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4-HYDROXY-2-QUINOLONES. 194*. 1-HYDROXY-3-OXO-6,7-DIHYDRO-3H,5H-PYRIDO[3,2,1-*ij*]QUINOLINE-2-CARBOXYLIC ACID ALKYLAMIDES. SYNTHESIS, STRUCTURE, AND BIOLOGICAL PROPERTIES

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Modified methods are proposed for the preparation of the ethyl ester and alkylamides of 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-ij]quinoline-2-carboxylic acid. A comparative analysis has been carried out of the steric structure and diuretic activity of the synthesized compounds and the previously studied, and closely structurally related, 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo-[3,2,1-ij]quinoline-2-carboxamides.

Keywords: 4-hydroxy-2-oxoquinoline-3-carboxylic acid alkylamides, amidation, diuretic activity, X-ray structural analysis.

The accidental discovery of stimulation of diuretic function of the kidney [2] using 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides (which had not previously been considered as a specific feature) has since then proved to be a trigger for carrying out a broad investigation targeted towards a novel class of diuretic chemicals. As a result, compounds have been synthesized which (due to the mechanism of the removal of a large volume of liquid [3]) have proved efficient agents in the fight against serious pathology such as hypertensive disease and also edema in the brain and lungs [4].

With the aim of discovering novel compounds which would be of interest as the basis for preparing therapeutically useful diuretic materials, one of the directions of our further work related to the 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid N-R-amides **1**. A justification for studying such substances is their close structural similarity to 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo-[3,2,1-*ij*]quinoline-2-carboxamides [4, 5] which have high diuretic activity. Expansion of the ring annelated to the quinolone nucleus by just one unit should certainly lead to a conformational rearrangement of of the basic molecule and this, in turn, can bring about changes in pharmacological properties.

In principle, the synthesis of the starting ethyl 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]-quinoline-2-carboxylate (**2**) can be achieved by the reaction of 1,2,3,4-tetrahydroquinoline (**3**) with triethyl-methane tricarboxylate (**4**) using different methods, i.e. holding a mixture of the amine and a twofold excess of acylating agent at 220ºC [6] or by the stepwise addition of the amine to an equimolar amount of the

* For Communication 193, see [1].

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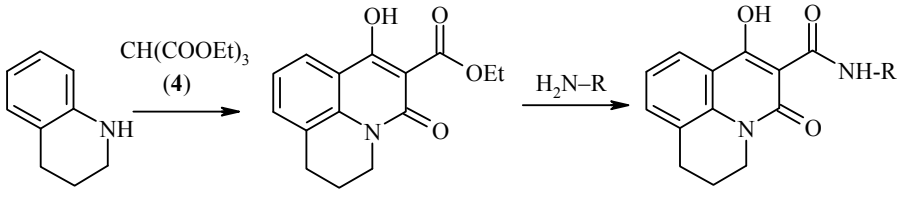
triester previously heated to 215ºC [7]. In should be noted that both variants only give good results for working with small amounts of the ester **2** (up to 0.1 mol). With larger loads, problems specific to each of the methods appear. In the first, besides the wasteful use of the expensive triethylmethane tricarboxylate, it becomes impossible to heat a bulky reaction mixture to the required 220ºC sufficiently rapidly. Side processes are activated, the main of which is partial transformation of the initially formed diethyl methanecarboxylate monoquinolin-1-ylamide not to the target product but to the methanedi- or tri(quinolin-1-yl)carboxamides. With use of the second method the reaction mixture becomes too viscous at the end of the reaction. For large quantities the mixing is severely challenged with the result that subsequent portions of the 1,2,3,4-tetrahydroquinoline (**3**) are markedly consumed not by reaction with the residual triethylmethane tricarboxylate (**4**) but by amidation of tricyclic ester **2** which became the main component of the mixture.



3 **2** **1a–q**

1 a R = Me; **b** R = Et; **c** R = All; **d** R = Pr; **e** R = *i*-Pr; **f** R = Bu; **g** R = *i*-Bu; **h** R = *s*-Bu; **i** R = C_5H_{11}; **j** R = *i*-C_5H_{11}; **k** R = C_6H_{13}; **l** R = 2-hydroxyethyl; **m** R = 3-hydroxypropyl; **n** R = *cyclo*-C_3H_5; **o** R = *cyclo*-C_5H_9; **p** R = *cyclo*-C_6H_{11}; **q** R = *cyclo*-C_7H_{13}

Our modified method for carring out this reaction adapted for large loads allows to remove mentioned drawbacks. In fact, this is the previously discussed second method differing only in the fact that the amine is added not to the triethylmethane tricarboxylate but to its solution in an inert, high boiling solvent (diphenyl ether or Dowtherm A). This apparently small change allows us to prepare not only ester **2** but also its numerous analogs in virtually any amount. The only limitation of the method can be the degree of thermal stability of the secondary amine used.

Refluxing ester **2** for 20 h with a 40% excess of the corresponding amine in bromobenzene [6] has previously been used for the preparation of 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid alkylamides **1**. We have meanwhile accumulated practical experience of the synthesis of 4-hydroxy-2-oxoquinoline-3-carboxamides and this infers that such rigorous conditions are clearly excessive. In fact, carrying out further experiments has shown that ester **2** is readily amidated by alkylamines in just refluxing ethanol. The reaction is complete after 2-4 h and its success needs only a 10% excess of the alkylamine.

All of the synthesized alkylamides **1a-q** (Table 1) are colorless, crystalline materials, soluble in alcohol, DMF or DMSO, and virtually insoluble in water, diethyl ether, and hexane. Their structure is confirmed from ^{1}H NMR spectroscopy (Table 2). The different feature from the previously reported analogous 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acids [8] is the signal for the protons of the methylene group at position 6 of the pyridoquinolone ring which appears as a quintet of intensity 2H in the region 2.1 ppm. In addition, to clarify the features of the steric structure of the group of compounds obtained, we have carried out an X-ray structural analysis of the *sec*-butylamide **1h** (see Figure 1 and Tables 3 and 4).

In this way it was shown that, thanks to the presence of the two intramolecular hydrogen bonds (O(2)–H(2O)···O(3) 1.72 Å. O–H···O 149º and N(2)–H(2N)···O(1) 1.96 Å. N–H···O 135º), the quinolone fragment in the polycyclic system and the carbamide group of this compound lie in a single plane to an accuracy of 0.01 Å. The formation of the hydrogen bonds also leads to a marked redistribution of electron density in this fragment, as shown by lengthening of the bonds O(1)–C(9) 1.241(2) and C(13)–O(3) 1.268(2) Å when compared with their mean value [9] of 1.210 Å and also of the C(7)–C(8) bond 1.370(3) (1.326 Å). The O(2)–C(7) bond 1.326(2) is markedly shortened (mean value 1.362 Å).

TABLE 1. Characteristics of the 1-Hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic Acid Alkylamides **1a-q**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (ethanol)	Yield, %	Diuretic activity, %*
		C	H	N			
1a	$C_{14}H_{14}N_2O_3$	65.23 / 65.11	5.55 / 5.46	10.93 / 10.85	147-149	97	-48
1b	$C_{15}H_{16}N_2O_3$	66.27 / 66.16	6.04 / 5.92	10.18 / 10.29	116-118	96	-73
1c	$C_{16}H_{16}N_2O_3$	67.47 / 67.59	5.59 / 5.67	9.96 / 9.85	135-137	94	-81
1d	$C_{16}H_{18}N_2O_3$	67.20 / 67.12	6.45 / 6.34	9.91 / 9.78	141-143	93	+27
1e	$C_{16}H_{18}N_2O_3$	67.23 / 67.12	6.46 / 6.34	9.88 / 9.78	137-139	78	-78
1f	$C_{17}H_{20}N_2O_3$	68.09 / 67.98	6.80 / 6.71	9.39 / 9.33	90-92	93	-76
1g	$C_{17}H_{20}N_2O_3$	68.07 / 67.98	6.83 / 6.71	9.42 / 9.33	103-105	95	+8
1h	$C_{17}H_{20}N_2O_3$	67.90 / 67.98	6.78 / 6.71	9.26 / 9.33	138-140	82	+11
1i	$C_{18}H_{22}N_2O_3$	68.65 / 68.77	6.94 / 7.05	8.83 / 8.91	75-77	90	-84
1j	$C_{18}H_{22}N_2O_3$	68.66 / 68.77	6.92 / 7.05	8.97 / 8.91	101-103	92	-81
1k	$C_{19}H_{24}N_2O_3$	69.58 / 69.49	7.45 / 7.37	8.44 / 8.53	69-71	95	-82
1l	$C_{15}H_{16}N_2O_4$	62.39 / 62.49	5.51 / 5.59	9.63 / 9.72	130-132	97	-5
1m	$C_{16}H_{18}N_2O_4$	63.46 / 63.57	5.92 / 6.00	9.19 / 9.27	109-111	96	-71
1n	$C_{16}H_{16}N_2O_3$	67.67 / 67.59	5.76 / 5.67	9.97 / 9.85	104-106	84	-26
1o	$C_{18}H_{20}N_2O_3$	69.32 / 69.21	6.55 / 6.45	9.08 / 8.97	156-158	88	+17
1p	$C_{19}H_{22}N_2O_3$	70.04 / 69.92	6.92 / 6.79	8.47 / 8.58	193-195	88	+43
1q	$C_{20}H_{24}N_2O_3$	70.48 / 70.57	7.22 / 7.11	8.15 / 8.23	162-164	85	+16
	Furosemide						+104

* "+" indicates an increase and "-" an inhibition of diuresis with respect to the control taken as 100%

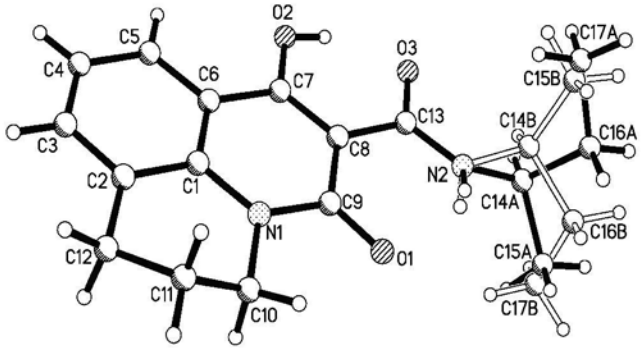


Fig. 1. Structure of the *sec*-butylamide **1h** molecule with atom numbering.

TABLE 2. ^{1}H NMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm (*J*, Hz)								
	1-OH (1H, s)	NH (1H)	Pyridoquinoline ring						R
			H-10 (1H, d)	H-8 (1H, d)	H-9 (1H, t)	5-CH_2 (2H, t)	7-CH_2 (2H, t)	6-CH_2 (2H, quin.)	
1	2	3	4	5	6	7	8	9	10
1a	17.09	10.18 (q, *J* = 4.1)	7.95 (*J* = 8.0)	7.39 (*J* = 7.4)	7.13 (*J* = 7.5)	4.09 (*J* = 5.8)	2.98 (*J* = 6.0)	2.11 (*J* = 5.8)	3.02 (3H, d, *J* = 4.9, CH_3)
1b	16.98	10.27 (t, *J* = 5.2)	7.96 (*J* = 8.0)	7.40 (*J* = 7.2)	7.15 (*J* = 7.7)	4.08 (*J* = 5.8)	2.98 (*J* = 6.0)	2.11 (*J* = 5.9)	3.48 (2H, quin., *J* = 6.3, $C\underline{H}_2CH_3$); 1.29 (3H, t, *J* = 6.9, $CH_2C\underline{H}_3$)
1c	16.93	10.42 (t, *J* = 5.3)	7.95 (*J* = 8.1)	7.40 (*J* = 7.3)	7.14 (*J* = 7.7)	See R	2.99 (*J* = 6.0)	2.11 (*J* = 5.8)	5.95 (1H, m, CH); 5.29 (1H, dd, *J* = 17.3 and *J* = 1.4, $NCH_2CH{=}C\underline{H}$-*trans*); 5.18 (1H, dd, *J* = 10.1 and *J* = 1.4, $NCH_2CH{=}C\underline{H}$-*cis*); 4.08 (4H, m, 5-CH_2 + $NC\underline{H}_2CH{=}CH_2$)
1d	17.16	10.33 (t, *J* = 5.3)	7.94 (*J* = 8.2)	7.39 (*J* = 7.2)	7.13 (*J* = 7.7)	4.08 (*J* = 5.8)	2.98 (*J* = 6.1)	2.10 (*J* = 6.0)	3.38 (2H, q, *J* = 6.7, $NC\underline{H}_2CH_2CH_3$); 1.67 (2H, m, $NCH_2C\underline{H}_2CH_3$); 1.03 (3H, t, *J* = 7.3, CH_3)
1e	17.17	10.24 (d, *J* = 6.9)	7.93 (*J* = 8.2)	7.40 (*J* = 7.4)	7.13 (*J* = 7.8)	4.07 (*J* = 6.0)	2.98 (*J* = 6.0)	2.09 (*J* = 6.0)	4.17 (1H, m, CH); 1.30 (6H, d, *J* = 6.5, $2CH_3$)
1f	17.16	10.33 (t, (*J* = 5.2)	7.94 (*J* = 8.0)	7.40 (*J* = 7.3)	7.14 (*J* = 7.8)	4.09 (*J* = 5.8)	2.98 (*J* = 6.1)	2.10 (*J* = 6.1)	3.41 (2H, q, *J* = 6.3, $NC\underline{H}_2$); 1.63 (2H, quin., *J* = 7.3, $NCH_2C\underline{H}_2$); 1.46 (2H, m, $NCH_2CH_2C\underline{H}_2CH_3$); 1.00 (3H, t, *J* = 7.2, CH_3)
1g	17.15	10.40 (t, *J* = 5.4)	7.93 (*J* = 8.0)	7.39 (*J* = 7.1)	7.13 (*J* = 7.7)	4.09 (*J* = 5.8)	2.99 (*J* = 6.1)	2.10 (*J* = 5.9)	3.26 (2H, t, *J* = 6.3, $NHC\underline{H}_2$); 1.93 (1H, m, CH); 1.02 (6H, d, *J* = 6.7, $2CH_3$)
1h	17.20	10.25 (d, *J* = 8.0)	7.93 (*J* = 8.0)	7.40 (*J* = 7.0)	7.13 (*J* = 7.5)	4.08 (*J* = 6.0)	2.98 (*J* = 6.0)	2.09 (*J* = 6.0)	4.02 (1H, m, $NC\underline{H}$); 1.62 (2H, quin., *J* = 7.2, $NCHC\underline{H}_2$); 1.27 (3H, d, *J* = 7.0, $NCHC\underline{H}_3$); 0.99 (3H, t, *J* = 7.4, $CH_2C\underline{H}_3$)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
1i	17.18	10.38 (t, J = 5.4)	7.91 (J = 8.1)	7.44 (J = 7.2)	7.16 (J = 7.8)	4.07 (J = 5.8)	2.97 (J = 6.1)	2.07 (J = 5.8)	3.38 (2H, q, J = 6.3, $NC\underline{H_2}$); 1.61 (2H, quin., J = 6.7, $NCH_2C\underline{H_2}$); 1.39 (4H, m, $(C\underline{H_2})_2CH_3$); 0.94 (3H, t, J = 6.7, CH_3)
1j	17.14	10.29 (t, J = 5.5)	7.92 (J = 8.0)	7.39 (J = 7.0)	7.14 (J = 7.5)	4.08 (J = 5.8)	2.98 (J = 6.0)	2.09 (J = 5.9)	3.42 (2H, q, J = 6.6, $NHC\underline{H_2}$); 1.72 (1H, m, CH); 1.53 (2H, q, J = 6.9, $NCH_2C\underline{H_2}$); 0.99 (6H, d, J = 6.2, $2CH_3$)
1k	17.15	10.30 (t, J = 5.4)	7.93 (J = 8.2)	7.39 (J = 7.3)	7.13 (J = 7.6)	4.08 (J = 6.0)	2.99 (J = 6.0)	2.09 (J = 5.8)	3.39 (2H, q, J = 6.6, $NC\underline{H_2}$); 1.63 (2H, quin., J = 7.0, $NCH_2C\underline{H_2}$); 1.40 (6H, m, $(C\underline{H_2})_3CH_3$); 0.92 (3H, t, J = 6.6, CH_3)
1l	17.20	10.40 (t, J = 5.0)	7.93 (J = 8.0)	7.40 (J = 7.4)	7.13 (J = 7.6)	4.10 (J = 6.0)	2.98 (J = 6.1)	2.10 (J = 5.9)	4.60 (1H, t, J = 4.6, OH); 3.61 (2H, q, J = 5.5, CH_2O); 3.48 (2H, q, J = 5.7, $NHC\underline{H_2}$)
1m	17.21	10.33 (t, J = 5.2)	7.92 (J = 8.2)	7.39 (J = 7.4)	7.12 (J = 7.8)	4.08 (J = 5.8)	2.98 (J = 6.0)	2.09 (J = 6.0)	4.22 (1H, t, J = 5.1, OH); 3.55 (2H, q, J = 6.0, CH_2O); 3.49 (2H, q, J = 6.0, $NC\underline{H_2}$); 1.77 (2H, quin., J = 6.4, $NCH_2C\underline{H_2}$)
1n	17.14	10.30 (d, J = 3.4)	7.94 (J = 8.1)	7.38 (J = 7.3)	7.13 (J = 7.6)	4.09 (J = 5.9)	2.99 (J = 6.0)	2.09 (J = 5.9)	2.91 (1H, m, CH); 0.87 (2H, m, CH_2 cyclopropane); 0.68 (2H, m, CH_2 cyclopropane)
1o	17.18	10.34 (d, J = 7.2)	7.93 (J = 8.0)	7.39 (J = 7.2)	7.13 (J = 7.7)	4.07 (J = 5.8)	2.98 (J = 6.1)	2.09 (J = 6.0)	4.32 (1H, m, CH); 2.03-1.57 (8H, m, $(CH_2)_4$ cyclopentane)
1p	17.19	10.37 (d, J = 7.1)	7.93 (J = 8.1)	7.40 (J = 7.1)	7.14 (J = 7.7)	4.10 (J = 5.9)	2.98 (J = 6.0)	2.09 (J = 5.9)	3.92 (1H, m, CH); 1.91-1.24 (10H, m, $(CH_2)_5$ cyclohexane)
1q	17.16	10.32 (d, J = 7.5)	7.92 (J = 8.0)	7.40 (J = 7.1)	7.13 (J = 7.6)	4.10 (J = 5.8)	2.99 (J = 6.1)	2.10 (J = 5.9)	4.08 (1H, m, CH); 1.94-1.45 (12H, m, $(CH_2)_6$ cycloheptane)

TABLE 3. Bond Lengths (*l*) in the *sec*-Butylamide **1h** Structure

Bond	*l*, Å	Bond	*l*, Å
N(1)–C(9)	1.377(2)	N(1)–C(1)	1.388(2)
N(1)–C(10)	1.477(2)	N(2)–C(13)	1.322(3)
N(2)–C(14B)	1.471(1)	N(2)–C(14A)	1.471(1)
O(1)–C(9)	1.241(2)	O(2)–C(7)	1.326(2)
O(3)–C(13)	1.268(2)	C(1)–C(2)	1.401(3)
C(1)–C(6)	1.409(2)	C(2)–C(3)	1.377(3)
C(2)–C(12)	1.494(3)	C(3)–C(4)	1.376(3)
C(4)–C(5)	1.364(3)	C(5)–C(6)	1.410(3)
C(6)–C(7)	1.434(3)	C(7)–C(8)	1.370(3)
C(8)–C(9)	1.451(3)	C(8)–C(13)	1.472(3)
C(10)–C(11)	1.464(3)	C(11)–C(12)	1.502(3)
C(14A)–C(16A)	1.540(1)	C(14A)–C(15A)	1.540(1)
C(16A)–C(17A)	1.540(1)	C(14B)–C(16B)	1.539(1)
C(14B)–C(15B)	1.539(1)	C(16B)–C(17B)	1.540(1)

TABLE 4. Valence Angles (ω) in the *sec*-Butylamide **1h** Structure

Angle	ω, deg	Angle	ω, deg
C(9)–N(1)–C(1)	123.6(2)	C(9)–N(1)–C(10)	116.4(2)
C(1)–N(1)–C(10)	120.0(2)	C(13)–N(2)–C(14B)	118.7(3)
C(13)–N(2)–C(14A)	128.4(4)	N(1)–C(1)–C(2)	120.8(2)
N(1)–C(1)–C(6)	119.3(2)	C(2)–C(1)–C(6)	120.0(2)
C(3)–C(2)–C(1)	117.7(2)	C(3)–C(2)–C(12)	121.3(2)
C(1)–C(2)–C(12)	121.0(2)	C(4)–C(3)–C(2)	123.2(2)
C(5)–C(4)–C(3)	119.7(2)	C(4)–C(5)–C(6)	119.8(2)
C(1)–C(6)–C(5)	119.7(2)	C(1)–C(6)–C(7)	118.5(2)
C(5)–C(6)–C(7)	121.8(2)	O(2)–C(7)–C(8)	122.4(2)
O(2)–C(7)–C(6)	116.5(2)	C(8)–C(7)–C(6)	121.1(2)
C(7)–C(8)–C(9)	120.1(2)	C(7)–C(8)–C(13)	118.5(2)
C(9)–C(8)–C(13)	121.4(2)	O(1)–C(9)–N(1)	119.2(2)
O(1)–C(9)–C(8)	123.4(2)	N(1)–C(9)–C(8)	117.4(2)
C(11)–C(10)–N(1)	111.7(2)	C(10)–C(11)–C(12)	113.1(2)
C(2)–C(12)–C(11)	111.1(2)	O(3)–C(13)–N(2)	121.2(2)
O(3)–C(13)–C(8)	119.8(2)	N(2)–C(13)–C(8)	119.0(2)
N(2)–C(14A)–C(16A)	105.0(5)	N(2)–C(14A)–C(15A)	114.7(7)
C(16A)–C(14A)–C(15A)	101.1(8)	C(14A)–C(16A)–C(17A)	112.1(6)
N(2)–C(14B)–C(16B)	102.9(4)	N(2)–C(14B)–C(15B)	114.4(5)
C(16B)–C(14B)–C(15B)	106.9(6)	C(14B)–C(16B)–C(17B)	110.3(7)

The tetrahydropyridine ring is found in a *sofa* conformation (folding parameters [10]: $S = 0.69$, $\Theta = 38.8$, $\Psi = 10.3^{\circ}$). The deviation of the C(11) atom from the mean square plane of the remaining ring atoms is -0.59 Å. An attractive interaction H(10a)···O(1) is found between the C(10)H_2 methylene group and the C(9)–O(1) carbonyl group (2.29 Å) (sum of van der Waal radii [11] 2.46 Å) which is not correctly to consider as an intramolecular hydrogen bond because of the acute C–H···O angle (101º).

The secondary butyl substituent at the N(2) atom is randomized in two positions (marked **A** and **B**) with equal population densities due to the rotation around the C(13)–N(2) and N(2)–C(14) bonds and is found in an antiperiplanar conformation relative to the C(8)–C(13) bond (torsional angle C(14)–N(2)–C(13)–C(8) 157.7(5)º in conformer **A** and -174.6(3)º in **B**). The methyl group in this substituent in conformer **A** exists in a -*ac*-conformation relative to the C(13)–N(2) bond but in **B** it is placed virtually perpendicularly to this bond

(torsional angle C(13)–N(2)–C(14)–C(15) -132.5(7)º in **A** and 81.7(6)º in **B**). The ethyl group is found in +*ac* and *ap*-conformations relative to the N(2)–C(13) bond in **A** and **B** respectively and is twisted relative to the N(2)–C(14) bond (torsional angles C(13)–N(2)–C(14)–C(16) 117.5(7)º in **A** and -162.8(5)º in **B**, N(2)–C(14)–C(16)–C(17) -54(1)º in **A** and 65.4(9)º in **B**). There also arise shortened intramolecular contacts H(17b)···N(2) 2.44 (2.67), H(17f)···N(2) 2.52 (2.67), and H(2Nb)···C(17b) 2.77 Å (2.87 Å).

In the crystal the molecules of the *sec*-butylamide **1h** form dimers, the molecules of which are placed head to tail with a distance between the planes of the quinolone fragments of 3.6 Å. This allows us to propose the existence of stacking interactions in the dimers.

A comparative analysis of the X-ray structural data for the *sec*-butylamide **1h** and its direct analog 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid *sec*-butylamide [8] shows that expansion of the ring annelated to the quinoline does bring about an arrangement of the molecule. In particular, by contrast with the completely planar pyrroloquinolone system, the tetrahydropyridine ring in the pyridoquinolone **1h** takes on a clear *sofa* type conformation. However, despite these differences in the steric structure of the two homologs, the remaining parameters remain virtually identical. It is of interest that the crystal packing of the *sec*-butylamide **1h** and its pyrroloquinolone analog are remarkably similar.

The pharmacological properties of the 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo- and 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acids alkylamides are also very similar, at least as regards their effect on the diuretic function of the kidney.

Studies were carried out on white, nonpedigree rats of weight 180-200 g by a standard method [12]. Furosemide [13] was used as the standard comparator. The investigated compounds were introduced orally in a dose of 25 mg/kg (the effective dose for furosemide) and diuresis was measured after 2 h. The structure – biological activity relationship found showed an almost identical absence of activity and even an antidiuretic effect in compounds with open alkyl chains in the amide fragments. The diuretic properties increased with a change to some of the cyclic derivatives (see Table 1).

EXERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Bruker WM-360 instrument (360 MHz) for solutions in DMSO-d_6 and with TMS as internal standard. Commercial 1,2,3,4-tetrahydroquinoline and triethylmethane tricarboxylate used in the synthesis of ethyl ester **2** were obtained from the Aldrich company.

1-Hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylic acid alkylamides **1a-q** were prepared by the methods reported in [8].

Ethyl 1-Hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylate (2). A mixture of triethylmethane tricarboxylate (**4**) (46.4 g, 0.2 mol) and diphenyl ether (100 ml) was heated to 215ºC and 1,2,3,4-tetrahydroquinoline (**3**) (25 ml, 0.2 mol) was added dropwise with stirring at such a rate that the reaction mixture temperature stayed within the limits of 215 ± 5ºC. The ethanol formed in the process was distilled off. After addition of all of the 1,2,3,4-tetrahydroquinoline the mixture was held for 20 min at 220ºC to complete the reaction. The product was cooled and diluted with a solution of Na_2CO_3 (30 g) in water (500 ml), vigorously stirred, and transferred to a separating funnel. After phase separation the aqueous layer was poured off and the extraction was repeated twice more (5 g Na_2CO_3 in 200 ml water). The solutions of the sodium salt of ester **2** obtained were combined, purified through carbon, and filtered, The filtrate was acidified with dilute (1:1) HCl to pH 4.5-5.0. The precipitated ester **2** was filtered, washed with cold water, and dried. Yield 51.9 g (95%); mp 102-104ºC (hexane). A mixed sample with a sample of ester **2** [7] did not give a depression of melting point and their ^{1}H NMR spectra were found to be identical.

X-ray Structural Analysis. Crystals of the *sec*-butylamide **1h** are triclinic (ethanol). At 20ºC: a = 6.938(5), b = 8.677(5), c = 13.257(5) Å, α = 101.335(5)º, β = 97.258(5)º, γ = 97.795(5)º, V = 765.6(8) Å^3, M_r = 300.35, Z = 2, space group $P\bar{1}$, d_{calc} = 1.303 g/cm^3, μ(MoKα) = 0.090 mm^{-1}, F(000) = 320. The unit cell parameters and intensities of 5947 reflections (2649 independent, R_{int} = 0.032) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 50º).

The structure was solved by the direct method using the *SHELXTL* program package [14]. For refinement of the structure, limits were placed on the bond lengths in the randomized fragment for N–C_{sp3} of 1.47(1) and C_{sp3}–C_{sp3} 1.54(1) Å. The positions of the hydrogen atoms were revealed by electron density difference synthesis and for the randomized part calculated geometrically and refined using the "riding" model with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bound to the given hydrogen (n = 1.5 for a methyl and hydroxyl group and n = 1.2 for remaining hydrogen atoms). The structure was refined using F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.090 for 2589 reflections (R_1 = 0.043 for 1095 reflections with $F > 4\sigma$ (F), S = 0.760). The complete crystallographic information has been placed in the Cambridge structural data bank (reference CCDC 801475). Interatomic distances and valence angles are given in Tables 3 and 4 respectively.

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