pyrido[3,2,1-*ij*]quinolinium tribromide (**2**) [4]. In cases of other tricyclic quinolines under similar conditions complete the absence of bromination in the ring was noted [5]. Nevertheless, the desired 9-bromo-7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]-quinoline-6-carboxylic acid ethyl ester (**3**) was formed in this reaction, although its yield did not exceed 50%.

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*For Communication 232, see [1].

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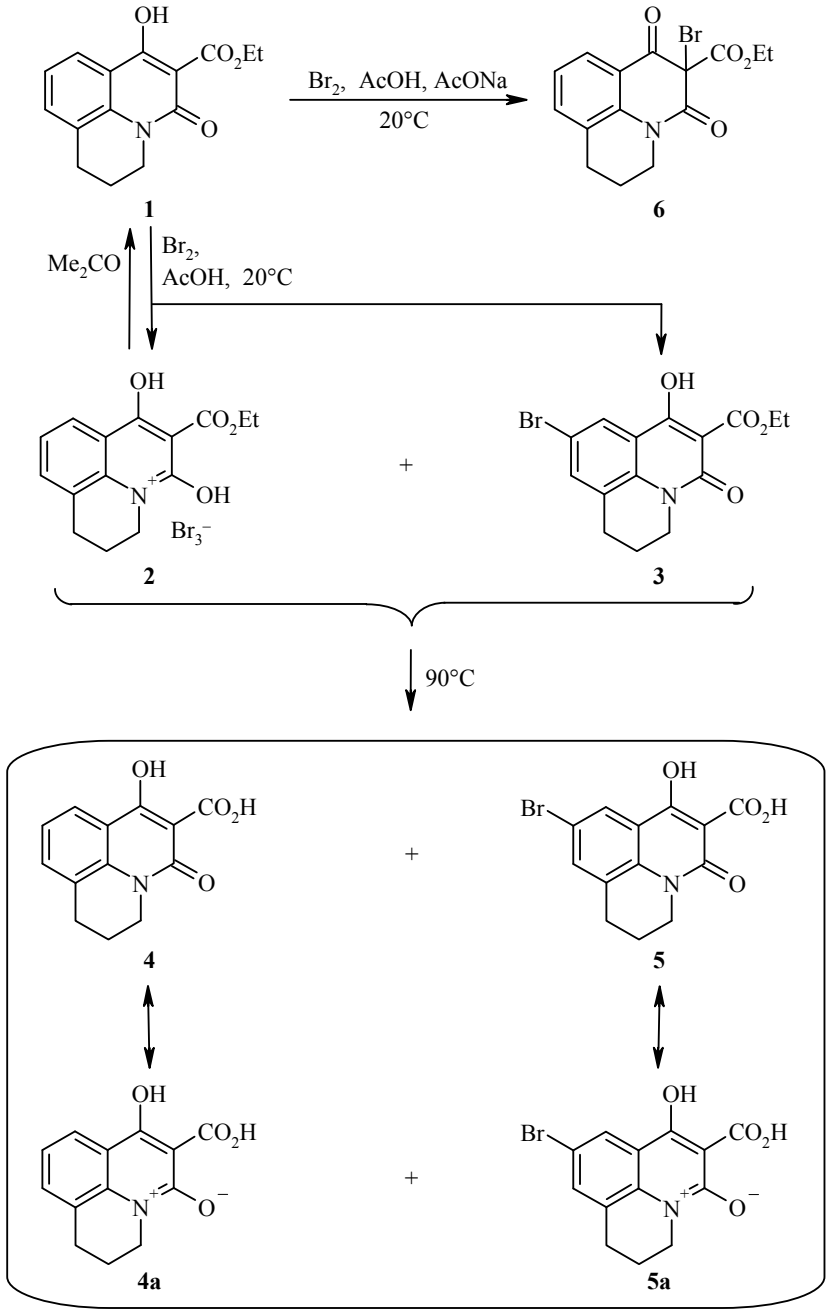


In principle, ester **3** might have been more efficiently obtained by the usual scheme, i.e., by the condensation of 6-bromo-1,2,3,4-tetrahydroquinoline with triethylmethane tricarboxylate. However, the high cost of commercially available 6-halo-substituted 1,2,3,4-tetrahydroquinolines stimulated the search for new synthetic solutions to this problem. Paying attention to the fact that tribromides of certain azaheterocycles are able to play the role of fairly active brominating agents of aromatic compounds [6] we attempted to increase the yield of 9-bromo-substituted ester **3** by means of the transformation of tribromide **2**. Thus, the reaction mixture was heated to dissolve the initially precipitated tribromide **2** and left to stand for several hours. The monocrystals obtained after dilution of the reaction mixture and recrystallization from acetic acid were subjected to X-ray structural analysis (Fig. 1), which showed that they were mixed and contained 7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-6-carboxylic acid (**4**) and its 9-bromo derivative **5** in a ratio

of 1:1. The positions of all the atoms in both molecules coincided, with the exception of the atoms of bromine and hydrogen at the C(4) carbon. This same relationship of acids **4** and **5** was confirmed by ^{1}H NMR spectroscopy of the crude product as well.

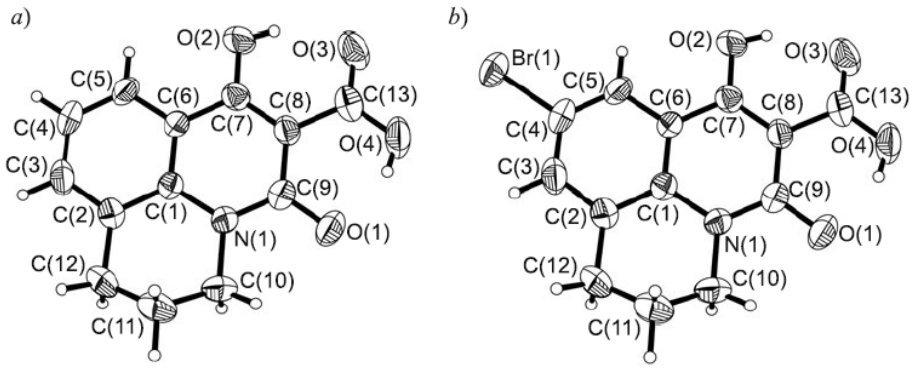


Fig. 1. The structure of molecules *a*) pyridoquinoline-6-carboxylic acid **4** and *b*) its 9-bromo-substituted analog **5** with representation of atoms by thermal vibration ellipsoids of 50% probability.

All the non-hydrogen atoms of acids **4** and **5**, with the exception of the atom C(11), lie in a plane with a precision of 0.02 Å. The deviation of the atom C(11) from this plane was -0.61 Å. The coplanarity of the carboxyl group with the plane of the quinoline moiety promotes the formation of intramolecular hydrogen bonds at O(2)–H···O(3) (H···O 1.83 Å, O–H···O 146°) and O(4)–H···O(1) (H···O 1.73 Å, O–H···O 151°). The formation of the hydrogen bond O(2)–H···O(3) also leads to lengthening of the bonds O(3)–C(13) 1.237(7) Å and C(7)–C(8) 1.370(6) Å in comparison with their average values [7] of 1.210 and 1.326 Å, respectively, and also to shortening of the O(2)–C(7) bond to 1.314(5) Å (the mean value 1.362 Å). The formation of the hydrogen bond O(4)–H···O(1) promotes shortening of the C(13)–O(4) bond to 1.292(6) Å (the mean value 1.308 Å). However, it was not possible to explain the significant lengthening of the C(9)–O(1) bond to 1.268(5) in comparison with the mean value of 1.210 Å for C(sp^2)=O bond. At the same time, the endocyclic N(1)–C(9) bond at 1.348(5) Å is significantly shorter than in quinolones (the mean value 1.378 Å [8]); it enables the suggestion that the zwitter-ionic forms **4a** and **5a** contribute significantly to the resonance hybrids of acids **4** and **5**.

In the crystal, molecules of acid **4** and its bromo derivative **5** form dimers as a result of intramolecular hydrogen bonds C(4)–H···Br(1)' (-*x*, 2-*y*, -*z*) (H···Br 3.06 Å, C–H···Br 159°).

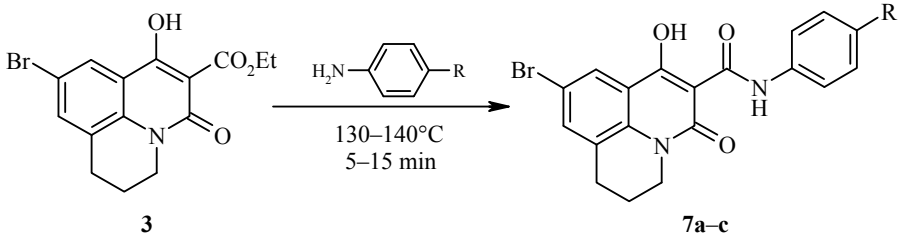
The experiment carried out showed convincingly that heating the reaction mixture upon bromination of ester **1** was unacceptable since in place of conversion of tribromide **2** into the desired bromo-substituted ester **3**, only decomposition of the ester group was observed.

Analysis of all the data obtained allowed to present the process of bromination of the tricyclic ester **1** in the following way. The bromide ion isolated at the beginning of the formation of 9-bromo derivative **3** reacts with unreacted bromine and forms tribromide anion, which, in turn, is rapidly bound with the bipolar tautomeric form of the initial ester **1** into quinolinium tribromide **2**, which is poorly soluble in acetic acid. As a result, only half of ester **1** is subjected to bromination. It is remarkable that unsubstituted ester **1** exclusively participates as a cation in formation of quinolinium tribromide **2**. It is perhaps due to the fact that the nitrogen atom in its composition has more marked basic properties in comparison to the nitrogen atom in brominated product **3** (by analogy with aniline and its *para*-bromo-substituted derivative).

It seemed that it might be possible to solve the synthetic challenge, which has risen by collecting the separated bromide ion, breaking down the chain of undesirable processes at their very beginning. Unfortunately, the problem did not prove to be simple. The anhydrous sodium acetate used in the reaction, readily bounds a

bromide ion, yet cardinally changing the direction of the reaction to form a completely different product, 2-bromo-1,3-dioxo-2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid ethyl ester (**6**).

Based on brominated ester **3**, which remains in the solution after separating the crystalline tribromide from the reaction mixture, a series of anilides **7a-c** was obtained. These products were of interest for clarifying structure–biological relationships in the series of quinolone diuretics being studied by us. In addition, 9-bromo-substituted analogs of only the most active diuretics, namely, 7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido-[3,2,1-*ij*]quinoline-6-carboxanilides [9], were synthesized. The by-product tribromide **2** may be converted into the starting ester **1** by one of the suitable methods, for example, by the treatment with acetone.

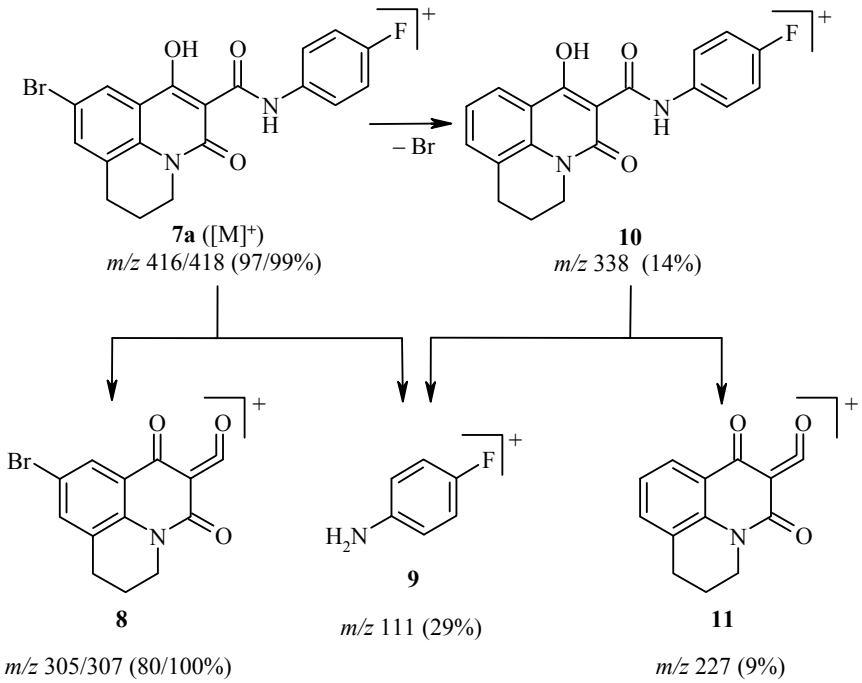


3 **7a–c**

7 a R = F, **b** R = Me, **c** R = OMe

Anilides **7a-c** are white crystalline substances with a yellow tint, with a narrow range of melting points. Upon heating they readily dissolve in DMF and DMSO, and are practically insoluble in water. ^{1}H NMR spectroscopy was used to confirm the structures of the compounds synthesized. Unfortunately, the relatively low solubility of anilides **7a-c** in DMSO-d_6 at room temperature did not permit the recording of their qualitative ^{13}C NMR spectra. Only the highly intense signals of all the aliphatic carbon atoms were clearly established in them, and the majority of the signals in the aromatic part of the spectrum were lost in the noise.

The presence of a bromine atom in the quinoline moiety of anilides **7a-c** was confirmed by mass spectrometry. This was indicated not only by establishing the molecular mass of the substances being analyzed, but also from the character of the peaks of the molecular and certain fragment ions, which have the form of doublets of close intensity due to isotopic bromine composition [10].



7a ([M]$^+$)
m/z 416/418 (97/99%)

10
m/z 338 (14%)

m/z 111 (29%)

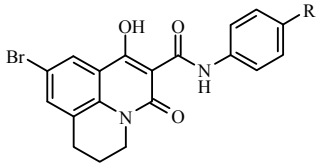
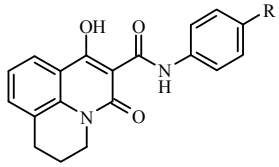
m/z 305/307 (80/100%)

m/z 227 (9%)

The main route of the primary decomposition caused by electron impact of the molecular ions of the compounds studied is shown in example of *para*-fluoroanilide **7a** (scheme above). It was accompanied by cleavage of the acyclic amide bond with the formation of tricyclic ketene **8** with *m*/*z* 305/307, general for all samples, and the specific splinter of aniline **9**. The probability of the second route for fragmentation of the molecular ions of anilides **7a-c**, the initial loss of a bromine atom, was significantly less since the intensity of the $[M\text{-}Br]^+$ peaks overall was only 2-14%.

The effect of the anilides **7a-c** synthesized on the urine excretory function of the kidney was studied in parallel with their non-brominated analogs. A comparative analysis of the results obtained indicates that with the appearance of a bromine atom in position 9 of a pyridoquinolone nucleus the diuretic properties of 7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-6-carboxanilides increased by 2 to 3 times (Table 1). This occurrence indicates that the modification carried out by us was extremely fortunate and is worthy of future study in both its chemical and pharmacological parts.

TABLE 1. Diuretic Activity of Anilides **7a-c** and their 9-*H*-Analogs [9]*

R		
F	268	104
Me	166	81
OMe	347	112

*Strengthening of diuresis (in %) in relation to the control taken as 100% (a significance level of the confidence interval $p \leq 0.05$ was taken in the work).

The present investigation has demonstrated that under anhydrous conditions the reaction of tricyclic 4-hydroxyquinolin-2-ones with molecular bromine occurs somewhat differently than in the case of their bicyclic analogs. In addition, it has been demonstrated experimentally that bromination of the quinoline moiety of the 7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-6-carboxanilide molecule has a positive effect on their biological properties.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Varian Mercury-400 spectrometer (400 MHz) in DMSO-d_6 solution, internal standard was TMS. The mass spectra were recorded on a Varian 1200L spectrometer in full-scanning mode in the range of 35-700 *m/z*, ionization by electron impact at 70 eV with direct insertion of the sample. Elemental analysis was carried out on a EuroVector EA 3000 microanalyzer. Melting points were determined in capillaries on a Stuart SMP10 digital melting point analyzer. Water was removed from commercial glacial acetic acid by drying over P_2O_5 and from bromine by shaking with conc. H_2SO_4.

9-Bromo-7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-6-carboxylic Acid Ethyl Ester (3). A solution of dry bromine (0.52 ml, 0.01 mol) in anhydrous acetic acid (5 ml) was added with vigorous stirring to a solution of compound **1** [11] (2.73 g, 0.01 mol) in the same solvent (20 ml). A yellow-orange

crystalline solid 6-ethoxycarbonyl-5,7-dihydroxy-2,3-dihydro-1*H*-pyrido[3,2,1-*ij*]quinolinium tribromide (**2**) began to form practically straight away. In 2 h the solid was filtered and dried. Yield 2.26 g (44%). Mp 86-88°C. For more detail on the characterictics of this product, see [4].

The filtrate remaining after isolation of tribromide **2** was diluted with cold water. The isolated solid 9-bromo-substituted ester **3** was filtered off, washed with water, and dried. Yield 1.69 g (48%), white needles with a yellow tint. Mp 173-175°C (EtOH). ^{1}H NMR spectrum, δ, ppm. (*J*, Hz): 12.76 (1H, s, OH); 7.91 (1H, s, H-8); 7.65 (1H, s, H-10); 4.28 (2H, q, *J* = 7.1, OCH_2); 3.92 (2H, t, *J* = 5.3, NCH_2); 2.89 (2H, t, *J* = 5.4, 1-CH_2); 1.93 (2H, quin, *J* = 5.3, 2-CH_2); 1.26 (3H, t, *J* = 7.1, CH_3). Found, %: C 51.26; H 4.09; N 3.89. $C_{15}H_{14}BrNO_4$. Calculated, %: C 51.16; H 4.01; N 3.98.

Mixture of 7-Hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-6-carboxylic Acid (4) and 9-Bromo-7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-6-carboxylic Acid (5). The reaction mixture obtained by the procedure of the previous experiment was heated to dissolve the solid quinolinium tribromide **2** and was left to stand at 90°C in a flask fitted with a reflux condenser for 12 h, then diluted with cold water. The solid, white with a yellow tint, was filtered off, washed with water, and dried. A crude product (2.67 g, 94%) containing acids **4** and **5** in a ratio of 1:1 according to ^{1}H NMR spectral data was obtained.

2-Bromo-1,3-dioxo-2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid Ethyl Ester (6). A solution of dry bromine (0.52 ml, 0.01 mol) in anhydrous acetic acid (5 ml) was added with vigorous stirring to a solution of ethyl ester (**1**) (2.73 g, 0.01 mol) and fused sodium acetate (0.90 g, 0.011 mol) in the same solvent (30 ml). The brown color of bromine changed directly to light-yellow. The reaction mixture was diluted with cold water and stored for several hours at room temperature. The yellow solid 2-bromo-substituted ester **6** isolated was filtered off, washed with cold water, and dried. Yield 3.16 g (90%). Mp 94-96°C (EtOH–H_2O, 3:2). In a mixing test with an authentic sample of ester **6** [2] there was no depression of the melting point. The ^{1}H NMR spectra of these compounds were identical.

7-Hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-6-carboxylic Acid Ethyl Ester (1) from Quinolinium Tribromide 2. Quinolinium tribromide **2** (5.13 g, 0.01 mol) was dissolved in acetone (20 ml), after which the reaction mixture was diluted with water. A practically colorless precipitate of the starting ester **1** was precipitated with a high degree of purity. It was filtered off, washed with cold water, and dried. Yield 2.64 g (97%). Mp 102-104°C. In a mixing test with an authentic sample of ester **1** [11] there was no depression of the melting point, the ^{1}H NMR spectra of these compounds were identical.

9-Bromo-7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline-6-carboxylic acid anilides 7a-c were obtained by reacting ester **3** with the corresponding aniline by the known procedure [12].

9-Bromo-*N*-(4-fluorophenyl)-7-hydroxy-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3.2.1-*ij*]quinoline-6-carboxamide (7a). Yield 98%, light-yellow crystals, mp 248-250°C (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.68 (1H, s, OH); 12.45 (1H, s, NH); 7.96 (1H, s, H-8); 7.66 (1H, s, H-10); 7.62 (2H, dd, ^3J = 8.5, $^4J_{H–F}$ = 4.6, H-2',6'); 7.17 (2H, t, ^3J = 8.5, $^3J_{H–F}$ = 8.2, H-3',5'); 4.08 (2H, t, *J* = 5.4, NCH_2); 2.96 (2H, t, *J* = 5.4, 1-CH_2); 2.05 (2H, quin, *J* = 5.4, 2-CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 416/418 $[M]^+$ (97/99), 338 $[M\text{-}Br]^+$ (14), 305/307 $[M\text{-}C_6H_6FN]^+$ (80/100), 227 $[M\text{-}Br\text{-}C_6H_6FN]^+$ (9), 111 $[C_6H_6FN]^+$ (29). Found, %: C 54.81; H 3.46; N 6.62. $C_{19}H_{14}BrFN_2O_3$. Calculated, %: C 54.70; H 3.38; N 6.71.

9-Bromo-7-hydroxy-*N*-(4-methylphenyl)-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3.2.1-*ij*]quinoline-6-carboxamide (7b). Yield 94%, light-yellow crystals, mp 222-250°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.73 (1H, s, OH); 12.40 (1H, s, NH); 7.98 (1H, s, H-8); 7.67 (1H, s, 10-H); 7.48 (2H, d, *J* = 7.7, H-2',6'); 7.18 (2H, d, *J* = 7.7, H-3',5'); 4.09 (2H, t, *J* = 5.3, NCH_2); 2.97 (2H, t, *J* = 5.3, 1-CH_2); 2.30 (3H, s, 4'-CH_3); 2.05 (2H, quin, *J* = 5.4, 2-CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 412/414 $[M]^+$ (98/100), 334 $[M\text{-}Br]^+$ (8), 305/307 $[M\text{-}C_7H_9N]^+$ (41/37), 227 $[M\text{-}Br\text{-}C_7H_9N]^+$ (8), 107 $[C_7H_9N]^+$ (17). Found, %: C 58.25; H 4.24; N 6.86. $C_{20}H_{17}BrN_2O_3$. Calculated, %: C 58.13; H 4.15; N 6.78.

9-Bromo-7-hydroxy-*N*-(4-methoxyphenyl)-5-oxo-2,3-dihydro-1*H*,5*H*-pyrido[3.2.1-*ij*]quinoline-6-carboxamide (7c). Yield 95%, light-yellow crystals, mp 227-229°C (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 16.50 (1H, s, OH); 12.33 (1H, s, NH); 7.98 (1H, s, H-8) ° 7.67 (1H, s, 10-H); 7.53 (2H, d, *J* = 8.1, H-2',6'); 6.97 (2H, d, *J* = 8.1, H-3',5'); 4.09 (2H, t, *J* = 5.3, NCH_2); 3.78 (3H, s, 4'-OCH_3); 2.97 (2H, t, *J* = 5.2, 1-CH_2); 2.06 (2H, quin, *J* = 5.3, 2-CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 428/430 $[M]^+$ (98/100), 350 $[M-Br]^+$ (2), 305/307 $[M-C_7H_9NO]^+$ (5/7), 227 $[M-Br-C_7H_9NO]^+$ (2), 123 $[C_7H_9NO]^+$ (40). Found, %: C 56.07; H 4.08; N 6.44. $C_{20}H_{17}BrN_2O_4$. Calculated, %: C 55.96; H 3.99; N 6.53.

X-ray Structural Investigation of a Mixture of Compounds 4 and 5. Cocrystals of acids **4** and **5** ($C_{13}H_{11}NO_4 \cdot C_{13}H_{10}BrNO_4$, *M* 569.36), obtained by recrystallization from AcOH, were triclinic, at 20°C: *a* 7.733(1), *b* 8.0596(8), *c* 9.973(1) Å; α 69.55(1), β 88.69(1), γ 79.366(9)°, *V* 571.8(1) Å^3, *Z* 1, space group $P\bar{1}$, d_{calc} 1.654 g/cm^3, μ(MoKα) 1.856 mm^{-1}, *F*(000) 290. The parameters of the unit cell and the intensities of 5598 reflections (2617 independent, R_{int} 0.031) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ 55°). The structure was solved by the direct method with the SHELXTL set of programs [13]. Absorption was taken into account by the semiempirical method from the results of multiscanning T_{min} 0.708, T_{max} 0.913. The positions of hydrogen atoms were made apparent from the electron density difference synthesis and were refined with a "rider" model with $U_{iso} = nU_{equiv}$ for a non-hydrogen atom bound with the given hydrogen (*n* = 1.5 for hydroxyl groups and *n* = 1.2 for the remaining hydrogen atoms). The structure was refined on F^2 with the full-matrix least-squares method in an anisotropic approximation for the non-hydrogen atoms to wR_2 0.237 for 2408 reflections (R_1 0.083 for 1797 reflections with $F > 4\sigma(F)$, *S* 1.040). Full crystallographic information has been deposited in the Cambridge Crystallographic Data Center (deposit CCDC 941058),

Diuretic activity of anilides **7a-c** was studied in white non-pedigree rats (about 6 animals for each sample) with the weight of 180-200 g according to the standard procedure [14]. The non-brominated analogs were used as reference drugs [9]. All substances tested were administered in the dose of 10 mg/kg perorally as fine aqueous suspensions stabilized with Tween 80. Diuresis was recorded after 5 h.

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