Chemistry of Heterocyclic Compounds, Vol. 44, No. 5, 2008

4-HYDROXY-2-QUINOLONES 144*. ALKYL-, ARYLALKYL-, AND ARYLAMIDES OF 2-HYDROXY-4-OXO-4H-PYRIDO[1,2-*a*]PYRIMIDINE-3-CARBOXYLIC ACID AND THEIR DIURETIC PROPERTIES

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Alkyl-, arylalkyl-, and arylamides of 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylic acid were prepared with a view to establishing a structure–biological activity relationship. A comparative analysis has been made of their diuretic properties and those of the structurally similar 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides.

Keywords: amides, 2-hydroxy-4-oxo-4H-pyrido-[1,2-*a*]pyrimidine-3-carboxylic acids, tricarbonylmethane heterocyclic derivatives, diuretic activity, X-ray structural analysis.

The problem of discovering novel classes of chemical substances capable of diuretic action, and particularly important, those which are highly efficient and safe diuretic medicines has not lost its urgency even over recent decades. Interesting substances investigated within this scheme are amidated 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids derivatives [2, 3]. Although for a long time high diuretic activity has not been considered a characteristic of quinolone compounds, several of these materials proved extremely promising and have been subjected to broad pharmacological investigation to this time. With this in mind we have carried out the synthesis and biological screening to reveal the ability of the series of structurally related 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid N-R-amides **1-3** to increase the diuretic kidney function.

It was found that the alkylamides **1a-u** (Table 1) can be prepared by the reaction of ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxylate (**4**) with a two, or better three, fold excess of the corresponding alkylamine in refluxing ethanol. It was initially proposed that it was necessary to use quite a large excess of the

* For Communication 143 see [1].

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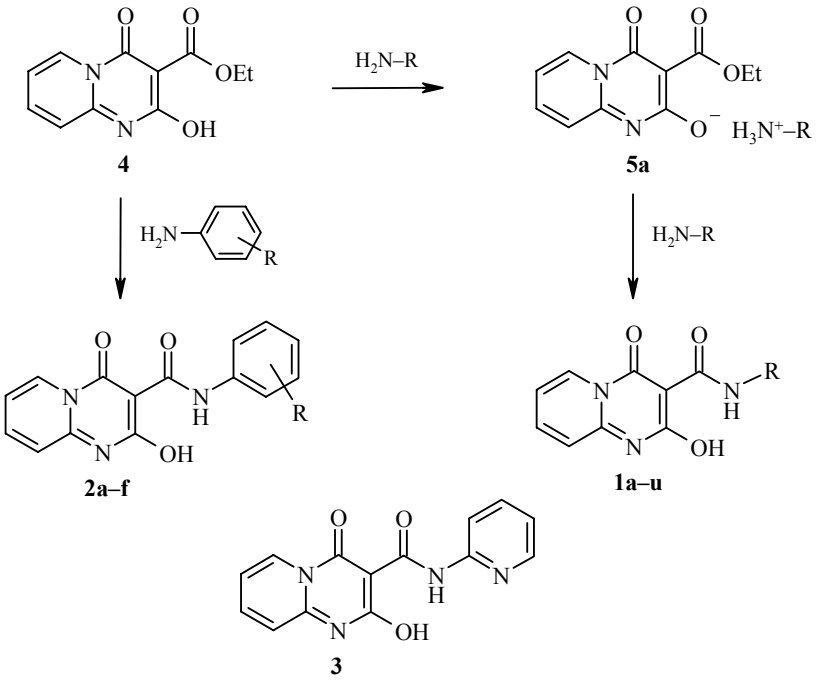
amine because of the clear acidic properties of the 2-OH group in ester **4** since at least an equimolar amount of amine was tied up as the salt **5** but has not proved not strictly correct. The experiments carried out showed that such ammonium salts are quite stable when formed under normal conditions and, in contrast to analogous salts formed by 4-hydroxy-2-oxo-3-ethoxycarbonyl-1,2-dihydroquinolines [4], can be readily separated and characterized.



1 a R = $CH_2CH{=}CH_2$, **b** R = *cyclo*-C_3H_5, **c** R = C_3H_7, **d** R = C_4H_9, **e** R = *i*-C_4H_9, **f** R = C_6H_{13}, **g** R = *i*-$C_3H_7O(CH_2)_3$, **h** R =$PhCH_2$, **i** R = 2-$ClC_6H_4CH_2$, **j** R = 4-$ClC_6H_4CH_2$, **k** R = 2-$MeOC_6H_4CH_2$, **l** R = 4-$MeOC_6H_4CH_2$, **m** R = 3,4-$(MeO)_2C_6H_3CH_2$, **n** R = PhCHMe, **o** R = $PhCH_2CH_2$, **p** R = 2-$ClC_6H_4CH_2CH_2$, **q** R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$, **r** R = furfuryl, **s** R = picolyl-2, **t** R = picolyl-3, **u** R = picolyl-4; **2 a** R = H, **b** R = 2-F, **c** R = 3-F, **d** R = 4-F, **e** R = 3-Cl, **f** R = 4-Cl, **5 a** R = CH_2CH_2OH

In addition it is known [5] that blocking an *o*-OH group *via* salt formation markedly lowers the reactivity of a neighboring ethoxycarbonyl group. From this it quite naturally followed that the low rate of amidation of ester **4** (or more accurately its salt **5**) needed no less than 25-30 h for completion despite the large excess of amine. Only in the single example of 2-aminoethanol amongst all of the variety of amines used in this study did the corresponding amide synthesis fail because the salt of ester **4** with this amino alcohol proved extremely stable to subsequent amidation. A similar selective inertness (but only with relation to ammonia) has been noted by us before in the ethyl 4-hydroxy-2-oxo- [4] and 4-chloro-2-oxo- [6] 1,2-dihydroquinoline-3-carboxylates. Moreover, factors determining this observed effect were then identified not so much as the properties of the individual functional groups or their reactivity but overall as the steric structure of the interacting molecules approaching one another (as a key to a lock) and in this way forming extremely stable adducts to further reaction. Most likely in the amidation ethyl 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**4**) by alkylamines of we are dealing with a similar effect maximaly showing up in the reaction with 2-aminoethanol. Hence the course of the reaction of ester **4** with amines is not largely determined by the acidity of the 2-OH group ($pK_a = 8.91 \pm 0.01$) but by the structural affinity of the starting components (although a constructive role for the group giving the reacting molecules a suitable orientation in space is not in doubt).

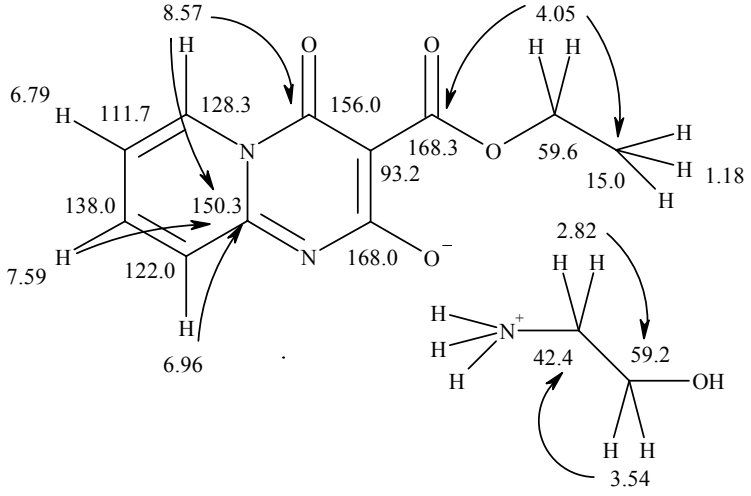
TABLE 1. Characteristics of the 2-Hydroxy-4-oxo-4H-pyrido[1,2-*a*]-pyrimine-3-carboxylic Acid N-R-Amides

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Diuretic activity*, % of control
		C	H	N			
1a	$C_{12}H_{11}N_3O_3$	58.86 / 58.77	4.63 / 4.52	17.05 / 17.13	132-134	83	-21.6
1b	$C_{12}H_{11}N_3O_3$	58.71 / 58.77	4.60 / 4.52	17.06 / 17.13	185-187	71	+ 7.8
1c	$C_{12}H_{13}N_3O_3$	58.20 / 58.29	5.21 / 5.30	16.88 / 16.99	140-142	75	-0.4
1d	$C_{13}H_{15}N_3O_3$	59.68 / 59.76	5.85 / 5.79	16.16 / 16.08	151-153	78	+ 36.7
1e	$C_{13}H_{15}N_3O_3$	59.66 / 59.76	5.73 / 5.79	16.00 / 16.08	166-168	76	-21.1
1f	$C_{15}H_{19}N_3O_3$	62.38 / 62.27	6.72 / 6.62	14.59 / 14.52	139-141	73	-72.3
1g	$C_{15}H_{19}N_3O_4$	59.10 / 59.01	6.18 / 6.27	13.66 / 13.76	104-106	70	-10.0
1h	$C_{16}H_{13}N_3O_3$	65.14 / 65.08	4.35 / 4.44	14.34 / 14.23	198-200	84	-21.5
1i	$C_{16}H_{12}ClN_3O_3$	58.20 / 58.28	3.61 / 3.67	12.68 / 12.74	192-194	82	+ 3.0
1j	$C_{16}H_{12}ClN_3O_3$	58.33 / 58.28	3.75 / 3.67	12.81 / 12.74	159-161	85	-17.9
1k	$C_{17}H_{15}N_3O_4$	62.85 / 62.76	4.58 / 4.65	12.83 / 12.92	181-183	80	-52.5
1l	$C_{17}H_{15}N_3O_4$	62.82 / 62.76	4.74 / 4.65	12.85 / 12.92	162-164	84	-12.3
1m	$C_{18}H_{17}N_3O_5$	60.77 / 60.84	4.90 / 4.82	11.73 / 11.82	173-175	81	-24.0
1n	$C_{17}H_{15}N_3O_3$	65.92 / 66.01	4.81 / 4.89	13.66 / 13.58	146-148	68	+ 4.1
1o	$C_{17}H_{15}N_3O_3$	66.07 / 66.01	4.95 / 4.89	13.68 / 13.58	140-142	83	+ 10.4
1p	$C_{17}H_{14}ClN_3O_3$	59.48 / 59.40	4.04 / 4.10	12.13 / 12.22	155-157	86	-20.5
1q	$C_{19}H_{19}N_3O_5$	61.67 / 61.78	5.11 / 5.18	11.30 / 11.38	168-170	80	-33.6
1r	$C_{14}H_{11}N_3O_4$	58.86 / 58.95	3.95 / 3.89	14.65 / 14.73	207-209	82	+ 15.4
1s	$C_{15}H_{12}N_4O_3$	60.77 / 60.81	4.13 / 4.08	18.83 / 18.91	202-204	76	-28.5
1t	$C_{15}H_{12}N_4O_3$	60.86 / 60.81	4.17 / 4.08	18.98 / 18.91	189-191	79	-3.5
1u	$C_{15}H_{12}N_4O_3$	60.88 / 60.81	4.02 / 4.08	18.95 / 18.91	213-215	81	-0.7
2a	$C_{15}H_{11}N_3O_3$	63.96 / 64.05	3.87 / 3.94	15.03 / 14.94	217-219	78	+ 6.5
2b	$C_{15}H_{10}FN_3O_3$	60.29 / 60.20	3.44 / 3.37	14.10 / 14.04	264-266	75	+ 2.6
2c	$C_{15}H_{10}FN_3O_3$	60.15 / 60.20	3.42 / 3.37	13.95 / 14.04	253-255	80	+ 18.4
2d	$C_{15}H_{10}FN_3O_3$	60.12 / 60.20	3.31 / 3.37	14.01 / 14.04	258-260	84	-4.7
2e	$C_{15}H_{10}ClN_3O_3$	57.15 / 57.07	3.28 / 3.19	13.26 / 13.31	263-265	81	+ 20.8
2f	$C_{15}H_{10}ClN_3O_3$	57.00 / 57.07	3.24 / 3.19	13.22 / 13.31	291-293	83	+ 26.3
	Hypothiazide	—	—	—	—	—	+ 48.0

* a + signifies an increase and a – signifies an inhibition of diuresis relative to the control taken as 100%.

For comparison the pK_a of the 4-OH group in ethyl 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates is about 8.6 [7] and similar complications did not arise in their amidation with the exception of the case of ammonia reported above. It was interesting that the stable salts formed by the alkylamides **1a-u** at the 2-OH group were not observed and their separation would not necessarily demand acidification of the reaction medium. As will be shown below the amides **1a-u** form a totally different system of intramolecular hydrogen bonds to those in the starting ester **4** [8]. It is possible that such a change in the acidity of the 2-OH group is the reason for its lowering by several order such that, for example, the pK_a of the 2-phenylethylamide **1o** is as low as 10.32 ± 0.02.

We have measured the ^{1}H and ^{13}C NMR spectra of the salt **5a** to determine its structure and it became clear that the starting components had reacted in the ratio 1:1. In addition we carried out ^{1}H–^{13}C heteronuclear correlation experiments through one (HMQC) and through 2-3 (HMBC) chemical bonds. Although the proton spectrum contained all of the signals for the heterocyclic and monoethanolamine fragments all of the active (OH and NH_2) protons exchanged with water present in the solvent to give a single broad signal at 3.4 ppm. Such a spectrum appearance did not make it possible to define a clear structure for the compound obtained. A salt structure is more likely for this in which the hydroxyl group proton of the heterocycle migrates to the basic amino group of the monoethanolamine to form an ionized compound. As an alternative we can also consider that the monoethanolamine fragment occurs as a substituent in the heterocyclic ring. We considered that the HMBC spectrum could determine the true structure of the compound formed. If it is a salt the signals of the monoethanolamine fragment would not correlate with the carbon atoms of the heterocycle since the bonding between them is not covalent. If dealing with substitution such a correlation has to occur.



All of the heteronuclear ^{1}H–^{13}C HMQC and HMBC correlations found are given in Table 2. With their help we could achieve a secure assignment of the signals in the carbon spectrum and deduce the structure of the compound. Hence the presence of an HMBC correlation between the methylene group protons in the ester fragment and the carbon atom signal at 168.3 ppm allows us to assign this signal to the carbonyl group of this substituent despite the fact that it is extremely close to a further signal at 168.0 ppm in the spectrum. Similarly the presence of an HMBC correlation for the H-6 proton at 8.57 ppm and the carbon atom signal at 156.0 ppm shows that this is the carbonyl C-4 carbon. The signal assignments made in this way are shown in the scheme and the arrows show the basis for the HMBC correlations.

The signals for which HMBC correlations were not observed proved to be those with chemical shifts of 168.0 and 93.2 ppm. We assign these to the C-2 and C-3 atoms of the pyrido[1,2-*a*]pyrimidine ring respectively and these are in agreement with the ^{13}C nuclea chemical shifts for compounds of similar structure studied by us before [8].

TABLE 2. Heteronuclear ^{1}H–^{13}C Correlations Found for Salt **5a**

δ, ppm	HMQC	HMBC
8.57	128.3	156.0; 150.3; 138.0; 111.7
7.59	138.0	150.3; 128.3
6.96	122.0	150.3; 111.7
6.79	111.7	128.3; 122.0
4.05	59.6	168.3; 15.0
3.54	59.2	42.4
2.82	42.4	59.2
1.18	15.0	59.6

As is evident from data in Table 2 HMBC correlations between the protons signals of the monoethanolamine and the carbon signals of the heterocyclic system are absent. From this we can deduce the studied compound **5a** has the structure of a salt. An additional supporting argument came from the spectrum measured in trifluoroacetic acid. In this solvent [for protonsof the monoethanolamine two signals for each type of the methylene groups] were observed in the intensity ratio 2:1. This suggests that an equilibrium is established in this solvent between compound **5a** and the salt of monoethanolamine and trifluoroacetic acid.

In contrast to the alkyl- and arylalkylamines, anilines don't show sterical affinity to ester **4** hence the corresponding 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid anilides **2a-f** (Table 1) were formed in good yields using an equimolar ratio of reagents but under more rigid conditions. Evidently this method is also applicable to the synthesis of hetarylamides although not specifically considered in this report but the pyridin-2-ylamide **3** tested in biological investigation as an azabiostere of the anilide **2a** (was obtained by condensation of the 2-aminopyridine with triethylmethanetricarboxylate as a side product [8]).

All of the alkylamides **1** and anilides **2** are colorless crystalline materials virtually insoluble in cold water, poorly in hot, and moderately soluble in DMF ad DMSO at room temperature. The structure in all of the cases was confirmed by ^{1}H NMR spectroscopy (Table 3) and, in the case of the 2-methoxybenzylamide **1k** additionally by X-ray analytical analysis (see Figure 1 and Tables 4, 5). The bicyclic fragment of the molecule of this compound and the $O_{(1)}$, $O_{(2)}$, $C_{(9)}$, $O_{(3)}$, $N_{(3)}$, and $C_{(10)}$ atoms lie in a single plane within an accuracy of 0.01 Å which is due to the formation of strong intramolecular hydrogen bonds $O_{(1)}$–$H_{(10)}$···$O_{(3)}$: H···O 1.43 Å, O–H···O 157º ad $N_{(3)}$–$H_{(3N)}$···$O_{(2)}$: H···O 1.91 Å, N–H···O 140º. This same reason leads to a marked redistribution of

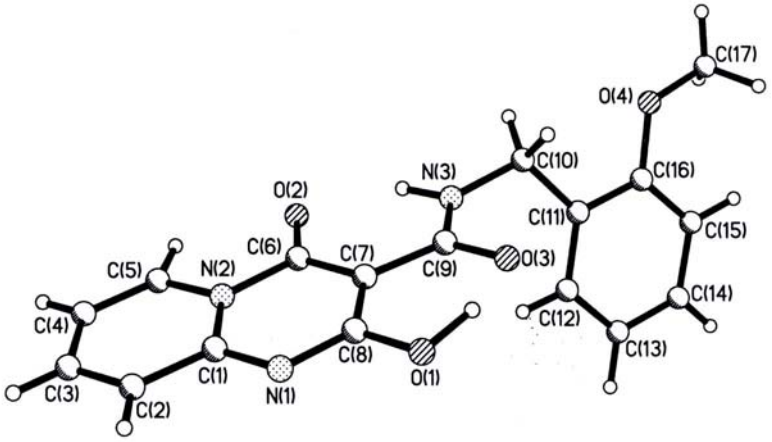


Fig. 1. Structure of the amide **1k** molecule with atomic numbering.

TABLE 3. ^{1}H NMR Spectra of Compounds **1a–u** and **2a–f**

Compound	Chemical shifts, δ, ppm (*J*, Hz)						
	OH (1H, s)	NH (1H)	Pyrido[1,2-*a*]pyrimidine ring				R and other functional groups
			H-6 (1H, d)	H-8 (1H, t)	H-9 (1H, d)	H-7 (1H, t)	
1	2	3	4	5	6	7	8
1a	15.84	9.66 (t, *J* = 6.2)	8.92 (*J* = 7.0)	8.07 (*J* = 7.8)	7.53 (*J* = 8.8)	7.36 (*J* = 7.2)	5.92 (1H, m, C<u>H</u>=CH$_2$); 5.21 (1H, d, *J* = 16.9, NCH$_2$CH=CH-*trans*); 5.13 (1H, d, *J* = 10.4, NCH$_2$CH=CH-*cis*); 4.01 (2H, t, *J* = 5.6, N<u>CH$_2$</u>)
1b	15.77	9.46 (d, *J* = 5.0)	8.87 (*J* = 7.0)	8.05 (*J* = 7.8)	7.50 (*J* = 8.9)	7.34 (*J* = 7.0)	2.91 (1H, m, NHC<u>H</u>); 0.80 (2H, q, *J* = 5.4, CH$_2$); 0.62 (2H, q, *J* = 3.5, CH$_2$)
1c	16.15	9.58 (t, *J* = 5.5)	8.87 (*J* = 7.0)	8.06 (*J* = 7.8)	7.52 (*J* = 8.8)	7.35 (*J* = 7.1)	3.35 (2H, q, *J* = 6.7, NHC<u>H$_2$</u>); 1.56 (2H, m, NHCH$_2$C<u>H$_2$</u>); 0.90 (3H, t, *J* = 7.4, CH$_3$)
1d	16.12	9.55 (t, *J* = 5.4)	8.90 (*J* = 7.1)	8.05 (*J* = 7.8)	7.51 (*J* = 8.9)	7.35 (*J* = 7.0)	3.37 (2H, q, *J* = 6.6, NHC<u>H$_2$</u>); 1.53 (2H, q, *J* = 7.2, NHCH$_2$C<u>H$_2$</u>); 1.34 (2H, m, C<u>H$_2$</u>CH$_3$); 0.90 (3H, t, *J* = 7.2, CH$_3$)
1e	16.07	9.62 (t, *J* = 5.5)	8.91 (*J* = 7.1)	8.06 (*J* = 7.8)	7.50 (*J* = 8.8)	7.35 (*J* = 7.0)	3.22 (2H, t, *J* = 6.4, NHC<u>H$_2$</u>); 1.85 (1H, m, NHCH$_2$C<u>H</u>); 0.91 (6H, d, *J* = 6.7, 2CH$_3$)
1f	16.13	9.54 (t, *J* = 5.4)	8.91 (*J* = 7.0)	8.05 (*J* = 7.8)	7.51 (*J* = 9.0)	7.34 (*J* = 6.9)	3.36 (2H, q, *J* = 6.3, NHC<u>H$_2$</u>); 1.54 (2H, q, *J* = 6.6, NHCH$_2$C<u>H$_2$</u>); 1.28 (6H, m, (C<u>H$_2$</u>)$_3$CH$_3$); 0.85 (3H, t, *J* = 6.7, CH$_3$)
1g	16.16	9.62 (t, *J* = 5.3)	8.90 (*J* = 7.1)	8.06 (*J* = 7.8)	7.52 (*J* = 8.8)	7.35 (*J* = 7.0)	3.52-3.39 (5H, m, NHC<u>H$_2$</u>+CH$_2$OCH); 1.74 (2H, q, *J* = 6.3, NHCH$_2$C<u>H$_2$</u>CH$_2$O); 1.08 (6H, d, *J* = 6.1, 2CH$_3$)
1h	15.48	9.93 (t, *J* = 5.1)	8.91 (*J* = 7.1)	8.06 (*J* = 7.9)	7.52 (*J* = 8.9)	See R	7.40-7.23 (6H, m, H-7 + C$_6$H$_5$); 4.60 (2H, d, *J* = 6.0, NHC<u>H$_2$</u>)
1i	15.67	10.00 (t, *J* = 5.8)	8.93 (*J* = 7.1)	8.08 (*J* = 7.8)	7.57 (*J* = 8.9)	See R	7.48-7.29 (5H, m, H-7 + H-3',4',5',6'); 4.65 (2H, d, *J* = 5.9, NHC<u>H$_2$</u>)
1j	15.82	9.98 (t, *J* = 5.6)	8.91 (*J* = 6.9)	8.07 (*J* = 7.8)	7.52 (*J* = 8.9)	See R	7.43-7.31 (5H, m, H-7 + H-2',3',5',6'); 4.57 (2H, d, *J* = 6.2, NHC<u>H$_2$</u>)
1k	15.93	9.93 (t, *J* = 5.5)	8.91 (*J* = 7.0)	8.05 (*J* = 7.7)	7.51 (*J* = 8.8)	7.34 (*J* = 7.1)	7.23 (2H, m, H-4',6'); 7.02 (1H, d, *J* = 8.2, H-3'); 6.90 (1H, t, *J* = 7.4, H-5'); 4.53 (2H, d, *J* = 5.9, NHC<u>H$_2$</u>); 3.85 (3H, s, OCH$_3$)
1l	15.51	9.87 (t, *J* = 5.6)	8.88 (*J* = 7.1)	8.05 (*J* = 7.9)	7.50 (*J* = 8.9)	7.33 (*J* = 6.9)	7.27 (2H, d, *J* = 8.3, H-3',5'); 6.89 (2H, d, *J* = 8.3, H-2',6'); 4.49 (2H, d, *J* = 5.9, NHC<u>H$_2$</u>); 3.71 (3H, s, OCH$_3$)

TABLE 3. (continued)

1	2	3	4	5	6	7	8
1m	15.92	9.85 (t, J = 5.5)	8.89 (J = 7.2)	8.06 (J = 7.8)	7.52 (J = 8.8)	7.34 (J = 7.0)	6.99 (1H, s, H-2'); 6.88 (2H, m, H-5',6'); 4.50 (2H, d, J = 5.9, NHC$\underline{H_2}$); 3.73 (3H, s, 3'-OCH_3); 3.71 (3H, s, 4'-OCH_3)
1n	15.74	9.94 (d, J = 6.5)	8.93 (J = 6.9)	8.07 (J = 7.8)	7.53 (J = 8.8)	Cm. R	7.43–7.26 (6H, m, H-7 + C_6H_5); 5.19 (1H, q, J = 7.0, NHC$\underline{H}CH_3$); 1.54 (3H, d, J = 7.1, CH_3)
1o	15.53	9.68 (t, J = 5.4)	8.85 (J = 7.1)	8.01 (J = 7.8)	7.45 (J = 8.9)	Cm. R	7.33-7.17 (6H, m, H-7 + C_6H_5); 3.60 (2H, q, J = 6.7, NHC$\underline{H_2}$); 2.85 (2H, t, J = 7.1, C$\underline{H_2}$-C_6H_5)
1p	15.56	9.73 (t, J = 5.5)	8.85 (J = 7.0)	7.99 (J = 7.8)	7.43 (J = 8.9)	Cm. R	7.34 (3H, m, H-7 + H-3',5'); 7.27 (2H, d, J = 7.2, H-2',6'); 3.58 (2H, q, J = 6.6, NHC$\underline{H_2}$); 2.85 (2H, t, J = 7.2, $NHCH_2C\underline{H_2}$)
1q	15.62	9.86 (t, J = 5.4)	8.82 (J = 7.1)	7.94 (J = 7.7)	7.38 (J = 8.9)	7.20 (J = 7.0)	6.95 (1H, s, H-2'); 6.84 (1H, d, J = 8.1, H-5'); 6.75 (1H, d, J = 7.6, H-6'); 3.70 (6H, s, $2OCH_3$); 3.56 (2H, q, J = 6.5, NHC$\underline{H_2}$); 2.97 (2H, t, J = 7.3, $NHCH_2C\underline{H_2}$)
1r	15.74	9.85 (t, J = 5.3)	8.91 (J = 7.2)	8.07 (J = 7.9)	7.52 (J = 8.9)	7.36 (J = 7.0)	7.60 (1H, d, J = 1.8, H-5'); 6.41 (1H, t, J = 2.3, H-4'); 6.34 (1H, d, J = 3.1, H-3'); 4.59 (2H, d, J = 5.8, NHC$\underline{H_2}$)
1s	15.86	10.23 (t, J = 5.0)	8.96 (J = 7.1)	8.07 (J = 7.8)	7.53 (J = 8.9)	See R	8.55 (1H, d, J = 4.8, H-6'); 7.77 (1H, t, J = 7.7, H-5'); 7.49–7.48 (3H, m, H-7 + H-3',4'); 4.71 (2H, d, J = 5.7, NHC$\underline{H_2}$)
1t	15.65	9.97 (t, J = 5.5)	8.91 (J = 7.1)	8.06 (J = 7.9)	7.52 (J = 8.8)	See R	8.58 (1H, s, H-2'); 8.46 (1H, d, J = 4.6, H-6'); 7.76 (1H, d, J = 7.9, H-4'); 7.36 (2H, m, H-7 + H-5'); 4.62 (2H, d, J = 5.9, NHC$\underline{H_2}$)
1u	15.62	10.01 (t, J = 5.0)	8.94 (J = 7.0)	8.09 (J = 7.7)	7.53 (J = 9.0)	7.37 (J = 6.9)	8.50 (2H, d, J = 4.6, H-2',6'); 7.30 (2H, d, J = 4.6, H-3',5'); 4.62 (2H, d, J = 5.7, NHC$\underline{H_2}$)
2a	14.83	11.61, s	8.98 (J = 6.9)	8.13 (J = 7.7)	7.55 (J = 8.8)	See R	7.64 (2H, d, J = 8.1, H-2',6'); 7.46–7.32 (3H, m, H-7 + H-3',5'); 7.13 (1H, t, J = 7.1, H-4')
2b	14.79	11.83, s	9.01 (J = 7.1)	8.15 (J = 7.8)	7.56 (J = 8.7)	7.41 (J = 6.9)	8.29 (1H, t, J = 7.7, H-3'); 7.34 (1H, d, J = 8.3, H-6'); 7.26–7.11 (2H, m, H-4',5')
2c	14.85	11.65, s	8.98 (J = 7.2)	8.15 (J = 7.8)	7.54 (J = 8.8)	See R	7.67 (1H, d, J = 11.3, H-2'); 7.45–7.28 (3H, m, H-7 + H-5',6'); 6.94 (1H, t, J = 8.1, H-4')
2d	14.88	11.53, s	8.97 (J = 7.0)	8.13 (J = 7.9)	7.55 (J = 8.8)	7.41 (J = 7.0)	7.66 (2H, d d, J = 8.9 и 4.9, H-2',6'); 7.19 (2H, t, J = 9.0, H-3',5')
2e	14.47	11.58, s	8.99 (J = 7.0)	8.12 (J = 7.8)	See R	See R	7.83 (1H, s, J = H-2'); 7.59–7.34 (4H, m, H-7,9 + H-5',6'); 7.18 (1H, d, J = 7.6, H-4')
2f	14.90	11.60, s	8.98 (J = 6.9)	8.15 (J = 7.7)	7.54 (J = 8.8)	See R	7.67 (2H, d, J = 8.9, H-2',6'); 7.46–7.38 (3H, m, H-7 + H-3',5')

TABLE 4. Bond Lengths (*l*) in the Amide **1k** Structure

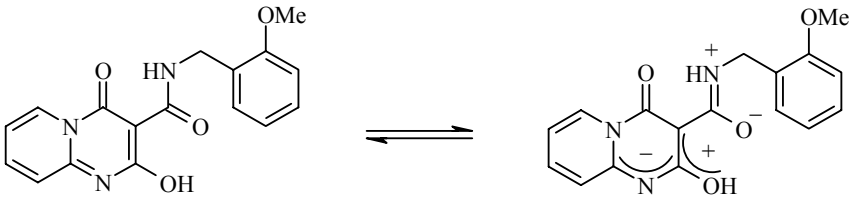
Bond	*l*, Å	Bond	*l*, Å
$O_{(1)}$–$C_{(8)}$	1.323(2)	$O_{(2)}$–$C_{(6)}$	1.234(2)
$O_{(3)}$–$C_{(9)}$	1.257(2)	$O_{(4)}$–$C_{(16)}$	1.372(2)
$O_{(4)}$–$C_{(17)}$	1.417(3)	$N_{(1)}$–$C_{(1)}$	1.330(2)
$N_{(1)}$–$C_{(8)}$	1.336(2)	$N_{(2)}$–$C_{(1)}$	1.375(2)
$N_{(2)}$–$C_{(5)}$	1.382(2)	$N_{(2)}$–$C_{(6)}$	1.440(2)
$N_{(3)}$–$C_{(9)}$	1.329(2)	$N_{(3)}$–$C_{(10)}$	1.451(2)
$C_{(1)}$–$C_{(2)}$	1.415(3)	$C_{(2)}$–$C_{(3)}$	1.352(3)
$C_{(3)}$–$C_{(4)}$	1.394(3)	$C_{(4)}$–$C_{(5)}$	1.341(3)
$C_{(6)}$–$C_{(7)}$	1.408(2)	$C_{(7)}$–$C_{(8)}$	1.402(2)
$C_{(7)}$–$C_{(9)}$	1.468(2)	$C_{(10)}$–$C_{(11)}$	1.505(2)
$C_{(11)}$–$C_{(12)}$	1.381(2)	$C_{(11)}$–$C_{(16)}$	1.391(2)
$C_{(12)}$–$C_{(13)}$	1.391(3)	$C_{(13)}$–$C_{(14)}$	1.374(3)
$C_{(14)}$–$C_{(15)}$	1.388(3)	$C_{(15)}$–$C_{(16)}$	1.382(2)

electron density in the molecule which is revealed in lengthening of the $O_{(2)}$–$C_{(6)}$ bonds 1.234(2) and $O_{(3)}$–$C_{(9)}$ 1.257(2) Å when compared with their mean value of 1.210 Å [9] and also the $N_{(1)}$–$C_{(1)}$ 1.330(2) and $C_{(7)}$–$C_{(8)}$ 1.402(2) Å bonds (mean values 1.313 and 1.331 Å respectively). The $O_{(1)}$–$C_{(8)}$ 1.323(2), $N_{(1)}$–$C_{(8)}$ 1.336(2), and $C_{(6)}$–$C_{(7)}$ 1.408(2) Å bonds are shortened when compared with their mean values of 1.333, 1.376, and 1.455 Å.

It should be noted that the intramolecular hydrogen bonds in the molecule of amide **1k** are stronger than those reported by us previously for the structurally closely related 2-hydroxy-8-methyl-4-oxo-4H-pyrido-[1,2-*a*]pyrimidine-3-carboxylic acid diethylaminoethylamide [10]. As a result of this the $C_{(1)}$–$N_{(1)}$ and $N_{(1)}$–$C_{(8)}$ bonds become virtually equal in length. Attention is also drawn to the marked difference in the strength of the two intramolecular hydrogen bonds giving a basis for confirming that the predominant contribution to delocalization relates to the very strong O–H···O bond. Hence the geometry of the substance studied can be represented as a resonance hybrid of the two canonical structures **1k** and **6**, the main contribution to which relates somewhat differently to the case of the above mentioned diethylaminoethylamide the bizwitterionic form **6**.

TABLE 5. Valence Angles (ω) in the Amide **1k** Structure

Angle	ω, deg	Angle	ω, deg.
$C_{(16)}$–$O_{(4)}$–$C_{(17)}$	118.2(2)	$C_{(1)}$–$N_{(1)}$–$C_{(8)}$	116.8(2)
$C_{(1)}$–$N_{(2)}$–$C_{(5)}$	121.5(2)	$C_{(1)}$–$N_{(2)}$–$C_{(6)}$	120.9(2)
$C_{(5)}$–$N_{(2)}$–$C_{(6)}$	117.6(2)	$C_{(9)}$–$N_{(3)}$–$C_{(10)}$	122.6(2)
$N_{(1)}$–$C_{(1)}$–$N_{(2)}$	123.5(2)	$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	119.7(2)
$N_{(2)}$–$C_{(1)}$–$C_{(2)}$	116.8(2)	$C_{(3)}$–$C_{(2)}$–$C_{(1)}$	121.1(2)
$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	120.3(2)	$C_{(5)}$–$C_{(4)}$–$C_{(3)}$	119.5(2)
$C_{(4)}$–$C_{(5)}$–$N_{(2)}$	120.8(2)	$O_{(2)}$–$C_{(6)}$–$C_{(7)}$	128.0(2)
$O_{(2)}$–$C_{(6)}$–$N_{(2)}$	117.1(2)	$C_{(7)}$–$C_{(6)}$–$N_{(2)}$	114.9(2)
$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	118.8(2)	$C_{(8)}$–$C_{(7)}$–$C_{(9)}$	119.4(2)
$C_{(6)}$–$C_{(7)}$–$C_{(9)}$	121.8(2)	$O_{(1)}$–$C_{(8)}$–$N_{(1)}$	114.4(2)
$O_{(1)}$–$C_{(8)}$–$C_{(7)}$	120.5(2)	$N_{(1)}$–$C_{(8)}$–$C_{(7)}$	125.1(2)
$O_{(3)}$–$C_{(9)}$–$N_{(3)}$	120.8(2)	$O_{(3)}$–$C_{(9)}$–$C_{(7)}$	119.8(2)
$N_{(3)}$–$C_{(9)}$–$C_{(7)}$	119.4(2)	$N_{(3)}$–$C_{(10)}$–$C_{(11)}$	115.3(2)
$C_{(12)}$–$C_{(11)}$–$C_{(16)}$	118.2(2)	$C_{(12)}$–$C_{(11)}$–$C_{(10)}$	123.8(2)
$C_{(16)}$–$C_{(11)}$–$C_{(10)}$	118.0(2)	$C_{(11)}$–$C_{(12)}$–$C_{(13)}$	121.4(2)
$C_{(14)}$–$C_{(13)}$–$C_{(12)}$	119.4(2)	$C_{(13)}$–$C_{(14)}$–$C_{(15)}$	120.4(2)
$C_{(16)}$–$C_{(15)}$–$C_{(14)}$	119.4(2)	$O_{(4)}$–$C_{(16)}$–$C_{(15)}$	123.5(2)
$O_{(4)}$–$C_{(16)}$–$C_{(11)}$	115.4(1)	$C_{(15)}$–$C_{(16)}$–$C_{(11)}$	121.2(2)



1k **6**

The methoxyphenyl substituent in amide **1k** is placed almost perpendicularly to the $C_{(9)}$–$N_{(3)}$ bond (torsional angle $C_{(9)}$–$N_{(3)}$–$C_{(10)}$–$C_{(11)}$ 80.3(2)º) and this is due to the repulsion between the aromatic ring and the carbamide group [shortened intramolecular contacts $H_{(12)}\cdots C_{(9)}$ 2.76 Å (sum of van der Waal radii [11] 2.87 Å), $H_{(12)}\cdots N_{(3)}$ 2.53 (2.67 Å)] and is coplanar to $N_{(3)}$–$C_{(10)}$ bond (torsional angle $N_{(3)}$–$C_{(10)}$–$C_{(11)}$–$C_{(12)}$ = -3.7(3)º). The methoxy group deviates from the plane of the aromatic ring (torsional angle $C_{(17)}$–$O_{(4)}$–$C_{(16)}$–$C_{(15}$ 9.4(3)º) as a result of the repulsion between the methyl group atoms and the benzene ring (shortened intramolecular contacts $H_{(15)}\cdots C_{(17)}$ 2.50 (2.87), $H_{(15)}\cdots H_{(17b)}$ 2.26 (2.34), $H_{(15)}\cdots H_{(17a)}$ 2.24 (2.34), $H_{(17a)}\cdots C_{(15)}$ 2.77 (2.87), and $H_{(17b)}\cdots C_{(15)}$ 2.69 (2.87 Å)).

A study of the diuretic properties of all of the 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid N-R-amides **1-3** has been made in parallel and in comparison with hypothiazide by a standard method [12] using white, nonpedigree male mice of mass 180-200 g. The studied compounds were introduced *per os* at a dose of 40 mg/kg (the effective dose of hypothiazide) as a fine aqueous suspension stabilized by Tween-80. All laboratory animals received an aqueous charge through a stomach probe based on 25 mg/kg. The urinary secretion was measured over 4 h. Comparing the data in Table 1 for the pharmacological study of amides **1-2** with the results of our previous work it should be noted that exchange of the 4-hydroxy-2-oxo-1,2-dihydroquinoline ring for the 2-hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine is accompanied by a marked lowering of diuretic activity in the majority of cases hence the search for potential diuretics can be identified as of little promise. Principally such a conclusion relates to the alkyl and arylalkylamides **1a-u**. The pyridin-2-ylamide **3** also shows activity at a level of only +8.4% when compared to the control and almost no difference to the unsubstituted anilide **2a**. In the series of substituted anilides **2b-f** against a background of the overall tendency to fall, the dependence of the diuretic effect on the substituent in the aromatic ring is preserved as in the 4-hydroxy-2-oxoquinoline analogs. Thus amongst the monofluoroanilides the most active is the *meta* isomer **2c** while the diuresis is always expressed more clearly in the para-substituted compound for the chloro derivatives.

EXPERIMENTAL

^{1}H NMR spectra for the N-R-amides **1** and **2** were recorded on a Varian Mercury VX-200 instrument (200 MHz). The ^{1}H and ^{13}C NMR spectra and also the heteronuclear HMQC and HMBC experiments were carried out on a Varian Mercury-400 spectrometer (400 and 100 MHz respectively). All 2D experiments were carried out with gradient selection of useful signals. The mixing times in the pulse sequence were respectively $^1J_{CH}$ = 140 and $^{2\text{-}3}J_{CH}$ = 8 Hz. The numbers of increments in the HMQC and HMBC experiments were 128 and 400 respectively. In all cases the solvent used was DMSO-d_6 and the internal standard TMS. The study of the acid-base equilibrium was carried out using method [13] with 80% aqueous dioxane solvent. Preparation of a mixed solvent used freshly distilled bidistillate freed from CO_2 and dioxane for UV from the Labscan company. The titrant was 0.01 molar aqueous KOH solution freed from CO_2. The concentration of the titration solution was 0.0005 molar at the neutral point. The potentiometric titration was carried out on a SevenEasy S-20-K Mettler Toledo stationary pH meter using an InLab 413 combination electrode at 25ºC. Titrations were performed three times for each compound. The accuracy of the obtained results was estimated by mathematic statistics [14].

2-Hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acid Alkylamides 1a-u (General Method). The corresponding alkylamine (0.03 mol) was added to a solution of ethyl 2-hydroxy-4-oxo-4H-pyrido-[1,2-*a*]pyrimidine-3-carboxylate **4** (2.34 g, 0.01 mol) in ethanol (10 ml) and refluxed for 30 h. The reaction mixture was cooled, the precipitated amide **1a-u** filtered, carefully washed with ether, and dried.

X-ray Structural Study. Crystals of the amide **1k** are monoclinic (ethanol), at 20ºC: a = 7.877(1), b = 10.303(1), c = 18.885(2) Å, β = 101.19(1)º, V = 1503.4(2) Å^3, M_r = 325.32, Z = 4, space group P2/n, d_{calc} = 1.437 g/cm^3, μ(MoKα) = 0.105 mm^{-1}, F(000) = 680. Unit cell parameters and intensities of 6319 reflections (2607 independent with R_{int} = 0.021) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω scanning to $2\theta_{max}$ = 50º).

The structure was solved by a direct method using the SHELXTL program package [15]. The positions of the hydrogen atoms were revealed from electron density difference synthesis and refined isotropically. The structure was refined in F^2 full matrix least squares analysis in the anistropic approximation for non-hydrogen atoms to wR_2 = 0.093 for 2549 reflections (R_1 = 0.035 for 1457 reflections with $F > 4\sigma(F)$, S = 0.883). The full crystallographic information has been placed in the Cambridge structural database (reference CCDC 650598). Interatomic distances and valence angles are given in Tables 4 and 5.

2-Hydroxy-4-oxo-4H-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acid Anilides 2a-f (General Method). A mixture of compound **4** (2.34 g, 0.01 mol), the corresponding aniline (0.01 mol), and DMF (1 ml) was stirred and held for 15 min at 160ºC. After cooling, ethanol (10-15 ml) was added and triturated carefully. The precipitated anilides **2a-f** were filtered off, washed with alcohol, dried, and crystallized from DMF.

2-Hydroxyethyl-1-ammonium 3-Ethoxycarbonyl-4-oxo-4H-pyrido[1,2-*a*]pyrimidin-2-olate (5a). 2-Aminoethanol (0.9 ml, 0.015 mol) was added to a solution of compound **4** (2.34 g, 0.01 mol) in ethanol (20 ml) and carefully stirred. A white precipitate formed immediately after mixing the reagents. It was filtered off, carefully washed with ethanol, and dried. For the separation of salts of ester **4** with other alkylamines it was necessary to dilute the reaction mixture with ether. Yield 2.8 g (95%); mp 226-228ºC. ^{1}H NMR spectrum, δ, ppm (J, Hz): 8.57 (1H, d, J = 6.8, H-6); 7.59 (1H, t, J = 7.2, H-8); 6.96 (1H, d, J = 8.8, H-9); 6.79 (1H, t, J = 6.8, H-7); 4.05 (2H, q, J = 7.2, OC$\underline{H}_2$CH$_3$); 3.54 (2H, t, J = 5.2, OC$\underline{H}_2$CH$_2$N); 2.82 (2H, t, J = 5.2, OCH$_2$C$\underline{H}_2$N); 1.18 (3H, t, J = 7.2, CH$_3$). ^{13}C NMR spectrum, δ, ppm: 168.3 (CO$_2$), 168.0 (C$_{(2)}$), 156.0 (C$_{(4)}$), 150.3 (C$_{(9a)}$), 138.0 (C$_{(8)}$), 128.3 (C$_{(6)}$), 122.0 (C$_{(9)}$), 111.7 (C$_{(7)}$), 93.2 (C$_{(3)}$), 59.6 (O$\underline{C}$H$_2$CH$_3$), 59.2 (O$\underline{C}$H$_2$CH$_2$N), 42.4 (OCH$_2\underline{C}$H$_2$N), 15.0 (CH$_3$). Found, %: C 52.97; H 5.92; N 14.34. $C_{11}H_9N_2O_4 \cdot C_2H_8NO$. Calculated, %: C 52.88; H 5.80; N 14.23.

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