Chemistry of Heterocyclic Compounds, Vol. 47, No. 7, October 2011 (Russian original Vol. 47, No. 7, July, 2011)

4-HYDROXY-2-QUINOLONES. 197*. THE SEARCH FOR NOVEL DIURETICS AMONGST HALO-SUBSTITUTED 6-HYDROXY-2-METHYL-4-OXO-1,2-DIHYDRO-4*H*-PYRROLO-[3,2,1-*ij*]QUINOLINE-5-CARBOXYLIC ACID ANILIDES

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A targeted synthesis of a series of halo-substituted 6-hydroxy-2-methyl-4-oxo-1,2-dihydro-4H-pyrrolo-[3,2,1-ij]quinoline-5-carboxylic acid anilides have been carried out. Peculiarites of the ^{1}H NMR spectra and the results of investigating the diuretic activity of these compounds are discussed.

Keywords: anilides, 4-hydroxy-2-oxoquinoline-3-carboxylic acids, methylindoline, amidation, diuretic activity.

Hypertensive disease is not by chance considered to be one of the main problems in current medicine. This is not simply a disease, but it intrinsically decreases the quality of human life. Unfortunately, it is also a factor triggering a cascade of many pathological changes in various organs and tissues and leads to a whole series of other illnesses and pathological conditions, which contribute to widespread complications and a sharp increase in mortality. In the last decade, diuretics have secured a place in the treatment of arterial hypertension and chronic heart failure. Although being not strictly antihypertensive medicines, they lead to the elimination of a large amount of liquid from the organism thus lowering arterial pressure to a physiological norm [2, 3]. Indapamide is a particularly widely used medicine amongst this pharmacological group [4–9]. Our interest in this medicine is due not only to its biological properties. Its known structure [10] is a 2-methylindoline derivative. Quite recently, compounds with a high diuretic activity and clear antihypertensive and anti-edematous properties have been found amongst 1-hydroxy-3-oxo-5,6-dihydro-3*H*-pyrrolo[3,2,1-*ij*]quinoline-2-carboxamides [11] structurally based on an unsubstituted indoline. From this there arose the idea of including methylated analogs of the above mentioned pyrroloquinolines into our search for novel diuretic compounds.

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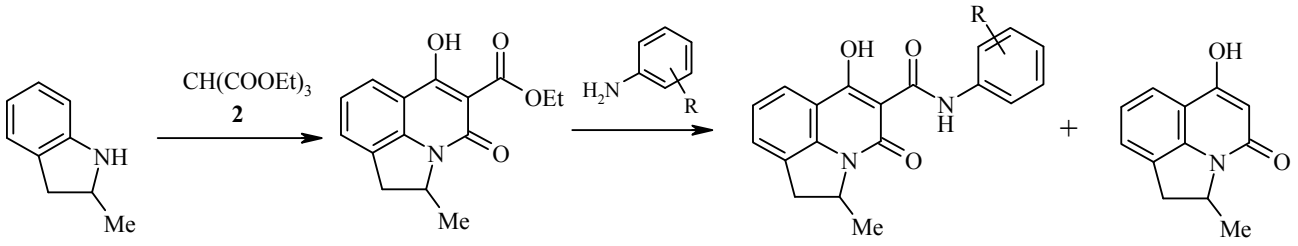
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 1009–1017, July, 2011. Original article submitted June 22, 2010.

In order to achieve this particular goal, 2-methylindoline (**1**) was condensed with triethylmethane tricarboxylate (**2**) by our previously reported method [12]. The ethyl 6-hydroxy-2-methyl-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (**3**) obtained in this way reacts with primary amines to give the corresponding anilides **4a–r**. In order to avoid breakdown of ester **3,** the amidation was carried out at temperature not higher than 140ºC. At a higher temperature, the final product is contaminated with an admixture of the side 6-hydroxy-2-methyl-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (**5**).



1 **3** **4a–r** **5**

4 a R = H, **b** R = 2-F, **c** R = 3-F, **d** R = 4-F, **e** R = 3,4-F_2, **f** R = 2-Cl, **g** R = 3-Cl, **h** R = 4-Cl, **i** R = 2,4-Cl_2, **j** R = 2,5-Cl_2, **k** R = 5-Cl-2-OMe, **l** R = 2-Br, **m** R = 3-Br, **n** R = 4-Br, **o** R = 2-Br-4-Me, **p** R = 2-CF_3, **q** R = 3-CF_3, **r** R = 4-CF_3

All of the anilides **4a–r** obtained (Table 1) are colorless or white with a yellowish tinge, crystalline substances. At room temperature, they are moderately soluble in DMF and DMSO, slightly soluble in alcohol, and practically insoluble in water. The structure of the compounds synthesized was confirmed by their ^{1}H NMR spectra (Table 2).

Overall, the interpretation of the proton signals does not cause a problem. A question arises only in the more specific task, in particular of assigning the protons of the methylene group in the pyrroline ring. All of the compounds studied contain a "rigid" methylpyrroline fragment, the protons and methyl group of which have fixed orientations giving rise to this problem in the detailed structural analysis. Thus, in the ^{1}H NMR spectrum of the starting ester **3**, the pyrroline ring protons appear as a doublet at 1.42 ppm for the CH_3 group, a multiplet for a methine proton at 4.83 ppm, and two double doublets for the methylene group protons centred at 3.57 and 2.90 ppm. The first two of these signals are clear, but a specific assignment of the methylene group protons signals is impossible without additional study. Theoretically, to solve the stereochemical problems the well known Karplus equation or its graphical representation [13], which relates the value of the dihedral angle between interacting protons to their ^3J spin-spin coupling value, can be used.

At first, a steric model of the compound studied should be constructed by one of the available methods. We used the HyperChem computer modelling program. In the case of ester **3** the calculations indicated that one proton of the methylene group in the pyrrole plane ring is found in a *trans* orientation to the methine proton and has a torsional angle of 117º and the second proton in the *cis* position is at the angle of 6.3ºC. From the graphically presented Karplus formula it follows that a vicinal spin-spin coupling of 2.6 Hz corresponds to the angle of 117º and the coupling of 8.5 Hz corresponds to the angle 6.3º. As mentioned above, the ^{1}H NMR spectrum of ester **3** shows an ABX spin system corresponding to the methine proton multiplet and the two double doublets for the methylene group protons. They arise from the combination of geminal and vicinal spin-spin coupling. Standard geminal spin-spin couplings ^2J are about 17 Hz, while the vicinal are somewhat smaller. Thanks to this it is possible to show that in the double doublet at 3.56 ppm the vicinal coupling is 9.4, while in the double doublet at 2.89 ppm it is 3.6 Hz. The experimental values determined are quite close to those calculated and this allows us to confirm unambiguously that the proton signal for the methylene group having a *cis* partner in spin-spin coupling is observed in the lower field.

TABLE 1. Characteristics of 6-Hydroxy-2-methyl-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid Anilides **4a–r**

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C (DMF–ethanol)	Yield, %	Diuretic activity, %*
		C	H	N			
4a	$C_{19}H_{16}N_2O_3$	71.12 / 71.24	4.95 / 5.03	8.83 / 8.74	127–129	91	-28
4b	$C_{19}H_{15}FN_2O_3$	67.34 / 67.45	4.54 / 4.47	8.39 / 8.28	179–181	83	+42
4c	$C_{19}H_{15}FN_2O_3$	67.52 / 67.45	4.55 / 4.47	8.36 / 8.28	156–158	88	+21
4d	$C_{19}H_{15}FN_2O_3$	67.34 / 67.45	4.53 / 4.47	8.38 / 8.28	143–145	90	+105
4e	$C_{19}H_{14}F_2N_2O_3$	63.95 / 64.04	4.08 / 3.96	7.97 / 7.86	190–192	92	+24
4f	$C_{19}H_{15}ClN_2O_3$	64.40 / 64.32	4.35 / 4.26	7.86 / 7.90	197–199	80	+5
4g	$C_{19}H_{15}ClN_2O_3$	64.43 / 64.32	4.37 / 4.26	7.81 / 7.90	166–168	85	+5
4h	$C_{19}H_{15}ClN_2O_3$	64.25 / 64.32	4.31 / 4.26	7.96 / 7.90	171–173	89	+5
4i	$C_{19}H_{14}Cl_2N_2O_3$	58.52 / 58.63	3.54 / 3.63	7.11 / 7.20	208–210	77	+14
4j	$C_{19}H_{14}Cl_2N_2O_3$	58.50 / 58.63	3.55 / 3.63	7.13 / 7.20	203–205	80	+9
4k	$C_{20}H_{17}ClN_2O_4$	62.54 / 62.42	4.58 / 4.45	7.19 / 7.28	195–197	78	--26
4l	$C_{19}H_{15}BrN_2O_3$	57.07 / 57.16	3.66 / 3.79	6.91 / 7.02	174–176	76	+17
4m	$C_{19}H_{15}BrN_2O_3$	57.24 / 57.16	3.90 / 3.79	7.12 / 7.02	188–190	88	+83
4n	$C_{19}H_{15}BrN_2O_3$	57.25 / 57.16	3.86 / 3.79	7.07 / 7.02	171–173	94	+4
4o	$C_{20}H_{17}BrN_2O_3$	58.03 / 58.13	4.22 / 4.15	6.67 / 6.78	185–187	75	-21
4p	$C_{20}H_{15}F_3N_2O_3$	61.78 / 61.86	3.80 / 3.89	7.14 / 7.21	150–152	77	+13
4q	$C_{20}H_{15}F_3N_2O_3$	61.95 / 61.86	3.98 / 3.89	7.33 / 7.21	155–157	90	+4
4r	$C_{20}H_{15}F_3N_2O_3$	61.94 / 61.86	3.96 / 3.89	7.30 / 7.21	196–198	87	-37
	Hydrochlorothiazide						+59

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

The diuretic properties of the compounds synthesized were studied on white, nonpedigree rats of both sexes of weight 180–200 g by the standard method [14]. The test samples were introduced using gastric intubation as a fine aqueous suspension stabilized by Tween-80. The primary screening was carried out at the dose of 10 mg/kg corresponding to the ED_{50} of one of the most active 6-hydroxy-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]-quinoline-5-carboxylic acid amides [11]. Diuresis indicators were recorded in 4 h and compared with the control and with the known diuretic hydrochlorothiazide [15] used at its effective dose of 40 mg/kg.

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

Compound	Chemical shifts, δ, ppm (*J*, Hz)									
	OH (1H, s)	NH (1H, s)	2-Methylpyrroloquinoline nucleus							R
			H-7 (1H, d)	H-8 (1H, d)	H-9 (1H, t)	CHMe (1H, m)	NCHCH$_2$-*cis* (1H, dd)	NCHCH$_2$-*trans* (1H, dd)	CH_3 (3H, d)	
1	2	3	4	5	6	7	8	9	10	11
4a	16.52	12.66	7.70 (*J* = 8.3)	7.16 (*J* = 7.3)	See R	4.97	3.63 (*J* = 17.2, *J* = 9.4)	2.97 (*J* = 17.2, *J* = 3.4)	1.50 (*J* = 6.4)	7.61 (3H, m, H-9,2',6'); 7.39 (2H, t, *J* = 7.6, H-3',5'); 7.25 (1H, t, *J* = 7.6, H-4')
4b	16.19	12.90	7.71 (*J* = 8.2)	See R	See R	4.99	3.63 (*J* = 17.2, *J* = 9.5)	2.98 (*J* = 17.2, *J* = 3.6)	1.49 (*J* = 6.5)	8.27 (1H, td, *J* = 7.6, *J* = 2.0, H-3'); 7.59 (1H, d, *J* = 7.1, H-6'); 7.40–7.15 (4H, m, H-8,9,4',5')
4s	16.20	12.81	7.71 (*J* = 8.4)	7.26 (*J* = 7.7)	7.34 (*J* = 7.3)	4.97	3.63 (*J* = 17.0, *J* = 9.3)	2.98 (*J* = 17.0, *J* = 3.4)	1.50 (*J* = 6.3)	7.64 (1H, dd, *J* = 7.8, *J* = 2.1, H-2'); 7.57 (1H, d, *J* = 7.4, H-6'); 7.43 (1H, t, *J* = 7.7, H-5'); 6.99 (1H, td, *J* = 8.0, *J* = 1.9, H-4')
4d	16.45	12.64	7.72 (*J* = 8.0)	7.27 (*J* = 7.5)	7.59 (*J* = 7.3)	4.98	3.64 (*J* = 17.3, *J* = 9.4)	2.98 (*J* = 17.3, *J* = 3.3)	1.50 (*J* = 6.4)	7.64 (2H, td, *J* = 7.4, *J* = 1.9, H-3',5'); 7.19 (2H, d, *J* = 7.6, H-2',6')
4e	16.13	12.75	7.71 (*J* = 8.0)	7.26 (*J* = 7.6)	7.58 (*J* = 7.2)	4.98	3.63 (*J* = 17.1, *J* = 9.4)	2.97 (*J* = 17.1, *J* = 3.4)	1.51 (*J* = 6.4)	7.84 (1H, dd, *J* = 7.9, *J* = 2.0, H-2'); 7.41 (2H, m, H-5',6')
4f	16.22	12.99	7.70 (*J* = 8.2)	7.25 (*J* = 7.6)	See R	4.99	3.62 (*J* = 17.2, *J* = 9.3)	2.97 (*J* = 17.2, *J* = 3.3)	1.49 (*J* = 6.3)	8.33 (1H, dd, *J* = 8.5, *J* = 1.5, H-6'); 7.56 (2H, m, H-9,3'); 7.37 (1H, td, *J* = 7.9, *J* = 1.5, H-5'); 7.17 (1H, td, *J* = 7.7, *J* = 1.5, H-4')
4g	16.11	12.76	7.68 (*J* = 8.1)	See R	7.56 (*J* = 7.4)	4.94	3.61 (*J* = 17.3, *J* = 9.2)	2.96 (*J* = 17.3, *J* = 3.3)	1.49 (*J* = 6.4)	7.84 (1H, s, H-2'); 7.45–7.14 (4H, m, H-8,4',5',6')
4h	16.32	12.75	7.73 (*J* = 8.1)	7.29 (*J* = 7.5)	7.60 (*J* = 7.3)	4.99	3.64 (*J* = 17.1, *J* = 9.3)	2.98 (*J* = 17.1, *J* = 3.3)	1.50 (*J* = 6.4)	7.67 (2H, d, *J* = 8.6, H-2',6'); 7.43 (2H, d, *J* = 8.6, H-3',5')

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11
4i	16.04	13.09	See R	7.28 (J = 7.6)	7.61 (J = 7.3)	5.01	3.64 (J = 17.0, J = 9.3)	2.99 (J = 17.0, J = 3.4)	1.49 (J = 6.3)	8.37 (1H, d, J = 8.6, H-6'); 7.73 (2H, m, H-7,3'); 7.46 (1H, t, J = 8.6, H-5')
4j	15.81	13.17	7.71 (J = 8.1)	7.26 (J = 7.7)	7.60 (J = 7.2)	4.99	3.62 (J = 17.2, J = 9.2)	2.98 (J = 17.2, J =3.3)	1.49 (J = 6.3)	8.44 (1H, d, J = 2.6, H-6'); 7.56 (1H, d, J = 8.6, H-3'); 7.21 (1H, d, J = 8.6, H-4')
4k	16.27	12.93	7.74 (J = 8.0)	7.27 (J = 7.6)	7.60 (J = 7.2)	5.00	3.63 (J = 17.3, J = 9.3)	2.99 (J = 17.3, J = 3.4)	1.50 (J = 6.4)	8.36 (1H, d, J = 2.5, H-6'); 7.19 (1H, dd, J = 8.9, J = 2.5, H-4'); 7.12 (1H, d, J = 8.9, H-3'); 3.93 (3H, s, CH_3)
4l	16.28	12.87	See R	7.27 (J = 7.6)	7.61 (J = 7.1)	5.01	3.64 (J = 17.4, J = 9.4)	2.99 (J = 17.4, J = 3.4)	1.49 (J = 6.4)	8.25 (1H, dd, J = 8.3, J = 1.4, H-6'); 7.73 (2H, m, H-7,3'); 7.43 (1H, td, J = 7.9, J = 1.4, H-5'); 7.14 (1H, td, J = 7.8, J = 1.4, H-4')
4m	16.09	12.73	7.68 (J = 8.1)	7.23 (J = 7.6)	7.55 (J = 7.4)	4.95	3.61 (J = 17.3, J = 9.4)	2.96 (J = 17.3, J = 3.4)	1.50 (J = 6.4)	7.96 (1H, s, H-2'); 7.48 (1H, d, J = 7.8, H-6'); 7.32 (2H, m, H-4',5')
4n	16.24	12.69	7.66 (J = 8.1)	7.22 (J = 7.6)	See R	4.93	3.60 (J = 17.1, J = 9.3)	2.96 (J = 17.1, J = 3.3)	1.49 (J = 6.3)	7.57 (3H, m, H-9,2',6'); 7.49 (2H, d, J = 9.1, H-3',5')
4o	16.33	12.71	7.69 (J = 8.2)	7.24 (J = 7.6)	7.57 (J = 7.3)	4.98	3.61 (J = 17.3, J = 9.3)	2.96 (J = 17.3, J = 3.3)	1.48 (J = 6.3)	8.09 (1H, d, J = 8.3, H-6'); 7.51 (1H, d, J = 1.3, H-3'); 7.18 (1H, d, J = 8.3, H-5'); 2.30 (3H, s, CH_3)
4p	16.19	12.84	See R	7.29 (J = 7.7)	7.62 (J = 7.1)	5.03	3.64 (J = 17.2, J = 9.3)	2.99 (J = 17.2, J = 3.4)	1.49 (J = 6.3)	8.10 (1H, d, J = 8.2, H-6'); 7.67 (3H, m, H-7,3',5'); 7.44 (1H, td, J = 7.6, J = 1.5, H-4')
4q	16.04	12.87	7.77 (J = 8.1)	7.24 (J = 7.6)	See R	4.96	3.61 (J = 17.4, J = 9.3)	2.96 (J = 17.4, J = 3.4)	1.50 (J = 6.3)	8.11 (1H, s, H-2'); 7.68–7.57 (3H, m, H-9,4',6'); 7.50 (1H, t, J = 7.6, H-5')
4r	16.09	12.95	See R	7.29 (J = 7.6)	7.60 (J = 7.3)	5.01	3.66 (J = 17.2, J = 9.3)	2.99 (J = 17.2, J = 3.4)	1.53 (J = 6.4)	7.86 (2H, d, J = 8.7, H-2',6'); 7.73 (3H, m, H-7,3',5')

It has been found that the starting ethyl ester **3** has a weak diuretic effect increasing the diuresis by an average of 20%. Loss of the ethoxycarbonyl group markedly changed the biological effect and the 6-hydroxy-2-methyl-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (**5**) even lowered the loss of urine by 37% when compared with the control data, i.e. behaved as a rather strong antidiuretic agent. An even greater variation is shown when changing to the halo-substituted 6-hydroxy-2-methyl-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]-quinoline-5-carboxylic acid anilides **4a–r**. The indicators found for these experiments (Table 1) were so haphazard that no general structure–activity relationship was apparent. At the same time in a smaller series the relationship of the diuretic effect on the nature and position of the halogen in the anilide fragment is seen quite clearly. Hence amongst the fluoroanilides, only the *para* isomer **4d** showed strong diuretic properties – substantially greater than hydrochlorothiazide. However, an additional fluorine atom in a *meta* position (anilide **4e**) caused almost full deactivation of the molecule. For the bromo-substituted analogs, only the *meta* isomer **4m** attracted attention, while compounds with one or two chlorine atoms, similarly to the trifluoromethyl analogs, proved virtually inactive towards diuresis in the experimental animals.

Overall, the comparison of the halo-substituted anilides **4a–r** and the closely structurally related 1-hydroxy-3-oxo-5,6-dihydro-3*H*-pyrrolo[3,2,1-*ij*]quinoline-2-carboxamides with similar substituents in the anilide fragments [11] has demonstrated that the methylation of the pyrroline ring can increase the diuretic effect. As an obvious method for increasing these pharmacological properties this needs further study.

EXPERIMENTAL

^{1}H NMR spectra for the compounds synthesized were recorded on a Varian Mercury-VX-200 (200 MHz) instrument using DMSO-d_6 as solvent and TMS as internal standard.

The commercial 2-methylindoline (**1**) and triethylmethane tricarboxylate (**2**) were obtained from the Aldrich company.

Ethyl 6-hydroxy-2-methyl-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylate (3) was obtained by the reaction of 2-methylindoline (**1**) with a 30% excess of triethylmethane tricarboxylate (**2**) using the method in [12]. Yield 78%; mp 77–79ºC (diethyl ether). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.99 (1H, s, OH); 7.68 (1H, d, *J* = 8.3, H-7); 7.49 (1H, d, *J* = 7.2, H-9); 7.16 (1H, t, *J* = 7.5, H-8); 4.83 (1H, s, NCH); 4.30 (2H, q, *J* = 6.9, OC$\underline{H}_2$CH$_3$); 3.57 (1H, dd, *J* = 17.1, *J* = 9.4, NCHC$\underline{H}_2$-*cis*); 2.90 (1H, dd, *J* = 17.1, *J* = 3.6, NCHC$\underline{H}_2$-*trans*); 1.42 (3H, d, *J* = 6.4, NCHC$\underline{H}_3$); 1.28 (3H, t, *J* = 6.9, OCH$_2$C$\underline{H}_3$). Found, %: C 66.02; H 5.61; N 5.17. $C_{15}H_{15}NO_4$. Calculated, %: C 65.93; H 5.53; N 5.13.

6-Hydroxy-2-methyl-4-oxo-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-5-carboxylic Acid Anilides 4a–r (General Method). A mixture of ethyl ester **3** (2.73 g, 0.01 mol), the corresponding aniline (0.01 mol), and DMF (1 ml) was stirred and allow to stand at 140ºC for 10–15 min. The reaction mixture was then cooled to about 100ºC, ethanol (10–15 ml) was carefully added, and thoroughly triturated. The precipitated anilide **4a–r** was filtered off, washed with cold alcohol, dried, and recrystallized from the mixture of DMF and alcohol.

6-Hydroxy-2-methyl-1,2-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (5) was prepared as the main product from the reaction of the ethyl ester **3** with *ortho*-bromoaniline when the general reaction is carried out at 160ºC. Yield 69%; mp 293–295ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.24 (1H, s, OH); 7.49 (1H, d, *J* = 8.0, H-7); 7.36 (1H, d, *J* = 7.1, H-9); 7.08 (1H, t, *J* = 7.6, H-8); 5.73 (1H, s, H-3); 4.79 (1H, m, NCH); 3.56 (1H, dd, *J* = 17.0, *J* = 9.4, NCHC$\underline{H}_2$-*cis*); 2.88 (1H, dd, *J* = 17.0, *J* = 3.6, NCHC$\underline{H}_2$-*trans*); 1.39 (3H, d, *J* = 6.3, CH$_3$). Found, %: C 71.75; H 5.64; N 6.87. $C_{12}H_{11}NO_2$. Calculated, %: C 71.63; H 5.51; N 6.96.

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