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4-HYDROXY-2-QUINOLONES. 110*. BROMINATION OF 1-R-4-HYDROXY-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACID ANILIDES

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1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilides have been prepared. It has been shown experimentally that these compounds are brominated by molecular bromine in glacial acetic acid at position 4 of the anilide fragment. The antitubercular properties of the compounds synthesized are discussed.

Keywords: 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid amides, bromination, X-ray analysis, antitubercular activity.

1-R-4-Hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilides possess a broad spectrum of biological activity. They include substances with antithyroid [2], antitubercular [3, 4], analgesic, anti-inflammatory [5], and antioxidant properties [6]. In medicine, the antineoplastic linomide (roquinimex, 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid N-methylanilide [7]) is used. Many investigation of the modification of the structure of this medicinal compound have revealed potential compounds with antinephritic [8] and anti-angiogenic [9, 10] properties in a given series as well as novel synthetic immunomodulators [11].

In this report we continue our work studying the physicochemical and biological properties of 4-hydroxyquinol-2-ones and have investigated 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilides **1** and their 4-bromo-substituted analogs **2**. The target compounds (Tables 1-3) were prepared by amidation of the ethyl esters **3** with aniline and 4-bromoaniline respectively according to a previously developed method [12].

It is known that 3-alkyl-, 3-phenyl-, and 3-alkoxycarbonyl-substituted 4-hydroxy-2-oxo-1,2-dihydroquinolines (including N-phenyl) are brominated by molecular bromine in glacial acetic acid at position 3 to give 3-bromo-3-R-2,4-dioxo-1,2,3,4-tetrahydroquinolines [13, 14].

However, we later showed that with completely anhydrous solvents and reagents the indicated reaction occurs differently with electrophilic attack exclusively at position 6 of the quinolone [15]. With the anilides **1** a still further possible center for halogenation occurs (the phenylamide ring).

* For Communication 109 see [1].

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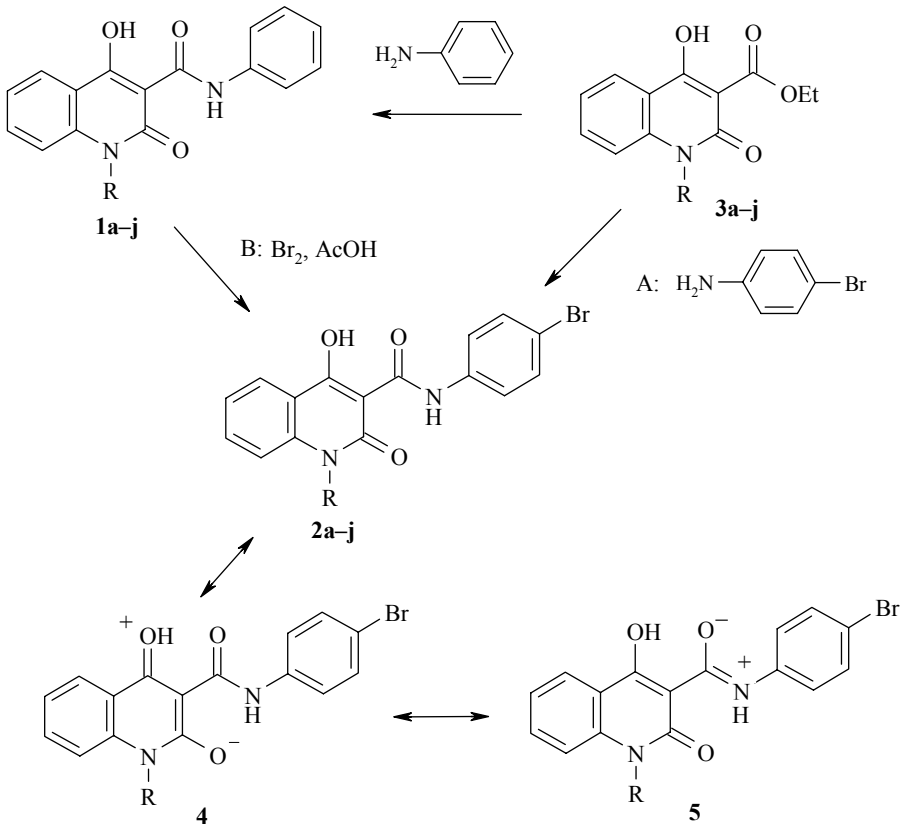
Scheme 1



1-3 a R = H, **b** R = Me, **c** R = Et, **d** R = $CH_2CH{=}CH_2$, **e** R = Pr, **f** R = Bu, **g** R = *i*-Bu, **h** R = C_5H_{11}, **i** R = *i*-C_5H_{11}, **j** R = C_6H_{13}

This situation also predetermined the subsequent investigation carried out on the N-methyl derivative **1b**. It was found that bromination of the compound occurs readily. With the aim of unambiguously determining the route for this reaction the sample was subjected to X-ray analysis (Fig. 1, Tables 4 and 5) which showed that bromination of the anilides **1** occurs not in the heterocyclic part of the molecule but at position 4 of the anilide fragment and this was confirmed using ^{1}H NMR spectroscopy.

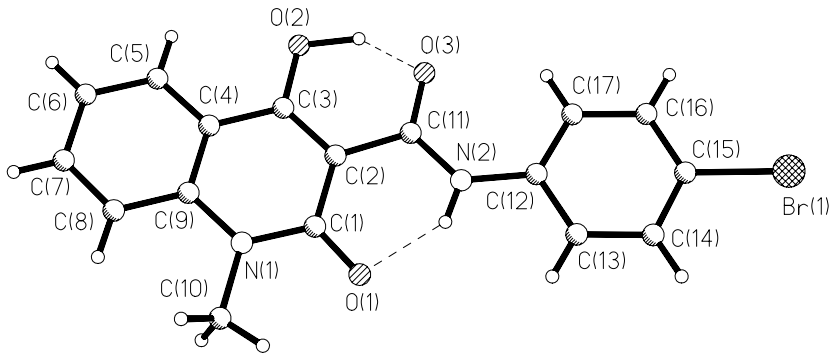


Fig. 1. Structure of the 4-bromoanilide **2b** molecule with atomic numbering. The dashed lines indicate intramolecular hydrogen bonds.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	mp, °C (DMF)	Found, % / Calculated, %			Yield, %	Inhibition of *Mycobacterium tuberculosis* growth at c = 6.25 μg/ml, %
			C	H	N		
1a	$C_{16}H_{12}N_2O_3$	298-303	68.45 / 68.57	4.39 / 4.32	9.91 / 9.99	98	0
1b	$C_{17}H_{14}N_2O_3$	196-198	69.50 / 69.38	4.87 / 4.79	9.44 / 9.52	91	0
1c	$C_{18}H_{16}N_2O_3$	169-171	70.23 / 70.12	5.35 / 5.23	9.16 / 9.09	90	0
1d	$C_{19}H_{16}N_2O_3$	161-163	71.15 / 71.24	5.16 / 5.03	8.66 / 8.74	91	0
1e	$C_{19}H_{18}N_2O_3$	142-144	70.90 / 70.79	5.77 / 5.63	8.78 / 8.69	93	0
1f	$C_{20}H_{20}N_2O_3$	138-140	71.34 / 71.41	5.90 / 5.99	8.39 / 8.33	88	85
1g	$C_{20}H_{20}N_2O_3$	130-132	71.32 / 71.41	5.87 / 5.99	8.42 / 8.33	90	89
1h	$C_{21}H_{22}N_2O_3$	123-125	71.91 / 71.98	6.45 / 6.33	7.93 / 7.99	86	81
1i	$C_{21}H_{22}N_2O_3$	115-117	71.86 / 71.98	6.40 / 6.33	7.88 / 7.99	83	100
1j	$C_{22}H_{24}N_2O_3$	104-106	72.62 / 72.51	6.77 / 6.64	7.56 / 7.69	85	87
2a	$C_{16}H_{11}BrN_2O_3$	321-323	53.59 / 53.50	3.14 / 3.09	7.86 / 7.80	91	9
2b	$C_{17}H_{13}BrN_2O_3$	210-212	54.82 / 54.71	3.59 / 3.51	7.44 / 7.51	94	23
2c	$C_{18}H_{15}BrN_2O_3$	184-186	55.76 / 55.83	3.98 / 3.90	7.35 / 7.23	92	57
2d	$C_{19}H_{15}BrN_2O_3$	173-175	57.07 / 57.16	3.67 / 3.79	7.00 / 7.02	90	48
2e	$C_{19}H_{17}BrN_2O_3$	197-199	56.96 / 56.87	4.37 / 4.27	6.87 / 6.98	90	32
2f	$C_{20}H_{19}BrN_2O_3$	170-172	57.95 / 57.84	4.54 / 4.61	6.88 / 6.75	89	57
2g	$C_{20}H_{19}BrN_2O_3$	156-158	57.90 / 57.84	4.50 / 4.61	6.67 / 6.75	91	64
2h	$C_{21}H_{21}BrN_2O_3$	129-131	58.68 / 58.75	4.98 / 4.93	6.45 / 6.53	87	75
2i	$C_{21}H_{21}BrN_2O_3$	120-122	58.83 / 58.75	4.85 / 4.93	6.44 / 6.53	84	79
2j	$C_{22}H_{23}BrN_2O_3$	114-116	59.71 / 59.60	5.14 / 5.23	6.38 / 6.32	88	58

All of the synthesized compounds are colorless crystalline materials, virtually insoluble in water and with sharp melting points (Table 1). The functional groups present in their structure were readily identified from the corresponding signal in their ^{1}H NMR spectra (Tables 2 and 3).

The 4-bromoanilide **2b** is virtually planar. Deviations from the mean square plane taken through all of the non hydrogen atoms did not exceed 0.07 Å. This is due to the formation of strong intramolecular hydrogen bonds as $O_{(2)}$–$H_{(2O)}$···$O_{(3)}$ 1.41 (angle O–H···O 146.0°) and $N_{(2)}$–$H_{(2N)}$···$O_{(1)}$ 1.87 Å (N–H···O 143.2°), the presence of which leads to a marked change in the geometry of the amidopyridone fragment.

The $O_{(3)}$–$C_{(11)}$ 1.249(6), $O_{(1)}$–$C_{(1)}$ 1.235(6), $C_{(2)}$–$C_{(3)}$ 1.386(7), $C_{(2)}$–$C_{(1)}$ 1.477(6), and $N_{(1)}$–$C_{(1)}$ 1.370(6) Å bonds are somewhat longer than the mean values [16] 1.211, 1.343, 1.460, and 1.355 Å respectively but the $O_{(2)}$–$C_{(3)}$ 1.329(6), $C_{(1)}$–$C_{(2)}$ 1.447(7), $C_{(3)}$–$C_{(4)}$ 1.431(6) and $N_{(2)}$–$C_{(11)}$ 1.335(6) Å were shortened compared with mean values of 1.363, 1.470, 1.455, and 1.355 Å respectively. It follows from this that the structure of the 4-bromoanilide **2b** is characterized by a significant contribution of the bipolar resonance structures **4** and **5** (see Scheme 1).

TABLE 2. ^{1}H NMR Spectra of Compounds **1a-j**

Compound	Chemical shifts, δ, ppm (*J*, Hz)*					
	H arom.					R
	H-5 (1H, d)	H-7 (1H, t)	H-8,2',6' (3H, m)	H-3',4',5' (3H, m)	H-6 (1H, t)	
1a	8.18 (8.0)	7.89 (7.9)	7.70	7.43	7.20 (7.4)	11.86 (1H, s, NH)
1b	8.11 (7.9)	7.83 (7.9)	7.65	7.39	7.18 (7.4)	3.66 (3H, s, CH_3)
1c	8.12 (8.0)	7.80 (7.9)	7.64	7.38	7.16 (7.4)	4.31 (2H, q, *J* = 7.3, NCH_2); 1.25 (3H, t, *J* = 7.1, CH_3)
1d	8.12 (8.1)	7.78 (8.0)	7.60	7.39	7.17 (7.4)	5.96 (1H, m, $NCH_2C\underline{H}$); 5.15 (1H, d, *J* = 10.5, H_{cis} in $=CH_2$); 5.09 (1H, d, *J* = 12.7, H_{trans} in $=CH_2$); 4.96 (2H, d, *J* = 4.4, NCH_2)
1e	8.10 (8.0)	7.81 (7.8)	7.63	7.38	7.16 (7.4)	4.22 (2H, t, *J* = 7.4, NCH_2); 1.62 (2H, m, $NCH_2C\underline{H}_2$); 0.97 (3H, t, *J* = 7.3, CH_3)
1f	8.09 (7.8)	7.80 (7.8)	7.64	7.38	7.16 (7.3)	4.24 (2H, t, *J* = 7.5, NCH_2); 1.59 (2H, q, *J* = 7.1, $NCH_2C\underline{H}_2$); 1.40 (2H, m, $C\underline{H}_2CH_3$); 0.92 (3H, t, *J* = 7.1, CH_3)
1g	8.11 (7.9)	7.83 (7.8)	7.63	7.39	7.18 (7.4)	4.19 (2H, d, *J* = 7.3, NCH_2); 2.16 (1H, m, CH); 0.92 (6H, d, *J* = 6.8, $2CH_3$)
1h	8.12 (8.0)	7.83 (7.9)	7.66	7.39	7.17 (7.3)	4.26 (2H, t, *J* = 7.5, NCH_2); 1.63 (2H, q, *J* = 6.9, $NCH_2C\underline{H}_2$); 1.36 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.87 (3H, t, *J* = 6.8, CH_3)
1i	8.08 (8.0)	7.81 (7.8)	7.60	7.37	7.16 (7.4)	4.24 (2H, t, *J* = 7.6, NCH_2); 1.72 (1H, m, CH); 1.48 (2H, q, *J* = 6.7, $NCH_2C\underline{H}_2$); 0.96 (6H, d, *J* = 6.7, $2CH_3$)
1j	8.09 (8.0)	7.82 (7.8)	7.64	7.38	7.16 (7.4)	4.23 (2H, t, *J* = 7.0, NCH_2); 1.60 (2H, q, *J* = 6.9, $NCH_2C\underline{H}_2$); 1.41-1.23 (6H, m, $(C\underline{H}_2)_3CH_3$); 0.86 (3H, t, *J* = 6.7, CH_3)

* The signals for the 4-OH protons and anilide NH groups appear as singlets in the regions 16.59-16.35 and 12.68-12.61 ppm respectively.

The antitubercular properties of the anilides **1** and their 4-bromo substituted analogs **2** were studied through the TAACF (Tuberculosis Antimicrobial Acquisition and Coordinating Facility). In the investigations the BACTEC 12B and radiometric system BACTEC 460 were used [17-20]. Analysis of the results of the primary microbiological screening (Table 1) shows that the anilides with the smaller N-alkyl substituents in the quinolone ring **1a-e** were ineffective against *Mycobacterium tuberculosis H37Rv* ATCC 27294 whereas the N-butyl, amyl, and hexyl derivatives were able to suppress the growth of the test strain by 81-100%. The minimum inhibitory concentration of the most active of these anilides **1i** was 1.56 μg/ml. The introduction of a bromine atom at position 4 of the anilide residue markedly increased the antitubercular activity of the compounds with the smaller alkyl substituents. However, such a modification led to a significant decrease in the antimicrobial activity of the remaining compounds. It should be noted that in the cases of the anilides **1f-i** and the 4-bromo analogs **2f-i** the substances with N-isoalkyl chains were somewhat more active that those with a normal chain structure.

TABLE 3. ^{1}H NMR Spectra of Compounds **1a-j**

Compound	Chemical shifts, δ, ppm (*J*, Hz)*					
	H arom.					R
	H-5 (1H, d)	H-7 (1H, t)	H-8,3',5' (3H, m)	H-2',6' (2H, d)	H-6 (1H, t)	
2a	8.19 (8.0)	7.86 (7.5)	7.74-7.68	7.57 (8.9)	7.42 (7.4)	11.90 (1H, s, NH)
2b	8.13 (8.0)	7.82 (7.9)	7.73-7.66	7.55 (9.0)	7.39 (7.3)	3.68 (3H, s, CH_3)
2c	8.14 (8.1)	7.84 (7.4)	7.71-7.65	7.56 (8.9)	7.40 (7.4)	4.34 (2H, q, *J* = 7.3, NCH_2); 1.24 (3H, t, *J* = 7.0, CH_3)
2d	8.13 (8.0)	7.80 (7.7)	7.68-7.59	7.45 (9.0)	7.38 (7.5)	5.56 (1H, m, $NCH_2C\underline{H}$); 4.75 (1H, d, *J* = 10.7, H_{cis} in $=CH_2$); 4.69 (1H, d, *J* = 13.2, H_{trans} in $=CH_2$); 4.55 (2H, d, *J* = 4.5, NCH_2)
2e	8.12 (8.0)	7.83 (7.7)	7.74-7.61	7.55 (8.9)	7.37 (7.3)	4.23 (2H, t, *J* = 7.4, NCH_2); 1.64 (2H, m, $NCH_2C\underline{H}_2$); 0.96 (3H, t, *J* = 7.3, CH_3)
2f	8.11 (8.1)	7.82 (7.6)	7.70-7.59	7.54 (8.9)	7.38 (7.4)	4.27 (2H, t, *J* = 7.2, NCH_2); 1.61 (2H, q, *J* = 7.0, $NCH_2C\underline{H}_2$); 1.42 (2H, m, $C\underline{H}_2CH_3$); 0.94 (3H, t, *J* = 7.2, CH_3)
2g	8.12 (7.9)	7.81 (7.5)	7.73-7.60	7.55 (8.9)	7.38 (7.4)	4.18 (2H, d, *J* = 7.3, NCH_2); 2.14 (1H, m, CH); 0.90 (6H, d, *J* = 6.7, $2CH_3$)
2h	8.10 (7.9)	7.80 (7.6)	7.72-7.61	7.54 (8.9)	7.37 (7.4)	4.23 (2H, t, *J* = 7.4, NCH_2); 1.66 (2H, q, *J* = 7.0, $NCH_2C\underline{H}_2$); 1.38 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.90 (3H, t, *J* = 6.9, CH_3)
2i	8.11 (8.0)	7.82 (7.7)	7.70-7.62	7.54 (8.9)	7.38 (7.4)	4.22 (2H, t, *J* = 7.7, NCH_2); 1.70 (1H, m, CH); 1.46 (2H, q, *J* = 6.9, $NCH_2C\underline{H}_2$); 0.94 (6H, d, *J* = 6.8, $2CH_3$)
2j	8.10 (8.0)	7.81 (7.7)	7.70-7.58	7.55 (8.9)	7.37 (7.5)	4.24 (2H, t, *J* = 6.9, NCH_2); 1.61 (2H, q, *J* = 6.9, $NCH_2C\underline{H}_2$); 1.44-1.22 (6H, m, $(C\underline{H}_2)_3CH_3$); 0.85 (3H, t, *J* = 6.6, CH_3)

* The signals for the 4-OH protons and anilide NH groups appear as singlets in the regions 16.41-16.29 and 12.76-12.69 ppm respectively.

TABLE 4. Bond Lengths (*l*) in the 4-Bromoanilide Structure **2b**

Bond	*l*, Å	Bond	*l*, Å
$Br_{(1)}$–$C_{(15)}$	1.902(4)	$N_{(1)}$–$C_{(1)}$	1.370(6)
$N_{(1)}$–$C_{(9)}$	1.395(6)	$N_{(1)}$–$C_{(10)}$	1.461(6)
$N_{(2)}$–$C_{(11)}$	1.335(6)	$N_{(2)}$–$C_{(12)}$	1.403(6)
$O_{(1)}$–$C_{(1)}$	1.235(6)	$O_{(2)}$–$C_{(3)}$	1.329(6)
$O_{(3)}$–$C_{(11)}$	1.249(6)	$C_{(1)}$–$C_{(2)}$	1.447(7)
$C_{(2)}$–$C_{(3)}$	1.386(7)	$C_{(2)}$–$C_{(11)}$	1.477(6)
$C_{(3)}$–$C_{(4)}$	1.431(6)	$C_{(4)}$–$C_{(5)}$	1.393(7)
$C_{(4)}$–$C_{(9)}$	1.394(7)	$C_{(5)}$–$C_{(6)}$	1.372(7)
$C_{(6)}$–$C_{(7)}$	1.379(8)	$C_{(7)}$–$C_{(8)}$	1.370(8)
$C_{(8)}$–$C_{(9)}$	1.397(6)	$C_{(12)}$–$C_{(13)}$	1.385(7)
$C_{(12)}$–$C_{(17)}$	1.392(7)	$C_{(13)}$–$C_{(14)}$	1.393(6)
$C_{(14)}$–$C_{(15)}$	1.384(7)	$C_{(15)}$–$C_{(16)}$	1.362(7)
$C_{(16)}$–$C_{(17)}$	1.386(7)		

TABLE 5. Valence Angles (ω) in the 4-Bromoanilide Structure **2b**

Angle	ω, deg	Angle	ω, deg.
$C_{(1)}$–$N_{(1)}$–$C_{(9)}$	123.1(4)	$C_{(1)}$–$N_{(1)}$–$C_{(10)}$	117.7(4)
$C_{(9)}$–$N_{(1)}$–$C_{(10)}$	119.2(4)	$C_{(11)}$–$N_{(2)}$–$C_{(12)}$	130.5(4)
$O_{(1)}$–$C_{(1)}$–$N_{(1)}$	118.6(4)	$O_{(1)}$–$C_{(1)}$–$C_{(2)}$	123.1(4)
$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	118.2(4)	$C_{(3)}$–$C_{(2)}$–$C_{(1)}$	119.3(4)
$C_{(3)}$–$C_{(2)}$–$C_{(11)}$	118.3(4)	$C_{(1)}$–$C_{(2)}$–$C_{(11)}$	122.4(4)
$O_{(2)}$–$C_{(3)}$–$C_{(2)}$	122.0(4)	$O_{(2)}$–$C_{(3)}$–$C_{(4)}$	117.1(4)
$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	120.9(4)	$C_{(5)}$–$C_{(4)}$–$C_{(9)}$	119.3(4)
$C_{(5)}$–$C_{(4)}$–$C_{(3)}$	121.7(4)	$C_{(9)}$–$C_{(4)}$–$C_{(3)}$	119.0(4)
$C_{(6)}$–$C_{(5)}$–$C_{(4)}$	121.1(5)	$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	119.0(5)
$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	121.4(5)	$C_{(7)}$–$C_{(8)}$–$C_{(9)}$	119.9(5)
$C_{(4)}$–$C_{(9)}$–$N_{(1)}$	119.4(4)	$C_{(4)}$–$C_{(9)}$–$C_{(8)}$	119.2(5)
$N_{(1)}$–$C_{(9)}$–$C_{(8)}$	121.4(4)	$O_{(3)}$–$C_{(11)}$–$N_{(2)}$	123.1(4)
$O_{(3)}$–$C_{(11)}$–$C_{(2)}$	120.1(4)	$N_{(2)}$–$C_{(11)}$–$C_{(2)}$	116.8(4)
$C_{(13)}$–$C_{(12)}$–$C_{(17)}$	119.0(4)	$C_{(13)}$–$C_{(12)}$–$N_{(2)}$	116.3(4)
$C_{(17)}$–$C_{(12)}$–$N_{(2)}$	124.7(5)	$C_{(12)}$–$C_{(13)}$–$C_{(14)}$	121.8(4)
$C_{(15)}$–$C_{(14)}$–$C_{(13)}$	117.1(5)	$C_{(16)}$–$C_{(15)}$–$C_{(14)}$	122.5(4)
$C_{(16)}$–$C_{(15)}$–$Br_{(1)}$	119.0(3)	$C_{(14)}$–$C_{(15)}$–$Br_{(1)}$	118.5(4)
$C_{(15)}$–$C_{(16)}$–$C_{(17)}$	119.8(4)	$C_{(16)}$–$C_{(17)}$–$C_{(12)}$	119.8(5)

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Mercury VX-200 (200 MHz) instrument using DMSO-d_6 and TMS as internal standard. Ethyl 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**3**) was prepared as in the reported method [21].

4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 4-Bromoanilide (2b). A. A mixture of ethyl 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylate (**3b**) (2.47 g, 0.01 mol), 4-bromoaniline (1.72 g, 0.01 mol), and DMF (1 ml) was stirred for 2-3 min at 170°C. The reagents dissolved and almost immediately ethanol began to separate and the final anilide crystallized out. Ethanol (20 ml) was added to the still warm reaction product and thoroughly stirred. After cooling, the precipitated 4-bromoanilide **2b** was filtered off, washed with alcohol, and dried. Yield 3.51 g (94%).

The remaining anilides **1** and **2** (Table 1) were prepared by a similar method.

B. Bromine (0.52 ml, 0.01 mol) was added with stirring to a solution of 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilide (**1b**) (2.94 g, 0.01 mol) in glacial acetic acid (50 ml). The product was left for 1 h at room temperature, diluted with water, and the precipitated 4-bromoanilide **2b** was filtered off washed with water, and dried. Yield 3.06 g (82%). A mixed sample with one prepared by method A did not give a depression of melting point. Their ^{1}H NMR spectra were identical.

X-ray Analysis. Crystals of the 4-bromoanilide **2b** were obtained from DMF and are triclinic. At 20°C: a = 7.993(5), b = 9.481(5), c = 10.058(6) Å; α = 90.04(2), β = 91.15(2), γ = 103.46(2)°; V = 741.1(8) Å^3; d_{calc} = 1.672 g/cm^3; space group $P\bar{1}$; Z = 2. Unit cell parameters and intensities of 2457 independent reflections (R_{int} = 0.07) were measured on a Siemens P3/PC, four circle automatic diffractometer (λMoKα, graphite monochromator, θ/2θ-scanning to $2\theta_{max}$ = 50°). Absorption was included semiempirically for Ψ scanning (T_{min} = 0.447, T_{max} = 0.974).

The structure was solved by a direct method using the SHELX97 program package [22]. The positions of the hydrogen atoms were calculated from electron density difference synthesis and refined using the "riding" method with fixed $U_{iso} = nU_{eq}$ for a non-hydrogen atom bonded to the given hydrogen (n = 1.5 for methyl groups and 1.2 for the remaining hydrogen atoms). Refinement for F^2 full-matrix least-squares analysis in the

anisotropic approximation for 2457 reflections for non-hydrogen atoms were taken to $wR2 = 0.118$ ($R_1 = 0.049$ for 1505 reflections with $F > 4\sigma(F)$, $S = 0.97$). Full crystallographic data has been deposited with the Cambridge structural database (deposit CCDC 283294).

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REFERENCES

1. I. V. Ukrainets, L. V. Sidorenko, O. V. Gorokhova, N. L. Bereznyakova, and S. V. Shishkina, *Khim. Geterotsikl. Soedin.*, 1502 (2006). [*Chem. Heterocycl. Comp.*, **42**, 1296 (2006)].
2. I. V. Ukrainets, S. G. Taran, P. A. Bezuglyi, S. N. Kovalenko, A. V. Turov, and N. A. Marusenko, *Khim. Geterotsikl. Soedin.*, 1223 (1993). [*Chem. Heterocycl. Comp.*, **29**, 1044 (1993)].
3. I. V. Ukrainets, A. Kh. N. Dakkakh, S. G. Taran, O. V. Gorokhova, L. V. Sidorenko, and S. G. Leonova, *Physiologically Active Substances* [in Russian], No. 1 (29), 18 (2000).
4. I. V. Ukrainets. A. Kh. N. Dakkakh, P. A. Bezuglyi, O. V. Gorokhova, L. V. Sidorenko, and T. V. Alekseeva, *Vestnik Farmatsii*, No. 1 (25), 9 (2001).
5. I. V. Ukrainets, E. A. Taran, O. I. Naboka, and I. V. Senyuk, *Vestnik Farmatsii*, No 4 (28), 16 (2001).
6. I. V. Ukrainets, E. A. Taran, L. N. Voronina, and O. I. Naboka, *Farm. Zh.*, No. 6, 48 (2001).
7. E. Eriksoo, E. B. M. Sandberg, and L. J. T. Stalhandske, US Patent 4738971 (1988). http://ep.espacenet.com.
8. K. Tsuji, G. W. Spears, K. Nakamura, T. Tojo, N. Seki, A. Sugiyama, and M. Matsuo, *Bioorg. Med. Chem. Lett.*, **12**, 85 (2002).
9. S. R. Khan, A. Mhaka, R. Pili, and J. T. Isaacs, *Bioorg. Med. Chem. Lett.*, **11**, 451 (2001).
10. J. Shi, Z Xiao, M. A. Ihnat, C. Kamat, B. Pandit, Z. Hu. and P. Li, *Bioorg. Med. Chem. Lett.*, **13**, 1187 (2003).
11. S. Jönsson. G. Andersson, T. Fex, T. Fristedt, G. Hedlund, K. Jansson, L. Abramo, I. Fritzson. O. Pekarski, A. Runström, H. Sandin, I. Thuvesson, and A. Björk, *J. Med. Chem.*, **47**, 2075 (2004).
12. I. V. Ukrainets, S. G. Taran, O. V. Gorokhova, E. A. Taran, N. A. Jaradat, and I. Yu. Petukhova, *Khim. Geterotsikl. Soedin.*, 203 (2000). [*Chem. Heterocycl. Comp.*, **36**, 166 (2000)].
13. I. V. Ukrainets, S. G. Taran O. A. Evtifeeva, O. V. Gorokhova, N. I. Filimonova, and A. V. Turov, *Khim. Geterotsikl. Soedin.*, 204 (1995). [*Chem. Heterocycl. Comp.*, **31**, 176 (1995)].
14. W. Stadlbauer, R. Laschober, H. Lutschounig, G. Schindler, and T. Kappe, *Monats. Chem.*, **123**, 617 (1992).
15. I. V. Ukrainets, L. A. Petrushova, L. V. Sidorenko, V. B. Rybakov, and V. V. Chernyshev, *Zh. Org. Farm. Khim.*, **2**, issue 3(7), 26 (2004).
16. H.-B. Burgi and J. D. Dunitz, *Struct. Correl.*, Vol. 4. VCH, Weinheim (1994), p. 741.
17. L. Collins and S. G. Franzblau, *Antimicrob. Agents Chemother.*, **41**, 1004 (1997).
18. S. H. Siddiqui in: H. D. Isenberg (editor), *Clinical Microbiological Procedures Handbook*, Vol. 1, American Society for Microbiology, Washington D.C. (1992), p. 5.14.2.
19. L. B. Heifets in L. B. Heifets (editor), *Chemistry of Mycobacterial Infections*, CRC Press, Boca Raton (1991), p. 89.
20. C. B. Inderleid and K. A. Nash in: V. Lorian (editor), *Antibiotics in Laboratory Medicine*, Williams and Wilkins, Baltimore (1996), p. 127.
21. I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezuglyi, A. V. Turov, N. A. Marusenko, and O. A. Evtifeeva, *Khim. Geterotsikl. Soedin.*, 958 (1994). [*Chem. Heterocycl. Comp.*, **30**, 829 (1994)].
22. G. M. Sheldrick, *SHELX97. PC Version. A System of Computer Programs for Crystal Structure Solution and Refinement*, Revision 2 (1998).