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4-HYDROXY-2-QUINOLONES

142*. 4-METHYL-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACID ANILIDES AS POTENTIAL DIURETICS

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A large series of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilides has been prepared as potential diuretic agents. The effect of all of the synthesized compounds on the urinary function of the kidney has been investigated. The appearance of a "structure – diuretic activity" relationship is discussed.

Keywords: anilides, diuretics, 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid, amidation.

In recent years along with the well known efficient use of diuretics in the treatment of kidney deficiency [2], glaucoma [3], epilepsy [4], and insipid diabetes [5, 6] the attention of pharmacologists and doctors has been increasingly paid to currently uncommon areas of use of the extrarenal effects of diuretic medicines in the treatment of bronchial obstruction syndrome, mucoviscidose [7], oncological [8, 9], and a series of other illnesses. There is particular interest in the medicinal uses of diuretics which show both their diuretic properties together with anti-inflammatory [10, 11], antioxidant [12, 13], antimicrobial [14, 15], cholagogue [16], hepato-protective [17], hypolipidemic [18], and other useful activity. Even a cursory glance at the literature shows a marked and steadily increasing tendency to broaden the catalog of indications for diuretic agents in clinical practice. At the same time, over the last 30 years not a single class of novel diuretic has appeared in the world pharmaceutical market although the need for such preparations is obvious.

It is interesting that quinoline type compounds have not been considered up to recent times as possible diuretic agents because such a type of pharmacological activity is considered atypical. None the less, in the process of carrying out systematic investigations, potential diuretics have been discovered by us amongst 4-hydroxyquinol-2-ones. It was possible to discover an interesting relationship, particularly fully and clearly identified in the case of amide derivatives of 1-hydroxy-3-oxo-5,6-dihydro-3H-pyrrolo[3,2,1-*ij*]quinoline-2-carboxylic acids. As a result it was convincingly shown that the level of the diuretic effect of the quinolone compounds depends significantly on the structure of the amide fragment and increases in the sequence: alkylamides < cycloalkylamides < 3-arylpropylamides < 2-arylethylamides < benzylamides << anilides [19, 20].

* For Communication 141 see [1]

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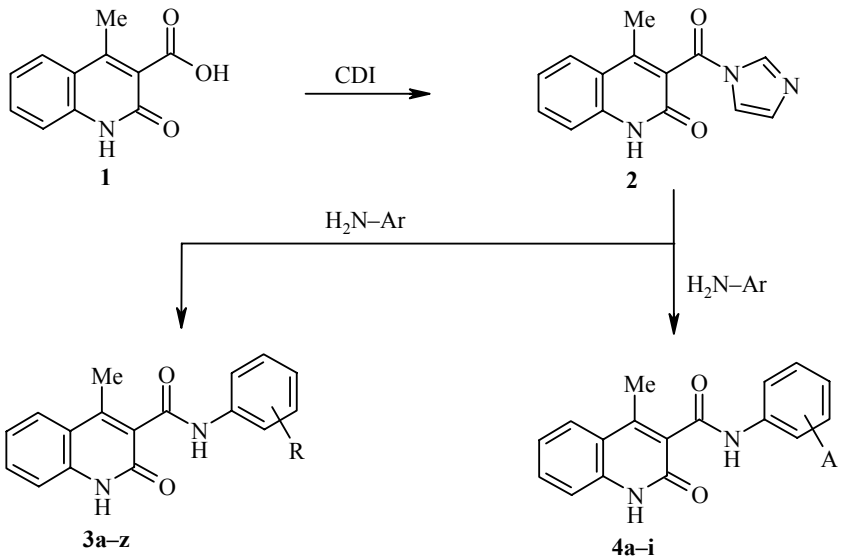
A similar dependence was found in a study of the alkyl- and arylalkylamides of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [21]. It follows that a high probability is retained of still higher diuretic properties on transition to the anilides of these acids. This proposal served as the basis for undertaking the current investigation.

Although, as shown earlier [21], amidation of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**) *via* the corresponding acid chloride is possible, it is somewhat complicated by the formation of cyanine dye by-products which can impart a red coloration to the final reaction products even at low concentration. With this in mind we have attempted to activate the carbonyl carbon atom of the carboxyl group in acid **1** by another means, *viz.* the use of the well known organic synthetic reagent N,N'-carbonyldiimidazole (CDI).

Carrying out the experiment showed that the 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid imidazolide (**2**) is formed quite readily and in virtually quantitative yield. However its reactivity with relation to N-nucleophiles proved extremely low and quite rigid conditions (prolonged refluxing with anilines in high boiling solvents) were needed for full transformation to the anilides **3** and **4**. An unusual inertness (at least at room temperature) was noted for the imidazolide **2** towards water and, in principle, it can be used for separation of this compound in the pure state even though similar treatment would inevitably end in hydrolysis. The intermediate imidazolides are generally not separable from the reaction mixture. Our case is not an exception and allsuccessive stages of the conversion of acid **1** to anilides are carried out in a single vessel.



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

All of the synthesised 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid anilides **3** and **4** (Table 1) are colorless or white tinged with yellow, crystalline substances insoluble in water at room temperature, of low solubility in alcohol, and moderately soluble in DMF and DMSO. A characteristic feature of the ^{1}H NMR spectra of anilides **3** and **4** (Table 2) is the grouping of the signals for 7-9 aromatic protons in a rather narrow (1 ppm) region of the spectrum hence specific assignments are frequently complex or quite not possible without the use of special NMR methods.

TABLE 1. Characteristics of 4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Anilides **3a-z**, **4a-i**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Diuretic activity,* % to control
		C	H	N			
1	2	3	4	5	6	7	8
3a	$C_{17}H_{14}N_2O_2$	73.46 / 73.37	5.13 / 5.07	10.15 / 10.07	280-282	82	+52
3b	$C_{17}H_{13}FN_2O_2$	68.97 / 68.91	4.34 / 4.42	9.40 / 9.45	275-277	75	+9
3c	$C_{17}H_{13}FN_2O_2$	68.99 / 68.91	4.51 / 4.42	9.53 / 9.45	283-285	78	0
3d	$C_{17}H_{13}FN_2O_2$	68.85 / 68.91	4.48 / 4.42	9.54 / 9.45	291-293	80	-9
3e	$C_{17}H_{12}F_2N_2O_2$	64.90 / 64.97	3.77 / 3.85	8.85 / 8.91	304-306	76	-11
3f	$C_{17}H_{13}ClN_2O_2$	65.22 / 65.29	4.14 / 4.19	9.03 / 8.96	295-297	72	+30
3g	$C_{17}H_{13}ClN_2O_2$	65.35 / 65.29	4.16 / 4.19	9.07 / 8.96	276-278	74	-11
3h	$C_{17}H_{13}ClN_2O_2$	65.37 / 65.29	4.28 / 4.19	8.99 / 8.96	307-309	77	-22
3i	$C_{17}H_{12}Cl_2N_2O_2$	58.88 / 58.81	3.40 / 3.48	8.00 / 8.07	322-324	70	+4
3j	$C_{17}H_{12}Cl_2N_2O_2$	58.75 / 58.81	3.55 / 3.48	8.14 / 8.07	335-337	73	-4
3k	$C_{17}H_{12}Cl_2N_2O_2$	58.73 / 58.81	3.53 / 3.48	8.12 / 8.07	330-332	71	-17
3l	$C_{17}H_{13}BrN_2O_2$	57.24 / 57.16	3.75 / 3.67	7.76 / 7.84	291-293	70	-4
3m	$C_{18}H_{15}BrN_2O_2$	58.21 / 58.24	4.11 / 4.07	7.50 / 7.55	283-285	72	-9
3n	$C_{17}H_{13}BrN_2O_2$	57.07 / 57.16	3.73 / 3.67	7.92 / 7.84	288-290	76	-30
3o	$C_{17}H_{13}BrN_2O_2$	57.10 / 57.16	3.62 / 3.67	7.94 / 7.84	304-306	80	+30
3p	$C_{18}H_{16}N_2O_2$	74.05 / 73.96	5.63 / 5.52	9.66 / 9.58	248-250	73	+9
3q	$C_{18}H_{16}N_2O_2$	73.90 / 73.96	5.59 / 5.52	9.63 / 9.58	269-271	75	0
3r	$C_{18}H_{16}N_2O_2$	73.88 / 73.96	5.50 / 5.52	9.53 / 9.58	275-277	79	+43
3s	$C_{19}H_{18}N_2O_2$	74.57 / 74.49	5.84 / 5.92	9.06 / 9.14	299-301	72	+57
3t	$C_{19}H_{18}N_2O_2$	74.55 / 74.49	5.98 / 5.92	9.19 / 9.14	250-252	74	+9
3u	$C_{19}H_{18}N_2O_2$	74.41 / 74.49	5.86 / 5.92	9.22 / 9.14	272-274	70	+22
3v	$C_{18}H_{16}N_2O_3$	70.20 / 70.12	5.31 / 5.23	9.16 / 9.09	228-230	70	+57
3w	$C_{18}H_{15}ClN_2O_3$	62.94 / 63.07	4.33 / 4.41	8.10 / 8.17	291-293	73	0
3x	$C_{18}H_{16}N_2O_3$	70.17 / 70.12	5.30 / 5.23	9.02 / 9.09	280-282	77	-35
3y	$C_{18}H_{16}N_2O_3$	70.18 / 70.12	5.27 / 5.23	9.13 / 9.09	264-266	85	+57
3z	$C_{19}H_{18}N_2O_3$	70.70 / 70.79	5.54 / 5.63	8.58 / 8.69	253-255	82	-13
4a	$C_{18}H_{13}F_3N_2O_2$	62.32 / 62.43	3.85 / 3.78	8.13 / 8.09	264-266	69	+9
4b	$C_{18}H_{13}F_3N_2O_2$	62.35 / 62.43	3.70 / 3.78	8.02 / 8.09	277-279	78	+52
4c	$C_{18}H_{13}N_3O_2$	71.33 / 71.28	4.39 / 4.32	13.94 / 13.85	296-298	72	-4
4d	$C_{18}H_{14}N_2O_4$	67.16 / 67.08	4.31 / 4.38	8.77 / 8.69	288-290	68	+9

TABLE 1. (continued)

1	2	3	4	5	6	7	8
4e	$C_{18}H_{14}N_2O_4$	67.12 / 67.08	4.42 / 4.38	8.64 / 8.69	355-357	74	-22
4f	$C_{18}H_{14}N_2O_4$	67.05 / 67.08	4.34 / 4.38	8.65 / 8.69	372-374	77	-2
4g	$C_{20}H_{18}N_2O_4$	68.64 / 68.56	5.23 / 5.18	8.06 / 8.00	256-258	83	+2
4h	$C_{18}H_{15}N_3O_3$	67.21 / 67.28	4.65 / 4.71	13.15 / 13.08	311-313	74	+30
4i	$C_{17}H_{15}N_3O_4S$	57.04 / 57.13	4.30 / 4.23	11.68 / 11.76	307-309	72	+30
	Hypothiazide	—	—	—	—	—	+57

* "+" represents an increase and "-" an inhibition of diuresis relative to control, taken as 100%.

Pharmacological screening for the appearance in the anilides **3** and **4** of the ability to stimulate the excretory function of the kidney in laboratory animals was carried out by a standard method described by us in detail before [21] in a parallel comparison with hypothiazide. On the basis of a comparison of the experimental data (Table 1) with the results of preceding investigations [20, 21] we found that the anilides prove to more active than the corresponding benzylamides with similar substituents in the aromatic ring. Only in one example (the 4-chloroanilide **3h**) where a methylene unit separating the amide nitrogen atom and the aromatic ring was removed were diuretic properties lowered. In all of the remaining cases the same change can be considered desirable.

In the group of anilides **4** which contain powerful electron-acceptor substituents attention was only merited by one compound (the *m*-trifluoromethyl derivative **4b**) in which the activity was not inferior to the known diuretic hypothiazide. It was interesting that diuretic properties were generally not present in the anilides **4d-f** which contain carboxyl groups as substituent or also in their structural analogs **4c,g** with groups able to undergo conversion to a carboxyl *in vivo*. The 2-sulfamoyl derivative **4i** and its neutral 2-carbamoyl analog **4h** show an identical moderate level of diuretic activity despite the marked difference in their acidic properties. This gives us grounds to propose that, as regards the mechanism of action of diuretic activity, the quinolone compounds differ somewhat from the widely used carbonic anhydrase inhibitors.

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Varian Mercury VX-200 (200 MHz) instrument using DMSO-d_6 solvent and TMS internal standard. The mass spectrum of the imidazolide **2** was taken on a Varian 1200L instrument with full scanning in the range 35-700 *m/z*, ionization energy 70 eV, and with direct introduction. Anhydrous DMF for peptide synthesis and N,N'-carbonyldiimidazole were used from the Fluka company.

4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Imidazolide (2). N,N'-Carbonyldiimidazole (1.78 g, 0.011 mol) was added to a solution of the acid **1** (2.03 g, 0.01 mol) in anhydrous DMF (10 ml) and protected from atmospheric moisture using a $CaCl_2$ tube. It was held for about 2 h at 90ºC until CO_2 evolution had ceased. The reaction mixture was cooled and diluted with cold water. The precipitated imidazolide **2** was filtered off, washed with cold water, and dried. Yield 2.50 g (99%); mp 295-297ºC (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.19 (1H, s, NH); 8.29 (1H, s, 2'-H imidazole); 7.88 (1H, dd, *J* = 8.2 and *J* = 1.0, H-5); 7.72 (1H, t,

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

Compound	Chemical shifts, δ, ppm (*J*, Hz)				
	NH` (1H, s)	NH-Ar (1H, s)	H arom., m	4-CH_3 (3H, s)	Other functional groups
3a	11.96	10.38	7.85-7.04 (9H)	2.42	—
3b	11.97	10.42	8.11-7.18 (8H)	2.45	—
3c	12.01	10.61	7.86-6.88 (8H)	2.41	—
3d	11.96	10.45	7.87-7.12 (8H)	2.41	—
3e	12.02	10.63	7.94-7.19 (7H)	2.43	—
3f	12.00	10.43	7.97-7.18 (8H)	2.56	—
3g	12.01	10.59	7.98-7.12 (8H)	2.41	—
3h	11.99	10.52	7.84-7.22 (8H)	2.41	—
3i	12.07	10.64	8.05-7.18 (7H)	2.57	—
3j	12.03	10.61	8.01-7.22 (7H)	2.55	—
3k	12.08	10.82	8.18-7.23 (7H)	2.58	—
3l	12.02	10.33	7.89-7.09 (8H)	2.56	—
3m	11.99	10.24	7.90-7.19 (7H)	2.57	2.30 (3H, s, 4'-CH_3)
3n	12.00	10.58	8.08-7.22 (8H)	2.42	—
3o	11.98	10.52	7.86-7.18 (8H)	2.41	—
3p	11.91	9.86	7.87-7.08 (8H)	2.43	2.28 (3H, s, 2'-CH_3)
3q	11.97	10.30	7.82-6.86 (8H)	2.40	2.29 (3H, s, 3'-CH_3)
3r	11.96	10.27	7.83-7.11 (8H)	2.39	2.26 (3H, s, 4'-CH_3)
3s	11.91	9.88	7.86-7.03 (7H)	2.44	2.26 (3H, s,CH_3); 2.17 (3H, s, CH_3)
3t	11.84	9.79	7.84-6.99 (7H)	2.45	2.25 (3H, s, CH_3); 2.22 (3H, s, CH_3)
3u	11.93	9.82	7.87-6.89 (7H)	2.44	2.27 (3H, s, CH_3); 2.21 (3H, s, CH_3)
3v	11.96	9.99	8.21-6.93 (8H)	2.52	3.79 (3H, s, 2'-OCH_3)
3w	12.01	10.35	8.39-7.00 (7H)	2.52	3.84 (3H, s, 2'-OCH_3)
3x	11.97	10.40	7.85-6.63 (8H)	2.42	3.75 (3H, s, 3'-OCH_3)
3y	11.94	10.22	7.84-6.87 (8H)	2.41	3.71 (3H, s, 4'-OCH_3)
3z	11.95	10.22	7.82-6.86 (8H)	2.41	3.97 (2H, q, *J* = 7.0, OCH_2); 1.29 (3H, t, *J* = 7.0, $OCH_2C\underline{H}_3$)
4a	12.00	10.43	7.90-7.20 (8H)	2.51	—
4b	12.04	10.76	8.22-7.18 (8H)	2.43	—
4c	12.02	10.84	7.89-7.22 (8H)	2.55	—
4d	12.05	11.57	8.66-7.20 (8H)	2.45	12.80 (1H, br. s, 2'-COOH)
4e	12.01	10.59	8.39-7.22 (8H)	2.41	13.00 (1H, br. s, 3'-COOH)
4f	12.02	10.72	7.98-7.21 (8H)	2.40	12.83 (1H, br. s, 4'-COOH)
4g	12.00	10.76	7.99-7.21 (8H)	2.42	4.28 (2H, q, *J* = 7.1, OCH_2); 1.30 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$)
4h	11.99	11.90	8.63-7.13 (8H)	2.45	8.28 (1H, s, CONH); 7.67 (1H, s, CONH);
4i	12.25	9.79	7.98-7.26 (10H, H arom. + SO_2NH_2)	2.56	See H arom.

J = 1.5, H-5' imidazole); 7.63 (1H, td, *J* = 7.7 and *J* = 1.2, H-7); 7.38 (1H, dd, *J* = 8.3 and *J* = 0.7, H-8); 7.29 (1H, td, *J* = 7.4 and *J* = 1.2, H-6); 7.10 (1H, dd, *J* = 1.8 and *J* = 1.0, H-4' imidazole); 2.38 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 253 $[M]^+$ (11), 186 $[M–imidazole]^+$ (100), 157 $[M–imidazole–CHO]^+$ (3), 142 $[M–imidazole–CHO–CH_3]^+$ (1), 130 (31), 103 (10), 77 (15). Found, %: C 66.47; H 4.49; N 16.65. $C_{14}H_{11}N_3O_2$. Calculated, %: C 66.40; H 4.38; N 16.59.

4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Anilides (3, 4) (General Method). At the end of the reaction of acid **1** (2.03 g, 0.01 mol) in anhydrous DMF (10 ml) with N,N'-carbonyldiimidazole (1.78 g, 0.011 mol) (see preceding example) the corresponding aniline (0.01 mol) was added to the reaction mixture and

refluxed for 6-8 h. It was cooled, diluted with cold water, and acidified with diluted (1:1) HCl to pH 4-5. The precipitated anilide **3** or **4** was filtered off, washed with water, dried, and crystallized from DMF.

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