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4-HYDROXY-2-QUINOLONES. 201*. SYNTHESIS, STRUCTURE, AND DIURETIC ACTIVITY OF HYDROXY- AND ALKOXY-ANILIDES OF 6-HYDROXY-2-METHYL-4-OXO-2,4-DIHYDRO-1*H*-PYRROLO[3,2,1-*ij*]QUINOLINE-5-CARBOXYLIC ACID

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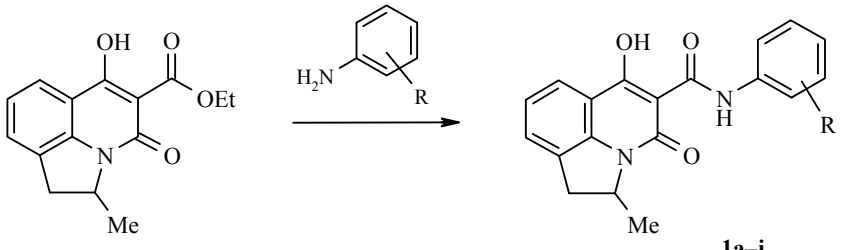
Hydroxy- and alkoxyanilides of 6-hydroxy-2-methyl-4-oxo-2,4-dihydro-1H-pyrrolo[3,2,1-ij]quinoline-5-carboxylic acids have been synthesized as potential diuretic agents. Features of their purification, their steric structure, and biological activity are discussed.

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

A comparative analysis of the effect of halo-substituted anilides of 6-hydroxy-4-oxo-2,4-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acids on the urinary function of the kidney has shown that methylation of the pyrroline ring at position 2 leads to an increased diuretic effect. As a method for improving the pharmacological properties of this class of compounds, it deserves more detailed attention [2]. The most promising substance or structural leader in the group of unmethylated derivatives was found to be the 6-hydroxy-4-oxo-2,4-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid 4-methoxyanilide [3]. Hence it was quite logical that the next step in our study should be examination of the corresponding alkoxy- and hydroxyanilides of 6-hydroxy-2-methyl-4-oxo-2,4-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic acid **1a-j**.



2 **1a–j**

1a R = 2-OH; **b** R = 3-OH; **c** R = 4-OH; **d** R = 2-OMe; **e** R = 3-OMe; **f** R = 4-OMe; **g** R = 2-Me-4-OMe; **h** R = 4-OEt; **i** R = 4-OPr; **j** R = 4-OC_6H_{13}

* For Communication 200, see [1].

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TABLE 1. Characteristics of Anilides **1a-j**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (DMF–EtOH)	Yield, %	Diuretic activity, %*
		C	H	N			
1a	$C_{19}H_{16}N_2O_4$	67.96 / 67.85	4.92 / 4.79	8.24 / 8.33	278–280	76	- 12
1b	$C_{19}H_{16}N_2O_4$	67.93 / 67.85	4.88 / 4.79	8.40 / 8.33	213–215	84	- 28
1c	$C_{19}H_{16}N_2O_4$	67.81 / 67.85	4.84 / 4.79	8.29 / 8.33	202–204	87	- 19
1d	$C_{20}H_{18}N_2O_4$	68.43 / 68.56	5.07 / 5.18	7.91 / 8.00	169–171	71	- 58
1e	$C_{20}H_{18}N_2O_4$	68.65 / 68.56	5.14 / 5.18	7.96 / 8.00	167–169	89	+ 3
1f	$C_{20}H_{18}N_2O_4$	68.47 / 68.56	5.23 / 5.18	8.07 / 8.00	163–165	92	+ 68
1g	$C_{21}H_{20}N_2O_4$	69.10 / 69.22	5.42 / 5.53	7.58 / 7.69	172–174	73	- 7
1h	$C_{21}H_{20}N_2O_4$	69.26 / 69.22	5.50 / 5.53	7.74 / 7.69	181–183	94	+ 6
1i	$C_{22}H_{22}N_2O_4$	69.92 / 69.83	5.95 / 5.86	7.51 / 7.40	135–137	90	+ 29
1j	$C_{25}H_{28}N_2O_4$	71.49 / 71.41	6.80 / 6.71	6.57 / 6.66	84–86	82	+ 26
	Hydrochlorothiazide						+ 59

* "+" indicates increase and "-" inhibition of diuresis when compared with the control taken as 100%.

The objects of this study were prepared by the reaction of ethyl ester **2** with the corresponding anilines at about 140ºC in the presence of a small amount of DMF. The syntheses occurred smoothly and generally in good yields (see Table 1). Problems, however, sometimes emerged at the time of purification. Thus, upon the addition to solutions of the substances synthesized in hot DMF (needed because of the poor solubility of anilides **1a-j** in most other organic solvents) of activated carbon, we often observed the appearance of a deep-blue coloration which was virtually impossible to remove subsequently. Neither the DMF itself nor other starting reagents dissolved in it showed similar properties.

It is unlikely that the reason for this phenomenon is the tendency for 4-hydroxyquinolones (including tricyclic) of anilide type **1** to form stable and frequently colored complexes with the cations of many heavy metals [4]. In this case a similar effect might be observed when working with the majority of quinoline carboxamides (if not all of the family) and this is not consistent with the facts. Moreover, purification by recrystallization from another solvent and then solution of such a compound in DMF no longer gave colored products upon addition of the carbon. Hence the source of the problem lies not in the quinoline carboxamides themselves but in admixtures formed in the process of side reactions which then, in the presence of activated carbon, form extremely intense dyes with DMF, which can give strongly colored solutions, even in low concentrations. We have already observed a similar effect in our work with other 2-quinolone derivatives [5, 6].

In order to overcome this drawback, one should initially test a small sample of quinoline carboxamide in boiling DMF with the addition of carbon. The appearance of a color will testify the necessity to change DMF for another more suitable solvent (e.g. alcohol, ethyl acetate, or dioxane). As a last resort, DMF can be used for recrystallization but without activated carbon.

The synthesized anilides **1a-j** were identified using ^{1}H NMR spectroscopy (Table 2).

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

Compound	Chemical shifts, δ, ppm (*J*, Hz)									
	6-OH (1H, s)	NH (1H, s)	2-Methylpyrrolo[3,2,1-*ij*]quinoline ring							 R
			H-7 (1H, d)	H-9 (1H, d)	H-8 (1H, t)	CH–CH$_3$ (1H, m)	NCHCH-*cis* (1H, dd)	NCHCH-*trans* (1H, dd)	CH$_3$ (3H, d)	
1a	16.85	12.67	7.71 (*J* = 8.0)	7.57 (*J* = 7.1)	7.25 (*J* = 7.4)	4.98	3.63 (*J* = 17.0, *J* = 9.5)	2.93 (*J* = 17.0, *J* = 3.4)	1.49 (*J* = 6.8)	10.14 (1H, s, OH); 8.21 (1H, d, *J* = 8.2, H-6'); 6.96 (2H, m, H-3',5'); 6.80 (1H, td, *J* = 6.8, *J* = 2.0, H-4')
1b	16.53	12.57	7.68 (*J* = 8.1)	7.55 (*J* = 7.1)	—*	4.94	3.60 (*J* = 17.2, *J* = 9.4)	2.95 (*J* = 17.2, *J* = 3.5)	1.48 (*J* = 6.6)	9.58 (1H, s, OH); 7.19 (3H, m, H-8,2',6'); 6.93 (1H, d, *J* = 7.6, H-4'); 6.57 (1H, dd, *J* = 7.6, *J* = 2.0, H-5')
1c	16.84	12.42	7.71 (*J* = 8.2)	7.59 (*J* = 7.2)	7.27 (*J* = 7.6)	4.98	3.63 (*J* = 17.4, *J* = 9.3)	2.97 (*J* = 17.4, *J* = 3.4)	1.49 (*J* = 6.5)	9.46 (1H, s, OH); 7.44 (2H, d, *J* = 8.9, H-2',6'); 6.77 (2H, d, *J* = 8.9, H-3',5')
1d	16.69	12.76	7.72 (*J* = 8.0)	7.58 (*J* = 7.2)	7.25 (*J* = 7.6)	5.00	3.62 (*J* = 17.1, *J* = 9.4)	2.97 (*J* = 17.1, *J* = 3.6)	1.49 (*J* = 6.3)	8.27 (1H, d, *J* = 8.1, H-6'); 7.12 (2H, m, H-3',5'); 6.97 (1H, td, *J* = 6.8, *J* = 2.7, H-4'); 3.90 (3H, s, OCH$_3$)
1e	16.46	12.68	7.70 (*J* = 8.0)	7.58 (*J* = 7.1)	—*	4.96	3.62 (*J* = 17.3, *J* = 9.4)	2.97 (*J* = 17.3, *J* = 3.5)	1.49 (*J* = 6.6)	7.28 (3H, m, H-8,2',6'); 7.14 (1H, d, *J* = 7.9, H-4'); 6.73 (1H, dd, *J* = 7.9, *J* = 2.1, H-5'); 3.75 (3H, s, OCH$_3$)
1f	16.70	12.49	7.70 (*J* = 8.2)	7.58 (*J* = 7.0)	7.25 (*J* = 7.6)	4.96	3.62 (*J* = 17.1, *J* = 9.4)	2.97 (*J* = 17.1, *J* = 3.3)	1.50 (*J* = 6.4)	7.50 (2H, d, *J* = 8.9, H-2',6'); 6.94 (2H, d, *J* = 8. 9, H-3',5'); 3.74 (3H, s, OCH$_3$)
1g	16.83	12.32	7.71 (*J* = 8.0)	7.58 (*J* = 7.2)	7.26 (*J* = 7.6)	4.99	3.62 (*J* = 17.0, *J* = 9.1)	2.97 (*J* = 17.0, *J* = 3.4)	1.49 (*J* = 6.4)	7.86 (1H, d, *J* = 8.7, H-6'); 6.87 (1H, d, *J* = 2.6, H-3'); 6.77 (1H, dd, *J* = 8.7, *J* = 2.6, H-5'); 3.73 (3H, s, OCH$_3$); 2.29 (3H, s, CH$_3$)
1h	16.71	12.48	7.70 (*J* = 8.0)	7.59 (*J* = 7.3)	7.25 (*J* = 7.6)	4.96	3.62 (*J* = 17.0, *J* = 9.3)	2.96 (*J* = 17.0, *J* = 3.3)	1.49 (*J* = 6.4)	7.50 (2H, d, *J* = 9.0, H-2',6'); 6.92 (2H, d, *J* = 9.0, H-3',5'); 3.94 (2H, q, *J* = 7.0, OCH$_2$);1.30 (3H, t, *J* = 7.0, OCH$_2$CH$_3$)
1i	16.70	12.49	7.70 (*J* = 8.0)	7.57 (*J* = 7.2)	7.26 (*J* = 7.5)	4.96	3.62 (*J* = 17.0, *J* = 9.2)	2.99 (*J* = 17.0, *J* = 3.2)	1.49 (*J* = 6.6)	7.50 (2H, d, *J* = 9.0, H-2',6'); 6.93 (2H, d, *J* = 9.0, H-3',5'); 3.89 (2H, t, *J* = 6.7, OCH$_2$); 1.70 (2H, m, *J* = 7.3, OCH$_2$CH$_2$); 0.96 (3H, t, *J* = 7.4, OCH$_2$CH$_2$CH$_3$)
1j	16.72	12.50	7.71 (*J* = 8.2)	7.58 (*J* = 7.2)	7.26 (*J* = 7.7)	4.97	3.63 (*J* = 17.1, *J* = 9.2)	2.97 (*J* = 17.1, *J* = 3.3)	1.50 (*J* = 6.3)	7.50 (2H, d, *J* = 9.0, H-2',6'); 6.92 (2H, d, *J* = 9.0, H-3',5'); 3.92 (2H, t, *J* = 6.5, OCH$_2$); 1.68 (2H, quin., *J* = 6.7, OCH$_2$CH$_2$); 1.31 (6H, m, (CH$_2$)$_3$CH$_3$); 0.86 (3H, t, *J* = 6.6, CH$_3$)

* The signal for this proton is overlapped with others and identification is included with the remaining protons.

For further information regarding the structure of studied compounds class we examined the 4-ethoxy-substituted anilide **1h** using X-ray structural analysis (see Figure 1 and Tables 3, 4).

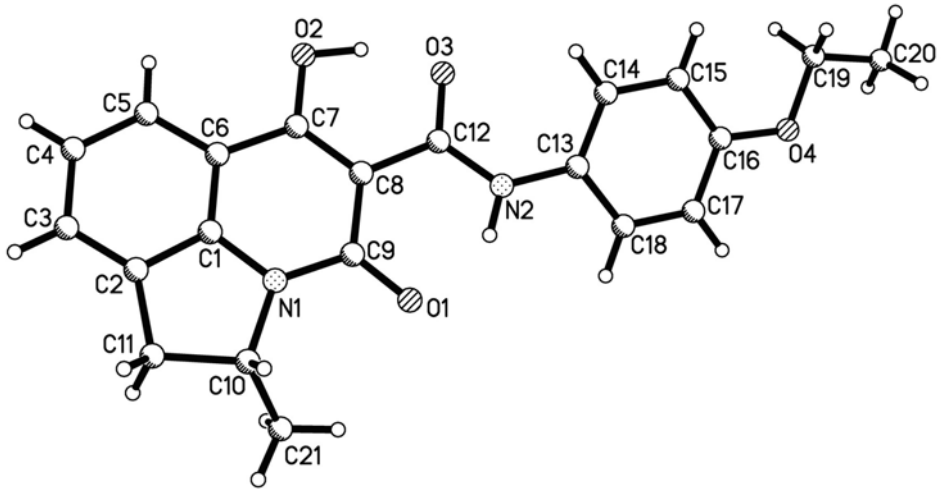

Fig. 1. The structure of the 4-ethoxyanilide **1h** molecule with atomic numbering.

In this way we obtained absolute confirmation for the previous conclusion, made on the basis of computer modelling, that the tricyclic pyrroloquinoline system in such compounds is planar [2]. The atoms O(1), O(2) and the carbamide group lie in virtually the same plane as the tricycle (accuracy 0.02 Å) and this is due to the presence of two, strong intramolecular hydrogen bonds O(2)–H(2O)···O(3) (H···O 1.49 Å, O–H···O 155º) and N(2)–H(2N)···O(1) (H···O 1.84 Å, N–H···O 145º). Formation of the hydrogen bonds also leads to marked lengthening of the O(1)–C(9) bond to 1.243(2) and O(3)–C(12) to 1.261(2) Å compared to their average value [7]

TABLE 3. Bond Lengths (*l*) in the 4-Ethoxyanilide **1h** Structure

Bond	*l*, Å	Bond	*l*, Å
N(1)–C(9)	1.367(2)	N(1)–C(1)	1.370(2)
N(1)–C(10)	1.489(2)	N(2)–C(12)	1.334(2)
N(2)–C(13)	1.416(2)	O(1)–C(9)	1.243(2)
O(2)–C(7)	1.326(2)	O(3)–C(12)	1.261(2)
O(4)–C(16)	1.370(2)	O(4)–C(19)	1.425(2)
C(1)–C(2)	1.382(2)	C(1)–C(6)	1.383(2)
C(2)–C(3)	1.365(2)	C(2)–C(11)	1.502(2)
C(3)–C(4)	1.396(2)	C(4)–C(5)	1.367(2)
C(5)–C(6)	1.398(2)	C(6)–C(7)	1.438(2)
C(7)–C(8)	1.380(2)	C(8)–C(9)	1.460(2)
C(8)–C(12)	1.466(2)	C(10)–C(21)	1.476(3)
C(10)–C(11)	1.555(2)	C(13)–C(14)	1.370(2)
C(13)–C(18)	1.387(2)	C(14)–C(15)	1.388(2)
C(15)–C(16)	1.374(2)	C(16)–C(17)	1.382(2)
C(17)–C(18)	1.376(2)	C(19)–C(20)	1.534(1)

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

Valence Angle	ω, deg.	Valence Angle	ω, deg.
C(9)–N(1)–C(1)	122.6(1)	C(9)–N(1)–C(10)	126.4(2)
C(1)–N(1)–C(10)	110.6(1)	C(12)–N(2)–C(13)	126.9(2)
C(16)–O(4)–C(19)	116.7(1)	N(1)–C(1)–C(2)	112.7(2)
N(1)–C(1)–C(6)	123.8(2)	C(2)–C(1)–C(6)	123.5(2)
C(3)–C(2)–C(1)	118.4(2)	C(3)–C(2)–C(11)	133.7(2)
C(1)–C(2)–C(11)	108.0(2)	C(2)–C(3)–C(4)	119.9(2)
C(5)–C(4)–C(3)	121.0(2)	C(4)–C(5)–C(6)	120.5(2)
C(1)–C(6)–C(5)	116.9(2)	C(1)–C(6)–C(7)	115.6(2)
C(5)–C(6)–C(7)	127.5(2)	O(2)–C(7)–C(8)	122.4(2)
O(2)–C(7)–C(6)	116.6(2)	C(8)–C(7)–C(6)	120.9(2)
C(7)–C(8)–C(9)	121.3(2)	C(7)–C(8)–C(12)	117.7(2)
C(9)–C(8)–C(12)	121.0(2)	O(1)–C(9)–N(1)	120.3(2)
O(1)–C(9)–C(8)	123.9(2)	N(1)–C(9)–C(8)	115.8(2)
C(21)–C(10)–N(1)	114.5(2)	C(21)–C(10)–C(11)	112.9(2)
N(1)–C(10)–C(11)	102.9(1)	C(2)–C(11)–C(10)	105.5(1)
O(3)–C(12)–N(2)	121.4(2)	O(3)–C(12)–C(8)	119.3(2)
N(2)–C(12)–C(8)	119.3(2)	C(14)–C(13)–C(18)	118.5(2)
C(14)–C(13)–N(2)	123.6(2)	C(18)–C(13)–N(2)	117.9(2)
C(13)–C(14)–C(15)	121.0(2)	C(16)–C(15)–C(14)	120.0(2)
O(4)–C(16)–C(15)	124.4(2)	O(4)–C(16)–C(17)	116.2(2)
C(15)–C(16)–C(17)	119.4(2)	C(18)–C(17)–C(16)	120.2(2)
C(17)–C(18)–C(13)	120.8(2)	O(4)–C(19)–C(20)	108.0(1)

of 1.210 Å and to shortening of the O(2)–C(7) bond to 1.326(2) Å (average value 1.362 Å). The C(7)–C(8) bond is lengthened to 1.380(2) Å (average value 1.326 Å) and this is characteristic for quinolone compounds series. The methyl group on atom C(10) is found in an equatorial position (torsional angle C(1)–N(1)–C(10)–C(21) 127.9(2)º). The *para*-ethoxyphenyl substituent is found in an *ap*-type conformation relative to the C(8)–C(12) bond and slightly twisted relative to the carbamide fragment plane (torsional angles C(13)–N(2)–C(12)–C(8) 174.7(2)º and C(12)–N(2)–C(13)–C(14) 30.5(3)º) despite the formation of the intramolecular hydrogen bond C(14)–H(14)···O(3) (H···O 2.35 Å, C–H···O 113º). The ethoxy group is coplanar with the aromatic ring (torsional angle C(19)–O(4)–C(16)–C(15) -3.9(2)º) despite the strong repulsion between the aromatic ring atoms and the ethyl group atoms (shortened intramolecular contacts H(15)···C(19) 2.51 Å (sum of van der Waal radii [8] 2.87 Å), H(15)···H(19b) 2.32 Å (2.34 Å), H(15)···H(19a) 2.27 Å (2.34 Å), H(19a)···C(15) 2.70 Å (2.87 Å), and H(19b)···C(15) 2.78 Å (2.87 Å)). The C(19)–C(20) bond is antiperiplanar to the C(16)–O(4) bond (torsional angle C(16)–O(4)–C(19)–C(20) 174.9(2)º)

The 4-ethoxyanilide **1h** molecules form stacks in the crystal along the crystallographic (1 0 0) direction. Within the stacks the molecules are positioned "head to tail" with a separation of 3.5 Å and it allows us to suggest the existence of a π-π type interaction in the stacks. There are also C–H···π type intermolecular interactions in the crystal: C(10)–H(10)···C(15)' [(*x*, *y*-1, *z*) H···π 2.74 Å, C–H···π 148º] and C(20)–H(20b)···C(18') [(1.5-*x*, 0.5+*y*, 0.5-*z*) H···π 2.81 Å, C–H···π 149º].

The diuretic activity of anilides **1a-j** was studied on white rats using a standard method [2, 9] by oral introduction and in comparison with hydrochlorothiazide [10]. Comparison of the experimental data obtained

(Table 1) with the results of the previous investigations [3] shows that, in the case of the hydroxy- and alkoxyanilides, the transition from pyrroloquinoline derivatives to their 5-methyl-substituted analogs is accompanied by some decrease in diuretic activity but that the overall nature of the structure–biological relationship remains the same.

EXPERIMENTAL

^{1}H NMR spectra of anilides **1a-j** were measured on a Varian Mercury VX-200 instrument (200 MHz) with DMSO-d_6 solvent and TMS as internal standard. The synthesis of ethyl 6-hydroxy-2-methyl-4-oxo-2,4-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (**2**) and its amidation by hydroxy- and alkoxyanilines was carried out by the method in the study [2].

X-ray Structural Investigation. Crystals of the 4-ethoxyanilide **1h** are monoclinic (DMF), at 20ºC: a = 7.5136(7), b = 9.8478(7), c = 23.673(2) Å, β = 96.160(7)º, V = 1741.5(2) Å^3, M_r = 364.39, Z = 4, space group $P2_1/n$, d_{calc} = 1.390 g/cm^3, μ(MoKα) = 0.097 mm^{-1}, F(000) = 768. Unit cell parameters and intensities for 13731 reflections (3062 independent, R_{int} = 0.047) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 50º).

The structure was interpreted by a direct method using the SHELXTL program package [11]. In the structure refinement a limit was placed on the ethyl group bond length of 1.54(1) Å. The positions of the hydrogen atoms were revealed from electron density difference synthesis and refined using the "rider" model with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bonded to the given hydrogen (n = 1.5 for a methyl group and n = 1.2 for other hydrogen atoms). Hydrogen atoms involved in formation of hydrogen bonds were refined in the isotropic approximation. The structure was interpreted by F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.073 for 3023 reflections (R_1 = 0.035 for 1585 reflections with $F > 4\sigma$ (F), S = 0.760). The full crystallographic information for the 4-ethoxyanilide **1h** has been placed in the Cambridge Crystallographic Data Center as deposit CCDC 801477. Interatomic distances and valence angles are given in Tables 3 and 4, respectively.

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