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4-HYDROXY-2-QUINOLONES 140*. SYNTHESIS AND DIURETIC ACTIVITY OF ARYLALKYLAMIDES OF 4-METHYL-2-OXO-1,2-DIHYDRO-QUINOLINE-3-CARBOXYLIC ACID

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The interaction of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid with thionyl chloride in oxygen-containing solvents leads to the formation of a significant amount of colored side products, consequently it was proposed the reaction be carried out in carbon tetrachloride. The synthesis of a series of amides was effected by the amidation of the obtained acid chloride with appropriate primary arylalkylamines. Results are presented of a study of the effect of the synthesized compounds on the urine-excreting function of the kidney.

Keywords: amides, 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid, diuretic action, X-ray structural analysis.

Diuretics are widely used in the treatment of illnesses accompanied by retention of fluid in the organism. Until recently indications to their use have been in the main limited only to edematous syndromes of heart, kidney, liver, or endocrine origin. However after revealing their antihypertensive action many diuretics acquired a new importance in medical practice and became basic agents for various forms and stages of hypertension, glaucoma, and other illnesses [2, 3].

Almost half the world market for diuretics today is provided by three biologically active substances, furosemide, hypothiazide, and spironolactone. A large number of different prepared medicinal forms and combined preparations has been designed based on these. Altogether the contemporary arsenal of drug substances capable of strengthening the eliminatory function of the kidney and authorized for medical use amounts to about 60 names [4]. Regrettably, not one of them is devoid of side effects, the most important of which, depending on the mechanism of action, may be hyper- or hypokalemia, hyperglycemia, exacerbation of sugar diabetes, deterioration of hearing, nausea, dermatitis, etc [2, 3]. Proceeding from this, the search for new potential diuretic agents with improved properties remains an urgent problem of pharmaceutical science.

Previously we have repeatedly noted the marked diuretic properties displayed by derivatives of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [5-8]. There is interest in the replacement of the 4-OH group in such compounds by methyl. A preliminary prognosis of biological properties carried out with the PASS

* For Communication 139 see [1].

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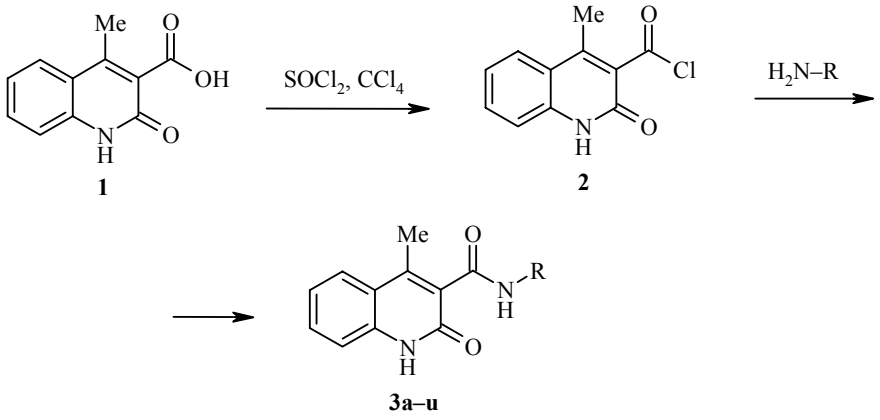
program [9] served as the basis for this modification, according to which the probability of the display of diuretic activity by amidated derivatives of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**) proved to be far higher than the 4-hydroxy analogs (on average 40% and 0 respectively).

Acid **1** and its esters, as is known, are inert towards primary aliphatic amines. Consequently for successful amidation, the preliminary activation of the 3-COOH group is necessary, for example, by way of conversion to the acid chloride **2** [10]. Acid **1** reacts with thionyl chloride in carbon tetrachloride without significant complications. Only the unusual pink coloration of the resulting acid chloride was noted. In oxygen-containing solvents, tetrahydrofuran, dioxane, and, especially, nitrobenzene, the reaction mixture acquired an intense dark-red coloration directly after mixing. The compound, isolated literally after several minutes from the start of the reaction, had a uniform bright-red color over the whole mass of crystals. To eliminate this with the aid of complexones (ethylenediaminetetraacetic acid, its disodium or ditriethylamine salt), usually effective in similar cases [11], was unsuccessful. Consequently the formation of complexes with metals may be excluded from the probable reasons for the display of color.



3 a R = $PhCH_2$, **b** R = 2-$FC_6H_4CH_2$, **c** R = 4-$FC_6H_4CH_2$, **d** R = 2-$ClC_6H_4CH_2$,
e R = 4-$ClC_6H_4CH_2$, **f** R = 4-$MeC_6H_4CH_2$, **g** R = 2-$MeOC_6H_4CH_2$, **h** R = 4-$MeOC_6H_4CH_2$,
i R = 3,4-$(MeO)_2C_6H_3CH_2$, **j** R = piperonyl, **k** R = furfuryl, **l** R = picolyl-2,
m R = picolyl-3, **n** R = picolyl-4, **o** R = PhCHMe, **p** R = $PhCH_2CH_2$,
q R = 3-$ClC_6H_4CH_2CH_2$, **r** R = 4-$ClC_6H_4CH_2CH_2$, **s** R = 4-$MeOC_6H_4CH_2CH_2$,
t R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$, **u** R = $Ph(CH_2)_3$

A special experiment was carried out. The acid (colorless substance) was dissolved in nitrobenzene and thionyl chloride was added. Straight away an intense dark-red coloration was displayed. The precipitated red solid was immediately filtered off (literally, a few minutes after adding the thionyl chloride), recrystallized from anhydrous acetone and investigated by X-ray structural analysis. It is interesting that according to the results of the X-ray structural analysis the compound being investigated was identified as the initial acid **1** (see Fig. 1 and Tables 1, 2). It is evident that after such a short time the acid simply did not have time to be converted into the acid chloride.

Evidently the content of the red substance formed in the crystal was so low that its presence did not interfere with such a type of investigation and was not essentially reflected in its results. Of the special features of the spatial structure of acid **1** it should be noted that its bicyclic fragment and the $O_{(1)}$ atom lie in one plane with a precision of 0.02 Å. The bond lengths in the pyridine ring are close to the bond lengths in 2-oxo-1,2-dihydroquinolines studied previously in [12-14], and in 4-methyl-substituted derivatives [15]. The formation of a very strong intramolecular hydrogen bond $O_{(3)}$–$H_{(30)}$···$O_{(1)}$ (H···O 1.63 Å, O–H···O 152°) leads to significant

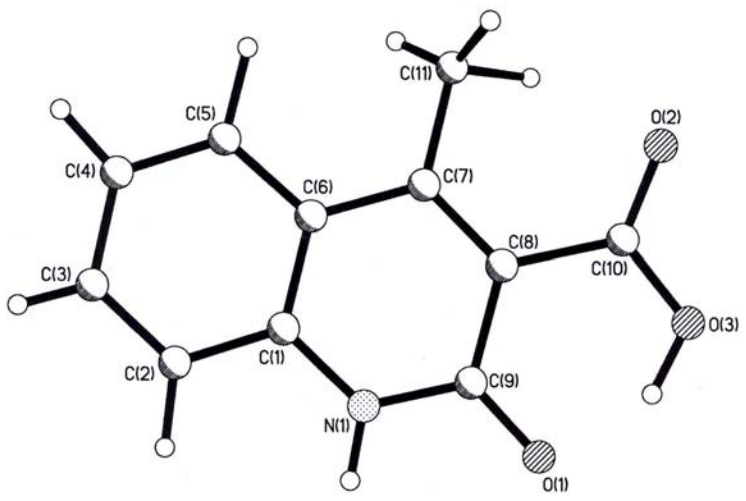


Fig. 1. Structure of the acid **1** molecule with numbering of atoms.

lengthening of the $O_{(1)}$–$C_{(9)}$ bond to 1.257(5) Å in comparison with its mean value [16] 1.210 Å and stabilizes the practically coplanar bicyclic orientation of the carboxyl group (torsion angle $C_{(9)}$–$C_{(8)}$–$C_{(10)}$–$O_{(3)}$ 9.8(6)°). Significant steric repulsion between the methyl group and the atoms of the aromatic ring [shortened intramolecular contacts $H_{(5)}\cdots C_{(11)}$ 2.64 Å (sum of van der Waals radii 2.87 Å [17], $H_{(5)}\cdots H_{(11c)}$ 2.05 (2.34) and $H_{(11c)}\cdots C_{(5)}$ 2.58 Å (2.87 Å)] leads to deviation of the methyl and carboxyl group from the plane of the quinolone nucleus (torsion angle $C_{(11)}$–$C_{(7)}$–$C_{(8)}$–$C_{(10)}$ is 8.6(6) °). A shortened intramolecular contact $H_{(11b)}\cdots O_{(2)}$ of 2.31 Å (2.46 Å) was detected between the methyl group and the $O_{(2)}$ oxygen atom.

TABLE 1. Bond Lengths (*l*) in the Structure of Acid **1**

Bond	*l*, Å	Bond	*l*, Å
$N_{(1)}$–$C_{(9)}$	1.346(5)	$N_{(1)}$–$C_{(1)}$	1.377(5)
$O_{(1)}$–$C_{(9)}$	1.257(5)	$O_{(2)}$–$C_{(10)}$	1.224(5)
$O_{(3)}$–$C_{(10)}$	1.321(5)	$C_{(1)}$–$C_{(2)}$	1.394(5)
$C_{(1)}$–$C_{(6)}$	1.420(5)	$C_{(2)}$–$C_{(3)}$	1.379(5)
$C_{(3)}$–$C_{(4)}$	1.403(6)	$C_{(4)}$–$C_{(5)}$	1.371(6)
$C_{(5)}$–$C_{(6)}$	1.420(5)	$C_{(6)}$–$C_{(7)}$	1.442(5)
$C_{(7)}$–$C_{(8)}$	1.380(6)	$C_{(7)}$–$C_{(11)}$	1.527(6)
$C_{(8)}$–$C_{(9)}$	1.464(6)	$C_{(8)}$–$C_{(10)}$	1.505(6)

TABLE 2. Valence Angles (ω) in the Structure of Acid **1**

Angle	ω, deg	Angle	ω, deg
$C_{(9)}$–$N_{(1)}$–$C_{(1)}$	124.8(3)	$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	119.9(4)
$N_{(1)}$–$C_{(1)}$–$C_{(6)}$	118.7(3)	$C_{(2)}$–$C_{(1)}$–$C_{(6)}$	121.3(3)
$C_{(3)}$–$C_{(2)}$–$C_{(1)}$	119.8(4)	$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	120.1(4)
$C_{(5)}$–$C_{(4)}$–$C_{(3)}$	120.7(4)	$C_{(4)}$–$C_{(5)}$–$C_{(6)}$	120.9(4)
$C_{(5)}$–$C_{(6)}$–$C_{(1)}$	117.1(3)	$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	123.7(4)
$C_{(1)}$–$C_{(6)}$–$C_{(7)}$	119.2(3)	$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	119.0(4)
$C_{(8)}$–$C_{(7)}$–$C_{(11)}$	122.0(4)	$C_{(6)}$–$C_{(7)}$–$C_{(11)}$	118.9(3)
$C_{(7)}$–$C_{(8)}$–$C_{(9)}$	120.7(3)	$C_{(7)}$–$C_{(8)}$–$C_{(10)}$	121.9(4)
$C_{(9)}$–$C_{(8)}$–$C_{(10)}$	117.4(3)	$O_{(1)}$–$C_{(9)}$–$N_{(1)}$	120.3(4)
$O_{(1)}$–$C_{(9)}$–$C_{(8)}$	122.5(3)	$N_{(1)}$–$C_{(9)}$–$C_{(8)}$	117.2(3)
$O_{(2)}$–$C_{(10)}$–$O_{(3)}$	120.5(4)	$O_{(2)}$–$C_{(10)}$–$C_{(8)}$	123.0(4)
$O_{(3)}$–$C_{(10)}$–$C_{(8)}$	116.4(4)		

TABLE 3. Characteristics of Arylalkylamides of 4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid **3a-u**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Diuretic activity*, % control
		C	H	N			
3a	$C_{18}H_{16}N_2O_2$	73.84 / 73.96	5.50 / 5.52	9.44 / 9.58	239-241 (ethanol)	90	+8.4
3b	$C_{18}H_{15}FN_2O_2$	69.78 / 69.67	4.96 / 4.87	9.11 / 9.03	266-268 (DMF)	86	-28.1
3c	$C_{18}H_{15}FN_2O_2$	69.70 / 69.67	4.91 / 4.87	9.07 / 9.03	261-263 (DMF)	89	-39.2
3d	$C_{18}H_{15}ClN_2O_2$	66.05 / 66.16	4.54 / 4.63	8.50 / 8.57	243-245 (DMF)	85	-44.6
3e	$C_{18}H_{15}ClN_2O_2$	66.22 / 66.16	4.71 / 4.63	8.48 / 8.57	256-258 (DMF)	94	+45.9
3f	$C_{19}H_{18}N_2O_2$	74.58 / 74.49	5.99 / 5.92	9.24 / 9.14	222-224 (ethanol)	91	+58.0
3g	$C_{19}H_{18}N_2O_3$	70.68 / 70.79	5.55 / 5.63	8.60 / 8.69	213-215 (ethanol)	90	+62.1
3h	$C_{19}H_{18}N_2O_3$	70.86 / 70.79	5.70 / 5.63	8.74 / 8.69	204-206 (ethanol)	92	- 44.9
3i	$C_{20}H_{20}N_2O_4$	68.28 / 68.17	5.81 / 5.72	7.86 / 7.95	209-211 (ethanol)	88	-8.4
3j	$C_{19}H_{16}N_2O_4$	67.74 / 67.85	4.70 / 4.79	8.25 / 8.33	234-236 (DMF)	89	-17.5
3k	$C_{16}H_{14}N_2O_3$	68.19 / 68.08	4.93 / 5.00	10.04 / 9.92	200-202 (DMF)	93	-50.9
3l	$C_{17}H_{15}N_3O_2$	69.53 / 69.61	5.04 / 5.15	14.22 / 14.33	228-230 (ethanol)	83	+6.4
3m	$C_{17}H_{15}N_3O_2$	69.55 / 69.61	5.07 / 5.15	14.39 / 14.33	243-245 (ethanol)	86	-18.1
3n	$C_{17}H_{15}N_3O_2$	69.70 / 69.61	5.26 / 5.15	14.21 / 14.33	247-249 (ethanol)	81	-74.0
3o	$C_{19}H_{18}N_2O_2$	74.58 / 74.49	5.86 / 5.92	9.06 / 9.14	206-208 (ethanol)	85	+39.3
3p	$C_{19}H_{18}N_2O_2$	74.44 / 74.49	5.87 / 5.92	9.10 / 9.14	211-213 (ethanol)	88	-1.1
3q	$C_{19}H_{17}ClN_2O_2$	66.88 / 66.96	4.95 / 5.03	8.31 / 8.22	202-204 (ethanol)	90	-6.0
3r	$C_{19}H_{17}ClN_2O_2$	66.90 / 66.96	5.09 / 5.03	8.17 / 8.22	240-242 (ethanol)	92	- 42.5
3s	$C_{20}H_{20}N_2O_3$	71.33 / 71.41	5.92 / 5.99	8.25 / 8.33	199-201 (ethanol)	86	+26.9
3t	$C_{21}H_{22}N_2O_4$	68.76 / 68.84	6.13 / 6.05	7.74 / 7.65	164-166 (ethanol)	85	-75.5
3u	$C_{20}H_{20}N_2O_2$	74.87 / 74.98	6.21 / 6.29	8.65 / 8.74	191-193 (ethanol)	84	-50.9
	Hypthiazide	—	—	—	—	—	+62.0

"+" indicates strengthening, "-" indicates suppression of diuresis compared to control taken as 100%.

In the crystal acid **1** molecules from stacks along the (0 0 1) crystallographic direction, which are linked with an intermolecular hydrogen bond $N_{(1)}$–$H_{(1H)}$···$O_{(2)}$, (0.5+*x*,1.5-*y*, *z*-1) H···O 1.83 Å, N-H···O 175°. Within the stacks the distance between the molecules is 3.82 Å, which enables an important stacking interaction to be assumed.

TABLE 4. ^{1}H NMR Spectra of Sythesized Compounds

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)							
	NH (1H, s)	NH–R (1H)	Quinolone nucleus					R
			H-5 (1H, d)	H-7 (1H, t)	H-8 (1H, d)	H-6 (1H, t)	4-CH_3(3H, s)	
1	2	3	4	5	6	7	8	9
3a	11.82	8.81 (t, *J* = 6.0)	7.77 (*J* = 8.1)	7.52 (*J* = 7.6)	See R	See R	2.34	7.44-7.16 (7H, m, H-8,6 + C_6H_5); 4.44 (2H, d, *J* = 6.2, NCH_2)
3b	11.83	8.82 (t, *J* = 6.0)	7.77 (*J* = 8.1)	See R	See R	See R	2.34	7.66-7.15 (7H, m, H-7,8,6 + H arom. Bn); 4.46 (2H, d, *J* = 6.0, NCH_2)
3c	11.83	8.82 (t, *J* = 6.1)	7.76 (*J* = 8.0)	7.51 (*J* = 7.9)	7.31 (*J* = 8.3)	7.21 (*J* = 7.6)	2.33	7.43 (2H, td, *J* = 7.9 and *J* = 2.8, H-3',5'); 7.13 (2H, d, *J* = 8.9, H-2',6'); 4.42 (2H, d, *J* = 6.1, NCH_2)
3d	11.85	8.88 (t, *J* = 6.1)	7.77 (*J* = 8.1)	7.53 (*J* = 7.7)	See R	7.22 (*J* = 7.7)	2.37	7.71 (1H, dd, *J* = 7.2 and *J* = 2.2, H-3'); 7.44 (1H, dd, *J* = 7.1 and *J* = 2.2, H-6'); 7.38-7.29 (3H, m, H-8 + H-4',5'); 4.48 (2H, d, *J* = 6.0, NCH_2)
3e	11.84	8.84 (t, *J* = 6.1)	7.76 (*J* = 8.1)	7.52 (*J* = 7.6)	7.30 (*J* = 8.1)	7.21 (*J* = 7.5)	2.33	7.45 (2H, d, *J* = 8.8, H-3',5'); 7.38 (2H, d, *J* = 8.9, H-2',6'); 4.42 (2H, d, *J* = 6.0, NCH_2)
3f	11.81	8.76 (t, *J* = 6.0)	7.75 (*J* = 8.1)	7.51 (*J* = 7.6)	See R	7.20 (*J* = 7.7)	2.32	7.33-7.26 (3H, m, H-8 + H-2',6'); 7.12 (2H, d, *J* = 8.2, H-3',5'); 4.37 (2H, d, *J* = 6.1, NCH_2); 2.26 (3H, s, CH_3)
3g	11.82	8.65 (t, *J* = 6.0)	7.76 (*J* = 8.1)	7.52 (*J* = 7.6)	7.30 (*J* = 8.1)	7.21 (*J* = 7.6)	2.36	7.46 (1H, dd, *J* = 7.6 and *J* = 1.8, H-3'); 7.23 (1H, dd, *J* = 7.7 and *J* = 1.8, H-6'); 6.95 (1H, t, *J* = 7.8, H-4'); 6.90 (1H, td, *J* = 7.4 and *J* = 1.1, H-5'); 4.38 (2H, d, *J* = 6.0, NCH_2); 3.80 (3H, s, OCH_3)
3h	11.81	8.75 (t, *J* = 5.9)	7.75 (*J* = 8.2)	7.51 (*J* = 7.8)	See R	7.20 (*J* = 7.6)	2.32	7.32 (3H, m, H-8 + H-3',5'); 6.88 (2H, d, *J* = 8.6, H-2',6'); 4.35 (2H, d, *J* = 5.9, NCH_2); 3.72 (3H, s, OCH_3)
3i	11.88	8.75 (t, *J* = 6.0)	7.76 (*J* = 8.2)	7.51 (*J* = 7.6)	7.30 (*J* = 8.3)	7.21 (*J* = 7.6)	2.35	7.13 (1H, s, H-2'); 6.87 (2H, s, H-5',6'); 4.37 (2H, d, *J* = 6.1, NCH_2); 3.76 (3H, s, OCH_3); 3.71 (3H, s, OCH_3)
3j	11.82	8.74 (t, *J* = 6.0)	7.75 (*J* = 8.0)	7.51 (*J* = 7.7)	7.30 (*J* = 8.1)	7.21 (*J* = 7.5)	2.33	7.00 (1H, s, H-2'); 6.84 (2H, d, *J* = 0.9, H-5',6'); 5.97 (2H, s, OCH_2O); 4.34 (2H, d, *J* = 5.9, NCH_2)

TABLE 4. (continued)

1	2	3	4	5	6	7	8	9
3k	11.81	8.76 (t, J = 6.1)	7.76 (J = 8.0)	7.51 (J = 7.7)	7.29 (J = 8.1)	7.20 (J = 7.6)	2.33	7.58 (1H, d, J = 2.0, H-5'); 6.30 (2H, m, H-3',4'); 4.41 (2H, d, J = 5.9, NCH_2)
3l	11.84	8.92 (t, J = 6.1)	See R	7.53 (J = 7.7)	7.32 (J = 7.5)	7.21 (J = 7.7)	2.39	8.49 (1H, d, J = 4.9, H-6'); 7.83–7.72 (2H, m, H-5 + H-5'); 7.62 (1H, d, J = 8.0, H-3'); 7.26 (1H, t, J = 6.1, H-4'); 4.51 (2H, d, J = 6.1, NCH_2)
3m	11.85	8.89 (t, J = 6.0)	7.76 (J = 8.2)	7.52 (J = 7.7)	7.30 (J = 8.3)	7.21 (J = 7.5)	2.32	8.61 (1H, d, J = 1.8, H-2'); 8.45 (1H, dd, J = 4.8 and J = 1.6, H-6'); 7.83 (1H, dt, J = 7.8 and J = 2.0, H-4'); 7.37 (1H, td, J = 4.9 and J = 1.0, H-5'); 4.46 (2H, d, J = 6.2, NCH_2)
3n	11.86	8.92 (t, J = 6.1)	7.77 (J = 8.2)	7.53 (J = 7.6)	7.32 (J = 8.2)	7.22 (J = 7.6)	2.37	8.51 (2H, dd, J = 4.7 and J = 1.8, H-2',6'); 7.45 (2H, dd, J = 4.6 and J = 1.8, H-3',5'); 4.46 (2H, d, J = 6.1, NCH_2)
3o	11.79	8.76 (d, J = 8.2)	7.75 (J = 8.3)	7.51 (J = 7.6)	See R	See R	2.28	7.44-7.16 (7H, m, H-8,6 + C_6H_5); 5.08 (1H, q, J = 7.4, CH); 1.39 (3H, d, J = 7.1, CH_3)
3p	11.80	8.36 (t, J = 6.0)	7.73 (J = 8.0)	7.50 (J = 7.7)	See R	7.20 (J = 7.6)	2.23	7.32-7.27 (6H, m, H-8 + C_6H_5); 3.44 (2H, q, J = 6.6, NCH_2); 2.80 (2H, t, J = 7.0, $C\underline{H}_2$–C_6H_5)
3q	11.82	8.37 (t, J = 5.9)	7.74 (J = 8.1)	7.51 (J = 7.7)	See R	7.19 (J = 7.6)	2.19	7.36 (1H, s, H-2'); 7.32–7.26 (4H, m, H-8 + H-4',5',6'); 3.45 (2H, q, J = 5.9, NCH_2); 2.81 (2H, t, J = 7.0, $C\underline{H}_2$–Ar)
3r	11.79	8.34 (t, J = 5.9)	7.74 (J = 8.1)	7.50 (J = 7.6)	See R	7.19 (J = 7.8)	2.22	7.37-7.25 (5H, m, H-8 + H-2',3',5',6'); 3.43 (2H, q, J = 6.3, NCH_2); 2.79 (2H, t, J = 7.0, $C\underline{H}_2$–Ar)
3s	11.80	8.33 (t, J = 5.8)	7.74 (J = 8.0)	7.50 (J = 7.7)	7.28 (J = 8.0)	See R	2.24	7.18 (3H, m, H-6 + H-3',5'); 6.84 (2H, d, J = 8.3, H-2',6'); 3.71 (3H, s, OCH_3); 3.39 (2H, q, J = 6.7, NCH_2); 2.73 (2H, t, J = 7.4, $C\underline{H}_2$–Ar)
3t	11.79	8.32 (t, J = 5.9)	7.74 (J = 8.1)	7.50 (J = 7.6)	7.28 (J = 8.2)	7.20 (J = 7.5)	2.26	6.90 (1H, s, H-2'); 6.85 (1H, d, J = 9.3, H-5'); 6.75 (1H, d, J = 8.3, H-6'); 3.74 (3H, s, OCH_3); 3.70 (3H, s, OCH_3); 3.41 (2H, q, J = 7.1, NCH_2); 2.73 (2H, t, J = 7.3, $C\underline{H}_2$–Ar)
3u	11.81	8.32 (t, J = 5.9)	7.76 (J = 8.1)	7.51 (J = 7.6)	See R	See R	2.36	7.33-7.15 (7H, m, H-8,6 + C_6H_5); 3.21 (2H, q, J = 5.9, NCH_2); 2.65 (2H, t, J = 7.8, $C\underline{H}_2$–Ar); 1.76 (2H, q, J = 7.8, $NCH_2C\underline{H}_2$)

Pure 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**1**), as is known [10], is colorless. On treatment of 4-hydroxy or 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acids with thionyl chloride the formation of intensivity colored substances was also not observed [18].

It therefore follows that the appearance of the red coloration in the case of 4-methyl-substituted analogs is caused by the presence of the methyl group in the molecule, which preferably takes part in intermolecular reactions leading to the formation of compounds of the cyanine dye type [19]. The experiments carried out by us showed that, after conversion of acid **1** into acid chloride **2** in carbon tetrachloride, the content of coloring substances proved to be insignificant and is usually readily removed with activated carbon at the stage of purifying the final N-R-amides **3**. The reasons by which oxygen-containing solvents significantly increase the rate of formation of undesirable coloring materials remain unclear, nonetheless the inexpediency of their use in the synthesis of acid chloride **2** is evident.

All the synthesized arylalkylamides of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid **3a-u** (Table 3) were colorless crystalline substances, practically insoluble in water, moderately soluble in hot alcohol, and very soluble in DMF and DMSO. Their structures were confirmed by ^{1}H NMR spectroscopy (Table 4).

The ability of amides **3a-u** to stimulate or, on the other hand, to depress the urine-excretory function of the kidney was studied by the method of Taylor and Topliss [20] in white mongrel rats in comparison with hypothiazide.

When analyzing the results of pharmacological testing given in Table 3, we may draw the conclusion that notwithstanding expectations the majority of the investigated arylalkylamides of 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid **3** display an expressed, but sometimes a very high (amides **3n**,**t**) antidiuretic effect. The initial acid **1** has practically no effect on diuresis. Its indicator was only +7.9% in comparison with control, consequently the structure of the amide fragment shows a significant influence on the biological properties of its derivatives **3**. However, to make any general conclusion for all the group of amides **3** clearly characterizing the interconnection between their chemical structure and the ability to influence the urine-secretory function of the kidney is impossible. Nonetheless, in the finer homologous series definite regularities can be traced successfully. For example, in the series of phenylalkylamides **3a→3p→3u** the ability to suppress diuresis clearly grows with the distancing of the phenyl nucleus from the amide nitrogen atom. An analogous picture is also observed in the case of *p*-chloro (**3e→3r**) and 3,4-dimethoxy (**3i→3t**) derivatives. At the same time the *p*-methoxyphenyl-substituted amides **3h** and **3s** in the indicated modification demonstrate a completely contrasting tendency towards a significant strengthening of diuretic properties. Only two compounds of the whole group tested merit special attention. These are the 4-methyl- and 2-methoxybenzylamides **3f** and **3g**, displaying diuretic action at the level of hypothiazide, which suggests the need for a more detailed pharmacological study of them.

EXPERIMENTAL

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

Arylalkylamides of 4-Methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 3a-u (General Method). Thionyl chloride (1.44 ml, 0.02 mol) was added to a solution of acid **1** (2.03 g, 0.01 mol) in dry CCl_4 (50 ml) and the mixture boiled until evolution of HCl and SO_2 had stopped (~2 h). The solvent and the excess of $SOCl_2$ were then distilled (finally, in vacuum). The residue (acid chloride **2**) was dissolved in dry acetone (20 ml) and the obtained solution was added dropwise with stirring and cooling to a mixture of the appropriate arylalkylamine (0.01 mol) and triethylamine (1.4 ml, 0.01 mol) in dry acetone (20 ml). After 3-4 h the reaction mixture was diluted with cold water and acidified with dilute (1:1) HCl to pH 4. The precipitated solid amide **3a-u** was filtered off, washed with cold water, and dried.

X-ray Structural Investigation. Crystals of acid **1** were rhombic (acetone), at -173°C: a = 12.233(2), b = 18.849(3), c = 3.816(1) Å, V = 879.9(3) Å^3, M_r = 203.19, Z = 4, space group $Pna2_1$, d_{calc} = 1.534 g/cm^3, μ(MoKα) = 0.113 mm^{-1}, F(000) = 424. The parameters of the unit cell and the intensities of 6454 reflections (1543 independent, R_{int} = 0.105) were measured on a Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 50°).

The structure was solved by the direct method with the SHELXTL set of programs [21]. The positions of hydrogen atoms were made apparent from an electron density difference synthesis and were refined according to the rider model with $U_{iso} = nU_{eq}$ of the non-hydrogen atom linked with the given hydrogen (n = 1.5 for a methyl group and n = 1.2 for the remaining hydrogen atoms). Refinement for the $H_{(30)}$ and $H_{(1N)}$ atoms was carried out isotropically. The structure was refined on F^2 by the full matrix least squares method in an anisotropic approach for the non-hydrogen atoms to wR_2 = 0.145 at 1496 reflections (R_1 = 0.065 at 1280 reflections with $F > 4\sigma(F)$, S = 1.041). Full crystallographic information has been deposited in the Cambridge structural database, deposit No. CCDC 650596. Interatomic distances and valence angles are given in Tables 1 and 2.

Determination of Diuretic Activity. Each test animal (white mongrel rats of weight 180-200 g) was given an aqueous charge of estimated 25 mg/kg through a stomach probe. The control group of animals received only the aqueous charge. The investigated compounds were introduced perorally at a dose of 40 mg/kg (the effective dose of hypothiazide) as a fine aqueous suspension, stabilized with Tween 80. After this the test animals were placed in volume cells. The amount of urine excreted by animals after 4 h served as a measure of the intensity of urine elimination. The results of the determination of diuretic activity are summarized in Table 3.

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