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4-HYDROXY-2-QUINOLONES 138*. SYNTHESIS AND STUDY OF STRUCTURE – BIOLOGICAL ACTIVITY RELATIONSHIPS IN A SERIES OF 1-HYDROXY-3-OXO-5,6-DIHYDRO-3H-PYRROLO[3,2,1-*ij*]QUINOLINE-2-CARBOXYLIC ACID ANILIDES

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Two methods are discussed and the synthesis of a series of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-ij]quinoline-2-carboxylic acid anilides has been carried out. The antitubercular activity and the effect on the urinary function of the kidney have been studied for the compounds prepared. A structure-biological activity relationship is discussed.

Keywords: anilides, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, diuretics, amidation, antitubercular activity.

In recent times the attention of synthetic chemists has been drawn to a search for biologically active substances in order to create from them novel medicinal compounds and it has been ever more attracted to 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilides [2-8]. This is explained not only by the broad spectrum of pharmaceutical activity of the studied 4-hydroxyquinol-2-ones and their natural occurrence but also by the ready chemical modification of their basic structure. Directed changes can be introduced into any part of the basic molecule by quite simple methods guaranteeing the best access to an almost unlimited range of analogs which, in turn, significantly increases the likelihood of discovering promising structural leads in subsequent study.

Condensation of primary aromatic amines with triethyl methanetricarboxylate in conventional conditions gives primarily the methanetricarboxylic acid trianilides. During microwave irradiation the reaction given occurs somewhat differently and indeed yields 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilides [7]. To some extent, the low yields are compensated by the synthesis of the target compounds in a single stage. This method is certainly of interest although the promising application of it is small since both the quinolone ring and the anilide fragment are formed from the same aniline.

* For Communication 137 see [1].

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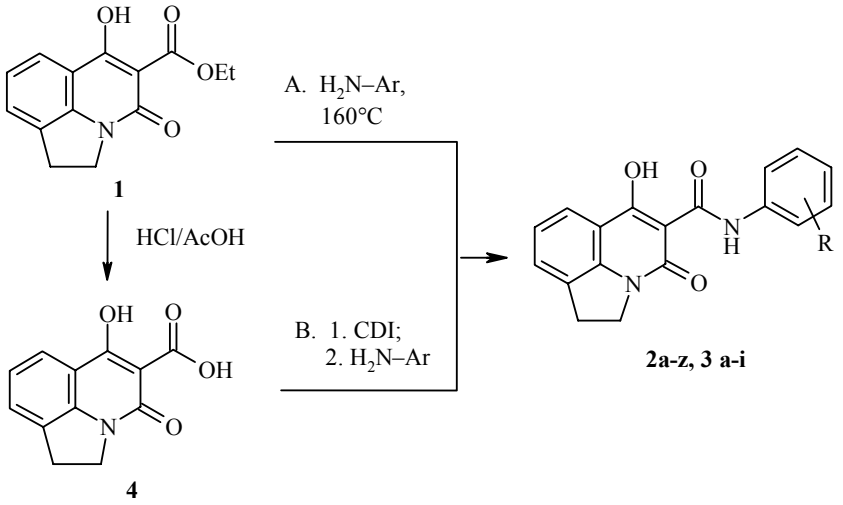
Removal of this restriction enables amidation of the previously prepared 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids and their esters. The lowest alkyl esters of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids are highly reactive [9] and efficiently acylate primary and secondary amines in the majority of cases. According to the methods frequently met in the literature amidation is brought about by refluxing the corresponding 3-alkoxycarbonylquinolone and a 40-150% excess of the aniline in a suitable solvent (pyridine, toluene, xylene, bromobenzene) for 3-36 h with simultaneous distillation of the alcohol evolved [3, 5, 10, 11]. We have, however, frequently noted the success of carrying out such a reaction without solvent or in the presence of a small amount of DMF and, very importantly, with an equimolar ratio of reagents [8, 12]. This method allows a more rational use of the amine and, in addition, shortens the reaction time to several minutes. Hence it was actually used in the amidation of ethyl 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylate (**1**) (method A) to yield a large series of the corresponding anilides **2** and **3**.



2 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 = 2,3-Cl_2; **j** R = 2,4-Cl_2; **k** R = 2-Br; **l** R = 2-Br–4-Me; **m** R = 3-Br; **n** R = 4-Br; **o** R = 2-Me; **p** R = 3-Me; **q** R = 4-Me; **r** R = 2,3-Me_2; **s** R = 2,4-Me_2; **t** R = 2,5-Me_2; **u** R = 2-OMe; **v** R = 2-OMe-5-Cl; **w** R = 3-OMe; **x** R = 4-OMe; **y** R = 4-OEt; **z** R = 2-CF_3; **3 a** R = 2-C≡N; **b** A = 2-COOMe; **c** R = 2-$CONH_2$; **d** R = 2-CONHMe; **e** R = 4-COOMe; **f** R = 4-COOEt; **g** R = 4-COOPr; **h** R = 4-COOBu; **i** R = 2-SO_2NH_2

The acylation of N-alkylanilines by 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids esters does not always occur smoothly, especially where there are electron-acceptor substituents present in the aniline. In such cases it is expediently the target esters initially to hydrolyze to the acids and then convert to more powerful acylating agents: anhydrides, acid chlorides, or mixed anhydrides [3, 5, 10]. N,N'-Dicyclohexylcarbodiimide is also suitable for increasing the electrophilic properties of the carboxyl group carbonyl [10]. In addition, the amine component can be activated by converting it to highly reactive derivatives with phosphorus trichloride [10]. In this way, many known methods for transformation of carboxylic acids to amides can be used. It is only necessary to remember that the 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids in the solution state are distinguished by a very high tendency towards decarboxylation. Thus in DMSO solution partial decomposition occurs in the course of a day, even at room temperature [13]. For this reason, it is not possible to use strong heating at the stage of activation of the 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids. This specific feature was taken into account by us in developing an alternative method for synthesizing amides **2, 3** from 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo-[3,2,1-*ij*]quinoline-2-carboxylic acid (**4**). By carrying out the reaction with N,N-carbonyldiimidazole (CDI) at a temperature less than 40ºC the

TABLE 1. Characteristics of the 1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid Anilides **2a-z**, **3a-i**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield*, %
		C	H	N		
1	2	3	4	5	6	7
2a	$C_{18}H_{14}N_2O_3$	70.65 / 70.58	4.70 / 4.61	9.08 / 9.15	192-194	93 (88)
2b	$C_{18}H_{13}FN_2O_3$	66.78 / 66.66	4.17 / 4.04	8.73 / 8.64	181-183	86
2c	$C_{18}H_{13}FN_2O_3$	66.75 / 66.66	4.14 / 4.04	8.56 / 8.64	189-191	89
2d	$C_{18}H_{13}FN_2O_3$	66.60 / 66.66	4.09 / 4.04	8.76 / 8.64	192-194	90
2e	$C_{18}H_{12}F_2N_2O_3$	63.07 / 63.16	3.44 / 3.53	8.09 / 8.18	217-219	85
2f	$C_{18}H_{13}ClN_2O_3$	63.53 / 63.44	3.92 / 3.85	8.30 / 8.22	162-164	83
2g	$C_{18}H_{13}ClN_2O_3$	63.40 / 63.44	3.88 / 3.85	8.17 / 8.22	169-171	88
2h	$C_{18}H_{13}ClN_2O_3$	63.51 / 63.44	3.77 / 3.85	8.16 / 8.22	226-228	94
2i	$C_{18}H_{12}Cl_2N_2O_3$	57.53 / 57.62	3.30 / 3.22	7.58 / 7.47	267-269	80
2j	$C_{18}H_{12}Cl_2N_2O_3$	57.55 / 57.62	3.14 / 3.22	7.40 / 7.47	240-242	82
2k	$C_{18}H_{13}BrN_2O_3$	56.19 / 56.12	3.47 / 3.40	7.35 / 7.27	167-169	80
2l	$C_{19}H_{15}BrN_2O_3$	57.25 / 57.16	3.86 / 3.79	7.11 / 7.02	225-227	84
2m	$C_{18}H_{13}BrN_2O_3$	56.20 / 56.12	3.49 / 3.40	7.22 / 7.27	199-201	87
2n	$C_{18}H_{13}BrN_2O_3$	56.10 / 56.12	3.36 / 3.40	7.24 / 7.27	236-238	91
2o	$C_{19}H_{16}N_2O_3$	71.33 / 71.24	5.14 / 5.03	8.66 / 8.74	178-180	85
2p	$C_{19}H_{16}N_2O_3$	71.30 / 71.24	5.12 / 5.03	8.81 / 8.74	145-147	89
2q	$C_{19}H_{16}N_2O_3$	71.35 / 71.24	5.16 / 5.03	8.65 / 8.74	202-204	90
2r	$C_{20}H_{18}N_2O_3$	71.77 / 71.84	5.35 / 5.43	8.30 / 8.38	225-227	81
2s	$C_{20}H_{18}N_2O_3$	71.92 / 71.84	5.54 / 5.43	8.29 / 8.38	214-216	84
2t	$C_{20}H_{18}N_2O_3$	71.94 / 71.84	5.51 / 5.43	8.42 / 8.38	227-229	82
2u	$C_{19}H_{16}N_2O_4$	67.78 / 67.85	4.86 / 4.79	8.39 / 8.33	188-190	86 (80)
2v	$C_{19}H_{15}ClN_2O_4$	61.67 / 61.55	4.15 / 4.08	7.46 / 7.55	224-226	86
2w	$C_{19}H_{16}N_2O_4$	67.93 / 67.85	4.70 / 4.79	8.25 / 8.33	163-165	90 (87)
2x	$C_{19}H_{16}N_2O_4$	67.91 / 67.85	4.86 / 4.79	8.39 / 8.33	184-186	93 (90)
2y	$C_{20}H_{18}N_2O_4$	68.47 / 68.56	5.11 / 5.18	8.07 / 8.00	195-197	95
2z	$C_{19}H_{13}F_3N_2O_3$	60.86 / 60.97	3.43 / 3.50	7.40 / 7.48	219-221	80
3a	$C_{19}H_{13}N_3O_3$	68.94 / 68.88	3.87 / 3.95	12.76 / 12.68	256-258	88
3b	$C_{20}H_{16}N_2O_5$	65.82 / 65.93	4.35 / 4.43	7.57 / 7.69	135-137	79
3c	$C_{19}H_{15}N_3O_4$	65.41 / 65.32	4.45 / 4.33	12.12 / 12.03	293-295	81

TABLE 1. (continued)

1	2	3	4	5	6	7
3d	$C_{20}H_{17}N_3O_4$	66.02 66.11	4.64 4.72	11.46 11.56	268-270	77
3e	$C_{20}H_{16}N_2O_5$	65.98 65.93	4.47 4.43	7.72 7.69	249-251	89
3f	$C_{21}H_{18}N_2O_5$	66.57 66.66	4.70 4.79	7.49 7.40	195-197	90
3g	$C_{22}H_{20}N_2O_5$	67.25 67.34	5.03 5.14	7.22 7.14	178-180	88
3h	$C_{23}H_{22}N_2O_5$	67.90 67.97	5.35 5.46	6.97 6.89	151-153	94
3i	$C_{18}H_{15}N_3O_5S$	56.02 56.10	3.81 3.92	10.83 10.90	257-259	73

* Yield using method A. For compounds **2a,u,w,x** the yields are given in brackets for method B.

imidazolide of acid **4** can be converted to the anilides **2** and **3** without any kind of complication (method B). It should be noted that method B can hardly be justified for the acylation of the majority of primary aromatic amines, in particular those used in the synthesis of anilides **2** and **3**. The introduction into the synthetic scheme of additional stages of hydrolysis of the ester function and subsequent activation of the carboxyl group is advisable only in those cases where hindrance to the use of method A occurs, e.g. in the acylation of thermally unstable anilines.

All of the synthesized 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1,-*ij*]quinoline-2-carboxylic acid anilides **2** and **3** (Table 1) are light-yellow crystalline materials and at room temperature are virtually insoluble in water, slightly soluble in alcohol, and moderately soluble in DMF and DMSO. ^{1}H NMR spectroscopy was used to confirm the chemical structure of the compounds obtained (Table 2).

The antitubercular activity of anilides **2** and **3** was studied *in vitro* by a radiometric method [14, 15] relative to *Mycobacterium tuberculosis* H37Rv ATCC 27294 at an initial concentration of 6.25 μg/ml. Primary microbiological experimental screening data showed that in contrast to our previous reports of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]-2-carboxylic acid heterylamides [12], which demonstrated a similarity in biological properties to the corresponding 1R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides with the lowest ($C_{(1)}$–$C_{(3)}$) alkyl substituents on the quinolone ring nitrogen atom, the anilides **2** and **3** showed an opposite trend in many respects. Hence, for example, if the absence of antitubercular activity in the unsubstituted anilide **2a** and its alkyl- and alkoxy-substituted analogs **2o-y** was fully expected, then the failure of inhibition of growth of the tubercular mycobacteria in the majority of the remaining compounds even to some degree was unexpected. It was found that exchange of a quinolone ring for pyrroloquinolone fully deactivates the normally highly active monofluoroanilides [16]. At the same time, in the case of 3,4-difluoro(**2e)**- and *ortho*-trifluoromethyl(**2z)**-substituted derivatives the indicated modification, conversely, slightly increases the antimycobacterial properties. In all of the group of synthesized materials only a single compound (the *meta*-chloroanilide **2g**) can be picked out as having 100% inhibition of the growth of the test strain in the first level of screening studies. However, the minimum inhibitory concentration (MIC) found at the subsequent step was 6.25 μg/ml for this compound which rules out any prospect of becoming a future antitubercular medicine (the MIC for such compounds should not exceed 1μg/ml).

The previously discovered [17] high level of diuretic activity shown by several 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid *cyclo*-alkylamides served as the theoretic reason for studying the effect of the synthesized compounds on the urinary function of the kidney. With the

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

Compound	Chemical shifts, δ, ppm (*J*,Hz)							
	1-OH (1H, s)	NH (1H, s)	Pyrroloquinoline					Anilide fragment
			H-9 (1H, d)	H-7 (1H, d)	H-8 (1H, t)	5-CH_2 (2H, t)	6-CH_2 (2H, t)	
1	2	3	4	5	6	7	8	9
2a	16.57	12.56	7.73 (*J* = 8.0)	7.46 (*J* = 7.4)	7.18 (*J* = 8.0)	4.38 (*J* = 8.0)	3.44 (*J* = 8.0)	7.66 (2H, d, *J* = 7.7, H-2',6'); 7.32 (2H, t, *J* = 8.0, H-3',5'); 7.09 (1H, t, *J* = 7.2, H-4')
2b	16.26	12.76	7.74 (*J* = 7.9)	7.42 (*J* = 7.3)	7.16 (*J* = 8.0)	4.41 (*J* = 8.2)	3.44 (*J* = 7.8)	8.41 (1H, t, *J* = 7.8, H-3'); 7.13-7.03 (3H, m, H-4',5',6')
2c	16.26	12.67	7.73 (*J* = 8.0)	7.42 (*J* = 7.2)	7.16 (*J* = 8.0)	4.37 (*J* = 8.0)	3.43 (*J* = 8.0)	7.64 (1H, d, *J* = 10.7, H-2'); 7.29 (2H, m, H-4',6'); 6.81 (1H, t, *J* = 7.7, H-5')
2d	16.43	12.56	7.72 (*J* = 7.8)	7.45 (*J* = 7.1)	7.17 (*J* = 7.6)	4.37 (*J* = 8.0)	3.44 (*J* = 7.9)	7.67 (2H, dd, *J* = 8.4 and *J* = 5.4, H-2',6'); 7.05 (2H, t, *J* = 8.4, H-3',5')
2e	16.14	12.71	7.73 (*J* = 7.8)	7.49 (*J* = 7.0)	7.17 (*J* = 7.8)	4.38 (*J* = 7.9)	3.45 (*J* = 7.8)	7.83 (1H, dd, *J* = 12.4 and *J* = 7.4, H-6'); 7.29 (1H, d, *J* = 8.7, H-2'); 7.22 (1H, t, *J* = 9.8, H-5')
2f	16.10	12.91	7.72 (*J* = 8.0)	7.58 (*J* = 7.2)	7.28 (*J* = 7.8)	4.37 (*J* = 8.0)	3.46 (*J* = 7.9)	8.35 (1H, dd, *J* = 8.5 and *J* = 2.0, H-6'); 7.55 (1H, dd, *J* = 8.4 and *J* = 2.1, H-3'); 7.39 (1H, t, *J* = 8.0, H-4'); 7.20 (1H, td, *J* = 7.8 and *J* = 2.0, H-5')
2g	16.03	12.74	7.71 (*J* = 8.0)	7.59 (*J* = 7.1)	7.27 (*J* = 7.9)	4.38 (*J* = 8.1)	3.44 (*J* = 8.0)	7.81 (1H, s, H-2'); 7.47 (1H, d, *J* = 7.9, H-6'); 7.38 (1H, t, *J* = 8.0, H-5'); 7.19 (1H, d, *J* = 7.9, H-4')
2h	16.33	12.68	7.74 (*J* = 8.1)	7.49 (*J* = 7.0)	7.20 (*J* = 7.9)	4.39 (*J* = 8.0)	3.45 (*J* = 8.0)	7.67 (2H, d, *J* = 8.9, H-2',6'); 7.31 (2H, d, *J* = 8.9, H-3',5')
2i	16.10	13.11	7.76 (*J* = 8.1)	7.52 (*J* = 7.0)	7.21 (*J* = 7.6)	4.44 (*J* = 8.0)	3.48 (*J* = 8.0)	8.43 (1H, d, *J* = 9.1, H-6'); 7.30-7.26 (2H, m, H-4',5')
2j	15.98	13.03	7.75 (*J* = 7.9)	7.60 (*J* = 7.0)	7.27 (*J* = 7.9)	4.41 (*J* = 8.0)	3.46 (*J* = 7.9)	8.40 (1H, d, *J* = 9.0, H-6'); 7.57 (1H, s, H-3'); 7.40 (1H, dd, *J* = 9.1 and *J* = 1.9, H-5')
2k	16.30	12.77	7.72 (*J* = 8.1)	7.47 (*J* = 7.0)	7.18 (*J* = 7.7)	4.40 (*J* = 8.0)	3.45 (*J* = 8.0)	8.39 (1H, d, *J* = 8.4, H-6'); 7.59 (1H, d, *J* = 7.9, H-3'); 7.33 (1H, t, *J* = 7.8, H-4'); 7.03 (1H, t, *J* = 7.7, H-5')
2l	16.31	12.74	7.71 (*J* = 8.1)	7.58 (*J* = 7.0)	7.21 (*J* = 7.7)	4.36 (*J* = 7.9)	3.41 (*J* = 7.8)	8.14 (1H, d, *J* = 8.0, H-6'); 7.52 (1H, s, H-3'); 7.29 (1H, d, *J* = 7.4, H-5'); 2.31 (3H, s, CH_3)
2m	16.24	12.71	7.74 (*J* = 8.0)	7.48 (*J* = 7.2)	7.20 (*J* = 7.8)	4.39 (*J* = 7.9)	3.45 (*J* = 7.9)	7.98 (1H, s, H-2'); 7.53 (1H, d, *J* = 7.7, H-6'); 7.27 (2H, m, H-4',5')
2n	16.26	12.69	7.72 (*J* = 8.1)	7.51 (*J* = 7.0)	7.21 (*J* = 7.6)	4.37 (*J* = 7.8)	3.44 (*J* = 7.7)	7.61 (2H, d, *J* = 8.3, H-2',6'); 7.46 (2H, d, *J* = 8.3, H-3',5')
2o	16.69	12.40	7.72 (*J* = 8.1)	7.46 (*J* = 7.3)	7.16 (*J* = 7.8)	4.38 (*J* = 8.0)	3.43 (*J* = 7.9)	8.16 (1H, d, *J* = 8.1, H-6'); 7.25-7.20 (2H, m, H-3',5'); 7.00 (1H, t, *J* = 7.5, H-4'); 2.42 (3H, s, CH_3)
2p	16.61	12.52	7.71 (*J* = 8.1)	7.44 (*J* = 7.2)	7.20 (*J* = 7.8)	4.37 (*J* = 8.1)	3.43 (*J* = 8.0)	7.55 (1H, d, *J* = 7.8, H-6'); 7.48 (1H, s, H-2'); 7.16 (1H, t, *J* = 7.4, H-5'); 6.90 (1H, d, *J* = 7.8, H-4'); 2.38 (3H, s, CH_3)
2q	16.68	12.47	7.73 (J = 7.9)	7.46 (J = 7.0)	7.18 (J = 7.8)	4.38 (J = 8.1)	3.44 (J = 8.0)	7.53 (2H, d, *J* = 8.3, H-2',6'); 7.11 (2H, d, *J* = 8.3, H-3',5'); 2.34 (3H, s, CH3)

TABLE 2. (continued)

1	2	3	4	5	6	7	8	9
2r	16.75	12.39	7.72 (J = 8.1)	7.55 (J = 7.2)	7.24 (J = 7.9)	4.39 (J = 8.0)	3.45 (J = 8.0)	7.81 (1H, d, J = 8.1, H-6'); 7.08 (1H, t, J = 8.0, H-5'); 6.99 (1H, d, J = 7.5, H-4'); 2.33 (3H, s, CH_3); 2.27 (3H, s, CH_3)
2s	16.84	12.31	7.75 (J = 8.1)	7.47 (J = 7.2)	7.18 (J = 7.7)	4.40 (J = 8.2)	3.46 (J = 8.1)	8.00 (1H, d, J = 8.1, H-6'); 6.99 (1H, s, H-3'); 6.94 (1H, d, J = 7.9, H-5'); 2.38 (3H, s, CH_3); 2.31 (3H, s, CH_3)
2t	16.68	12.41	7.72 (J = 8.1)	7.54 (J = 7.2)	7.23 (J = 7.8)	4.37 (J = 8.0)	3.44 (J = 7.9)	7.93 (1H, s, H-6'); 7.09 (1H, d, J = 7.5, H-3'); 6.87 (1H, d, J = 7.5, H-4'); 2.33 (6H, s, $2CH_3$)
2u	16.76	12.59	7.72 (J = 8.1)	7.40 (J = 7.1)	7.13 (J = 7.6)	4.38 (J = 8.0)	3.43 (J = 8.0)	8.40 (1H, d, J = 8.3, H-6'); 7.03 (1H, t, J = 7.9, H-4'); 6.94-6.88 (2H, m, H-3',5'); 3.99 (3H, s, OCH_3)
2v	16.35	12.76	7.71 (J = 8.0)	7.47 (J = 7.3)	7.17 (J = 7.7)	4.37 (J = 8.1)	3.44 (J = 8.0)	8.43 (1H, d, J = 2.2, H-6'); 7.02 (1H, dd, J = 8.7 and J = 2.7, H-4'); 6.95 (1H, d, J = 8.7, H-3'); 3.96 (3H, s, OCH_3)
2w	16.44	12.63	7.71 (J = 7.9)	7.54 (J = 6.9)	7.22 (J = 7.9)	4.36 (J = 7.9)	3.42 (J = 7.9)	7.31 (1H, s, H-2'); 7.27 (1H, t, J = 8.5, H-5'); 7.13 (1H, d, J = 7.9, H-6'); 6.71 (1H, d, J = 7.9, H-4'); 3.80 (3H, s, OCH_3)
2x	16.73	12.40	7.73 (J = 8.2)	7.44 (J = 7.1)	7.18 (J = 7.8)	4.38 (J = 8.2)	3.44 (J = 8.1)	7.57 (2H, d, J = 8.7, H-2',6'); 6.85 (2H, d, J = 8.7, H-3',5'); 3.79 (3H, s, OCH_3)
2y	16.65	12.46	7.70 (J = 8.2)	7.56 (J = 7.2)	7.24 (J = 7.9)	4.35 (J = 8.0)	3.41 (J = 7.9)	7.51 (2H, d, J = 9.0, H-2',6'); 6.92 (2H, d, J = 9.0, H-3',5'); 4.03 (2H, q, J = 7.2, OCH_2); 1.35 (3H, t, J = 7.2, CH_3)
2z	16.23	12.77	7.76 (J = 8.0)	7.47 (J = 7.2)	7.18 (J = 7.8)	4.44 (J = 8.1)	3.46 (J = 7.9)	8.25 (1H, d, J = 8.5, H-6'); 7.67 (1H, d, J = 8.0, H-3'); 7.59 (1H, t, J = 7.9, H-4'); 7.29 (1H, t, J = 7.8, H-5')
3a	15.89	13.13	7.83 (J = 8.0)	7.62 (J = 7.1)	7.28 (J = 7.7)	4.42 (J = 8.0)	3.45 (J = 7.9)	8.28 (1H, d, J = 8.0, H-6'); 7.77-7.71 (2H, m, H-3',4'); 7.37 (1H, t, J = 8.0, H-5')
3b	16.55	13.09	7.72 (J = 8.0)	7.44 (J = 7.2)	7.18 (J = 7.9)	4.41 (J = 8.1)	3.44 (J = 8.0)	8.39 (1H, d, J = 8.5, H-6'); 7.95 (1H, dd, J = 8.1 and J = 1.8, H-3'); 7.52 (1H, td, J = 7.7 and J = 1.8, H-4'); 7.14 (1H, t, J = 7.4, H-5'); 3.96 (3H, s, OCH_3)
3c	16.68	12.85	7.70 (J = 8.0)	7.48 (J = 7.2)	7.18 (J = 7.8)	4.36 (J = 8.0)	3.41 (J = 8.0)	8.12 (1H, d, J = 8.4, H-6'); 7.91 (1H, s, NH in NH_2); 7.60-7.54 (2H, m, H-3',4'); 7.38 (1H, s, NH in NH_2); 7.25 (1H, t, J = 7.9, H-5')
3d	16.65	12.79	7.71 (J = 8.2)	7.58 (J = 7.1)	7.17 (J = 7.8)	4.37 (J = 8.0)	3.42 (J = 7.9)	8.37 (1H, br. s, NH); 8.10 (1H, d, J = 7.9, H-6'); 7.51 (1H, d, J = 7.9, H-3'); 7.47 (1H, t, J = 7.9, H-4'); 7.26 (1H, t, J = 7.8, H-5'); 2.79 (3H, d, J = 4.5, CH_3)
3e	16.08	12.96	7.71 (J = 8.2)	7.59 (J = 7.1)	7.26 (J = 7.8)	4.35 (J = 7.9)	3.42 (J = 7.9)	7.57 (2H, d, J = 8.4, H-2',6'); 7.77 (2H, d, J = 8.4, H-3',5'); 3.84 (3H, s, OCH_3)
3f	16.21	12.85	7.72 (J = 8.0)	7.48 (J = 7.0)	7.19 (J = 7.7)	4.39 (J = 8.0)	3.45 (J = 8.0)	7.95 (2H, d, J = 8.4, H-2',6'); 7.78 (2H, d, J = 8.4, H-3',5'); 4.32 (2H, q, J = 7.0, OCH_2); 1.40 (3H, t, J = 7.0, CH_3)
3g	16.24	12.83	7.78 (J = 8.0)	7.48 (J = 7.2)	7.20 (J = 7.6)	4.41 (J = 8.0)	3.46 (J = 8.0)	7.98 (2H, d, J = 8.4, H-2',6'); 7.75 (2H, d, J = 8.4, H-3',5'); 4.24 (2H, t, J = 6.5, OCH_2); 1.81 (2H, m, $C\underline{H}_2CH_3$); 1.07 (3H, t, J = 7.5, CH_3)
3h	16.25	12.85	7.77 (J = 8.0)	7.47 (J = 7.0)	7.19 (J = 7.6)	4.39 (J = 7.9)	3.45 (J = 7.9)	7.95 (2H, d, J = 8.3, H-2',6'); 7.75 (2H, d, J = 8.3, H-3',5'); 4.26 (2H, t, J = 6.6, OCH_2); 1.75 (2H, q, J = 7.2, $OCH_2C\underline{H}_2$); 1.50 (2H, m, $C\underline{H}_2CH_3$); 1.02 (3H, t, J = 7.3, CH_3)
3i	16.34	12.59	7.73 (J = 7.9)	7.52 (J = 7.2)	7.32 (J = 7.6)	4.42 (J = 8.0)	3.46 (J = 8.0)	8.11 (1H, d, J = 8.1, H-6'); 7.95 (1H, dd, J = 8.1 and J = 1.8, H-3'); 7.58 (1H, td, J = 7.6 and J = 1.7, H-4'); 7.21 (3H, m, H-5' + SO_2NH_2)

arylalkylamides the diuretic effect is more strongly expressed while it has been shown experimentally that the benzylamides always appear more active than their 2-arylethyl and 3-arylpropyl analogs, i.e. exchange from a methylene separating the aromatic ring and the amide nitrogen atom to a chain of two or three methylenes leads to a marked lowering in activity. The question of how removal of a designated methylene group from the molecule reflects on the biological properties can only be answered experimentally. Interest in the testing of anilides close in structure to the arylalkylamides mentioned (**2** and **3)** is a result of this.

The studies were carried out by a known method [18] using white nonpedigree rats of weight 180-200 g. The results obtained in this way show that the transition from benzylamides to 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid anilides with the same substituents in the aromatic amide ring is generally accompanied by a marked increase in diuretic effects. As a rule, *m*-isomers proved more active than their *o*- and *p*-substituted analogs. For example, amongst the three monofluoroanilides **2b-d** an increase in diuresis is only caused by the *m*-fluoro derivative **2c** whereas the isomeric *o*- and *p*-fluoroanilides **2b,d** show no overall effect on urinary excretion. The same pattern has been observed by us before for monofluoro-benzylamides. It was interesting that the strength of the diuretic effect caused by the 3,4-difluoroanilide **2e** and its 3-fluoro-substituted precursor **2c** were identical. This fact gives us a basis for identifying the presence of a fluorine in the *p*-position of the anilide fragment as unwanted since its presence (or conversely absence) has no influence on the diuretic properties. An even more weighty argument supporting this conclusion is the well known dependence found when developing fluoroquinolone antibiotics: an increase in the number of fluorine atoms in the molecule causing an inherent increase in the toxicity of the chemical material [19].

In the series of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid anilides with electron-acceptor substituents (which have acidic properties or are able to be converted to them *in vivo*) a moderate increase in diuresis in experimental animals is only brought about by the 2-sulfamoyl derivative **3i**. The anilides **3a-h**, prepared from nitriles, amides, and esters of aromatic carboxylic amino acids, not only do not possess diuretic properties but, in several cases, e.g. the 2-carbamoyl anilide **3c**, even markedly depress urinary excretion.

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Bruker WM-360 (360 MHz) instrument for DMSO-d_6 solutions and with TMS as internal standard. 1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acid (**4**) and its ethyl ester **1** were prepared by the methods [20] and [21] respectively. Anhydrous DMF for peptide synthesis and N,N-carbonyldiimidazole from the Fluka company were used in the synthesis of the amides **2** and **3** by method B.

1-Hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic Acid Anilides 2a-z, 3a-i. A. A mixture of ester **1** (2.59 g, 0.01 mol), the corresponding aniline (0.01 mol) and DMF (1 ml) was held in a metal bath for 3-5 min at 160ºC. When the heating was complete the hot reaction mixture was treated with ethanol (15-20 ml) (Care ! The solution may boil over vigorously) and carefully triturated. This process stopped solidification of the reaction mass and significantly eased the separation and subsequent purification of the final product. The precipitated anilides **2a-z** or **3a-i** were filtered, washed with alcohol, dried, and crystallized from DMF.

B. N,N-Carbonyldiimidazole (1.78 g, 0.011 mol) was added to a solution of acid **4** (2.31 g, 0.01 mol) in anhydrous DMF (30 ml) protected from atmospheric moisture by a $CaCl_2$ tube and held at a temperature not greater than 40ºC until CO_2 evolution ceased (~ 5 h). The corresponding aniline (0.01 mol) was added, the reaction mixture heated to 90ºC, held at this temperature for 2 h, cooled, and diluted with acidified HCl water. The precipitated anilides **2** or **3** were filtered off, washed with water, and dried.

The identical nature of anilides **2** or **3** prepared by the different methods were proved by the absence of melting point depression for mixed samples and from their ^{1}H NMR spectra.

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