Chemistry of Heterocyclic Compounds, Vol. 48, No. 9, December, 2012 (Russian Original Vol. 48, No. 9, September, 2012)

4-HYDROXY-2-QUINOLONES. 204.* SYNTHESIS, BROMINATION, AND ANALGETIC PROPERTIES OF 1-ALLYL-4-HYDROXY- 6,7-DIMETHOXY-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACID ARYLALKYLAMIDES

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A simple method has been proposed and used for the preparation of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-di-hydroquinoline-3-carboxylic acid arylalkylamides. Similar to alkylamides of this acid, the arylalkylamides obtained are halogenated with cyclization by one equivalent of molecular bromine to give the corresponding 2-bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carbox-amides. However, the reaction proceeds quite differently when using an excess of bromine. After the usual initial oxazole ring closure, the excess bromine brominates the aromatic ring of the amide fragment. The results of testing for the analgesic activity of these products are presented.

Keywords: 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides, amidation, analgesic activity, bromination, halocyclization.

The synthesis and subsequent study of new compounds similar in structure to compounds, which have already proven themselves in one way or another remains one of the most effective methods for improving the useful properties of initially selected lead structures. This method has long been employed in many areas of science and technology, but has found an especially wide application in medicinal chemistry [2-4]. In the present communication, we applied this approach in a search for more powerful, non-narcotic analgesics among 4-hydroxy-2-oxoquinoline-3-carboxamides.

*For communication 203, see [1].

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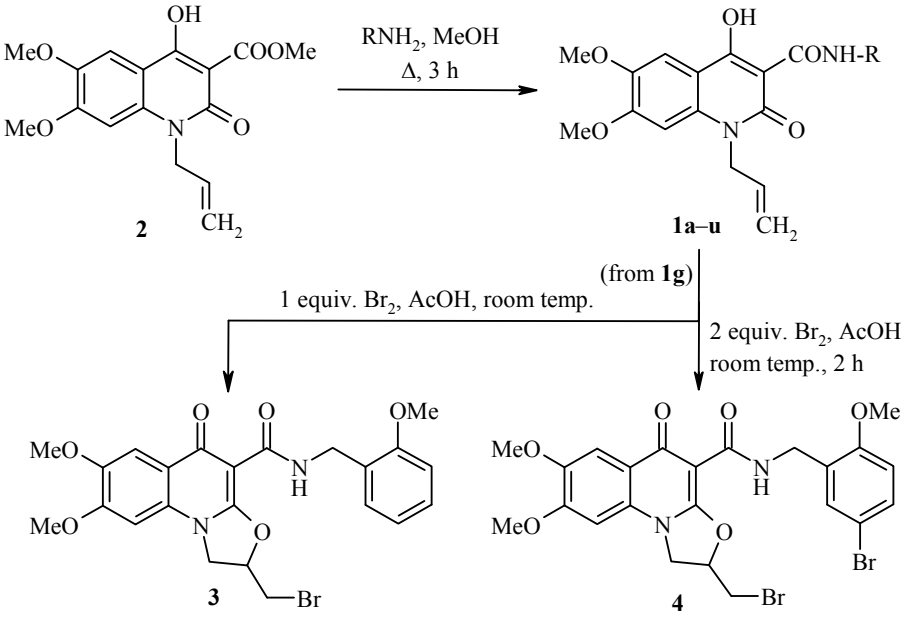
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1445-1455, September, 2012. Original article submitted June 3, 2011.

This study of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid arylalkylamides with general formula **1** was suggested by the sufficiently high analgesic activity of alkylamides of this acid [5] and the lack of marked acidity for these compounds [6]. The lower acidity of these compounds, which is 800-1000 times less than for known analgesics [7], allows to hope that the use of such compounds would permit a partial if not complete elimination of the ulcerogenic effect, which is the major cause for a whole series of contraindications when using non-narcotic analgesics [8].

A good solubility of the starting methyl 1-allyl-6,7-dimethoxy-4-hydroxy-2-oxo-1,2-dihydro-quinoline-3-carboxylate (**2**) in alcohols permits the amidation of this ester with arylalkylamines under relatively mild conditions, completely eliminating the possibility of thermal decomposition, which is characteristic for quinoline-3-carboxylates substituted in the benzene moiety [9]. Thus, the desired arylalkylamides **1a-u** were synthesized in good yields and purity (Tables 1 and 2).



1 a R = Bn, **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 = tetrahydrofurfuryl, **m** R = picolyl-2, **n** R = picolyl-3, **o** R = picolyl-4, **p** R = $PhCH(Me)CH_2$, **q** R = $PhCH_2CH_2$, **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 = $PhCH_2CH_2CH_2$

Similar to the 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid alkylamides described in our previous work [5], their arylalkyl analogs **1a-u** also undergo facile halocyclization upon the addition of an equivalent of molecular bromine in glacial acetic acid, to give the corresponding 2-bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5*H*-oxazolo[3,2-*a*]quinoline-4-carboxamides **3** (the example of compound **1g** is given in this work). However, in the presence of excessive bromine, the reaction takes an entirely different course due to the aromatic ring in the amide fragment. The introduction of the aromatic ring leads to an additional reaction site susceptible to halogenation. After closure of the new five-membered ring the excess of bromine is consumed in ordinary electrophilic aromatic substitution rather than giving oxazolo-[3,2-*a*]quinoline tribromides [5].

The course of the reaction examined was experimentally confirmed on the example of 1-allyl-6,7-dimethoxy-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid 2-methoxybenzylamide (**1g**). Thus, the characteristic change in the ^{1}H NMR spectrum indicates that after the reaction with an equivalent amount of bromine this compound is converted exclusively and in high yield to the 2-bromomethyl-7,8-dimethoxy-5-oxo-

TABLE 1. Characteristics of the Arylalkylamides **1a-u*** Synthesized

Compound	Empirical formula	Found, % / Calculated, %			Mp, °C	Yield, %	Analgetic activity*[2]
		C	H	N			
1a	$C_{22}H_{22}N_2O_5$	67.08 / 66.99	5.73 / 5.62	7.16 / 7.10	160-162	95	30.9
1b	$C_{22}H_{21}FN_2O_5$	64.15 / 64.07	5.21 / 5.13	6.87 / 6.79	164-166	90	9.5
1c	$C_{22}H_{21}FN_2O_5$	64.14 / 64.07	5.08 / 5.13	6.70 / 6.79	173-175	93	15.6
1d	$C_{22}H_{21}ClN_2O_5$	61.53 / 61.61	5.05 / 4.94	6.64 / 6.53	187-189	92	14.4
1e	$C_{22}H_{21}ClN_2O_5$	61.69 / 61.61	5.08 / 4.94	6.61 / 6.53	180-182	96	56.9
1f	$C_{23}H_{24}N_2O_5$	67.51 / 67.63	5.80 / 5.92	6.75 / 6.86	146-148	88	24.3
1g	$C_{23}H_{24}N_2O_6$	64.96 / 65.08	5.62 / 5.70	6.71 / 6.60	161-163	86	10.8
1h	$C_{23}H_{24}N_2O_6$	65.14 / 65.08	5.78 / 5.70	6.69 / 6.60	155-157	90	26.3
1i	$C_{24}H_{26}N_2O_7$	63.55 / 63.43	5.86 / 5.77	6.23 / 6.16	182-184	84	39.4
1j	$C_{23}H_{22}N_2O_7$	62.90 / 63.01	4.93 / 5.06	6.44 / 6.39	189-191	89	15.4
1k	$C_{20}H_{20}N_2O_6$	62.57 / 62.49	5.20 / 5.24	7.21 / 7.29	154-156	93	50.9
1l	$C_{20}H_{24}N_2O_6$	61.74 / 61.85	6.11 / 6.23	7.16 / 7.21	166-168	81	20.5
1m	$C_{21}H_{21}N_3O_5$	63.68 / 63.79	5.27 / 5.35	10.52 / 10.63	199-201	90	31.9
1n	$C_{21}H_{21}N_3O_5$	63.87 / 63.79	5.44 / 5.35	10.70 / 10.63	192-194	92	6.2
1o	$C_{21}H_{21}N_3O_5$	63.85 / 63.79	5.42 / 5.35	10.56 / 10.63	181-183	94	18.7
1p	$C_{23}H_{24}N_2O_5$	67.50 / 67.63	5.82 / 5.92	6.95 / 6.86	178-180	80	9.5
1q	$C_{23}H_{24}N_2O_5$	67.71 / 67.63	5.98 / 5.92	6.97 / 6.86	173-175	88	12.7
1r	$C_{23}H_{23}ClN_2O_5$	62.46 / 62.37	5.34 / 5.23	6.20 / 6.32	185-187	91	15.1
1s	$C_{24}H_{26}N_2O_6$	65.65 / 65.74	6.07 / 5.98	6.48 / 6.39	180-182	85	17.0
1t	$C_{25}H_{28}N_2O_7$	63.97 / 64.09	5.93 / 6.02	5.89 / 5.98	169-171	87	15.6
1u	$C_{24}H_{26}N_2O_5$	68.34 / 68.23	6.28 / 6.20	6.75 / 6.63	162-164	82	17.9

*The analgesic activity is 35.2 for diclofenac and 47.1 for ketorolac.

*[2]Increase of the pain threshold, %.

1,2-dihydro-5*H*-oxazolo[3,2-*a*]quinoline-4-carboxylic acid 2-methoxybenzylamide (**3**). The ^{1}H NMR spectrum of another compound obtained in a reaction of the same 2-methoxybenzylamide **1g** with a twofold excess of bromine shows that the initial halocyclization in this case is followed by bromination of the aromatic ring of the benzyl fragment. Both the substituents in the aromatic ring direct bromination to *ortho* and *para* positions. Thus, it would be entirely reasonable to expect competition in the substitution. It is not always possible to give a precise prediction of the final result of these reactions, but numerous observations show that groups producing an effect by means of lone electron pairs are more active than groups with an inductive effect [10]. In other words, the probability of substitution at the *ortho* or *para* position relative to the methoxy group in the bromination of the 2-methoxybenzyl fragment is higher than to such positions relative to the acylaminomethyl group. However, we should bear in mind that this is only a hypothesis and does not exclude the possibility of a completely opposite result.

Thus, structural characterization of the product of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid 2-methoxybenzylamide (**1g**) reaction with a twofold excess of bromine is reduced largely to determination of the bromine atom position in the benzyl fragment. In principle, such problems are rather simply solved by NMR spectroscopy using special methods, in particular, the nuclear Overhauser effect (NOE), although some difficulties may be encountered. For example, investigation of the structure of this product by the NOE method in the solution of DMSO-d_6, which is the most commonly employed solvent, failed completely for the simple reason that there was an unexpected overlap of the two methoxy group signals. This coincidence prevented studies involving their selective saturation. The spectrum in a mixed solvent consisting of DMSO-d_6 and deuterated benzene (1:1 mixture) was more suitable for analytical studies. All three methoxy groups in this spectrum appeared as separate signals, which allowed us to carry out straightforward NOE experiments. Figure 1 shows the chemical shifts of all the protons in this product; the arrows indicate enhanced signal intensity under stationary NOE conditions.

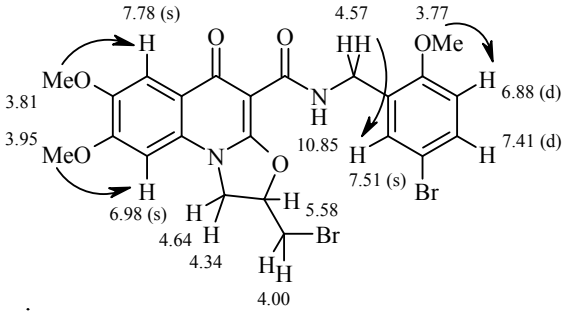


Fig. 1. NOE determination of the bromine atom position in the benzyl fragment of amide **4.**

We immediately notice the multiplicity of the signals in the aromatic part of the spectrum. Three singlets (7.78, 7.51, and 6.98 ppm) and two doublets (7.41 and 6.88 ppm) are observed. After subtracting out the two singlets due to quinolone protons, one singlet and two doublets remain for the benzyl fragment, which considerably simplifies the problem since such a combination of signals completely excludes the theoretically

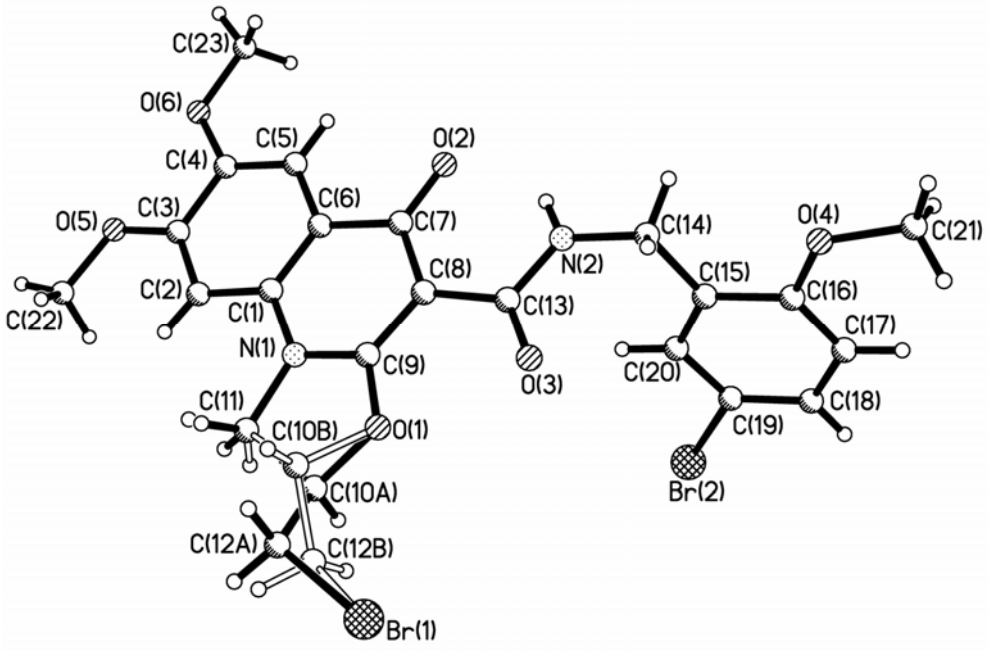


Fig. 2. Molecular structure of 5-bromo-2-methoxybenzylamide **4**.

TABLE 2. ^{1}H NMR Spectra of 1-Allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Arylalkylamides **1a-u**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)								
	OH (1H, s)	NH (1H, t)	H-5 (1H, s) H-8 (1H, s)	*N*-allyl fragment				$2OCH_3$ (3H, s) (3H, s)	R
				CH (1H, m)	CH=CH-*cis* (1H, d)	CH=CH-*trans* (1H, d)	NCH_2 (2H, d)		
1	2	3	4	5	6	7	8	9	10
1a	17.15	10.69 (*J* = 5.7)	7.39 6.91	6.01-5.81	5.14 (*J* = 10.5)	5.03 (*J* = 17.4)	4.93 (*J* = 4.6)	3.89 3.82	7.37-7.25 (5H, m, H Ph); 4.56 (2H, d, *J* = 5.5, NCH_2)
1b	16.98	10.71 (*J* = 5.8)	See R 6.92	6.01-5.81	5.15 (*J* = 10.6)	5.04 (*J* = 17.5)	4.94 (*J* = 4.5)	3.89 3.82	7.46-7.13 (5H, m, H-5,3',4',5',6'); 4.62 (2H, d, *J* = 5.6, NCH_2)
1c	17.11	10.68 (*J* = 5.7)	7.37 6.90	6.01-5.81	5.15 (*J* = 10.3)	5.03 (*J* = 17.4)	4.93 (*J* = 4.4)	3.89 3.82	7.42 (2H, t, *J* = 7.1, H-3',5'); 7.16 (2H, d, *J* = 8.9, H-2',6'); 4.54 (2H, d, *J* = 5.8, NCH_2)
1d	17.08	10.75 (*J* = 5.9)	See R 6.93	6.02-5.82	5.14 (*J* = 10.5)	5.04 (*J* = 17.6)	4.94 (*J* = 4.5)	3.90 3.83	7.70 (1H, d, *J* = 7.3, H-3'); 7.47 (1H, d, *J* = 7.1, H-6'); 7.40-7.29 (3H, m, H-5,4',5'); 4.65 (2H, d, *J* = 5.9, NCH_2)
1e	17.07	10.71 (*J* = 6.1)	See R 6.92	6.00-5.80	5.15 (*J* = 10.5)	5.04 (*J* = 17.3)	4.94 (*J* = 4.5)	3.90 3.82	7.44-7.33 (5H, m, H-5,2',3',5',6'); 4.64 (2H, d, *J* = 5.9, NCH_2)
1f	17.19	10.64 (*J* = 5.5)	7.39 6.91	6.01-5.81	5.13 (*J* = 10.5)	5.03 (*J* = 17.5)	4.94 (*J* = 4.2)	3.89 3.82	7.24 (2H, d, *J* = 8.0, H-2',6'); 7.15 (2H, d, *J* = 8.0, H-3',5'); 4.51 (2H, d, *J* = 5.8, NCH_2); 2.26 (3H, s, CH_3)
1g	17.23	10.66 (*J* = 5.8)	7.40 6.91	6.01-5.81	5.14 (*J* = 10.6)	5.03 (*J* = 17.7)	4.94 (*J* = 4.4)	3.89 3.82	7.33-7.21 (2H, m, H-3',4'); 7.02 (1H, d, *J* = 7.9, H-6'); 6.94 (1H, t, *J* = 8.0, H-5'); 4.52 (2H, d, *J* = 5.8, NCH_2); 3.84 (3H, s, OCH_3)
1h	17.22	10.61 (*J* = 5.9)	7.39 6.90	6.00-5.80	5.14 (*J* = 10.3)	5.02 (*J* = 17.4)	4.92 (*J* = 4.4)	3.89 3.82	7.28 (2H, d, *J* = 8.5, H-3',5'); 6.92 (2H, d, *J* = 8.5, H-2',6'); 4.48 (2H, d, *J* = 5.8, NCH_2); 3.71 (3H, s, OCH_3)
1i	17.24	10.64 (*J* = 5.7)	7.41 See R	6.00-5.80	5.14 (*J* = 10.2)	5.03 (*J* = 17.3)	4.94 (*J* = 4.5)	3.89 3.82	6.99 (1H, s, H-2'); 6.94-6.87 (3H, m, H-8,5',6'); 4.48 (2H, d, *J* = 5.4, NCH_2); 3.73 (3H, s, OCH_3); 3.71 (3H, s, OCH_3)
1j	17.17	10.62 (*J* = 6.0)	7.40 6.91	6.00-5.80	5.14 (*J* = 10.4)	5.03 (*J* = 17.3)	4.93 (*J* = 4.5)	3.89 3.82	6.99 (1H, s, H-2'); 6.88-6.82 (2H, m, H-5',6'); 5.98 (2H, s, OCH_2O); 4.47 (2H, d, *J* = 5.6, NCH_2)
1k	16.98	10.61	7.39	6.01-5.81	5.14	5.03	4.94	3.89	7.62 (1H, d, *J* = 1.8, H-5'); 6.41 (1H, t, *J* = 2.2, H-4');

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
1k	16.98	10.61 (J = 5.8)	7.39 6.91	6.01-5.81	5.14 (J = 10.6)	5.03 (J = 17.8)	4.94 (J = 4.2)	3.89 3.82	7.62 (1H, d, J = 1.8, H-5'); 6.41 (1H, t, J = 2.2, H-4'); 6.35 (1H, d, J = 2.7, H-3'); 4.58 (2H, d, J = 5.8, NCH_2)
1l	17.29	10.45 (J = 5.5)	7.39 6.91	6.02-5.82	5.15 (J = 10.4)	5.03 (J = 17.9)	4.95 (J = 4.3)	3.89 3.82	4.03-3.93 (1H, m, OCH); 3.80-3.43 (4H, m, NCH_2, OCH_2); 1.98-1.45 (4H, m, 3',4'-CH_2)
1m	17.16	10.95 (J = 5.3)	7.40 6.93	6.02-5.82	5.16 (J = 10.4)	5.05 (J = 17.8)	4.96 (J = 4.3)	3.90 3.83	8.56 (1H, d, J = 4.5, H-6'); 8.09 (1H, d, J = 7.9, H-3'); 7.78 (1H, t, J = 7.9, H-5'); 7.31 (1H, t, J = 7.8, H-4'); 4.70 (2H, d, J = 5.7, NCH_2)
1n	17.00	10.73 (J = 5.7)	7.39 6.91	6.01-5.81	5.15 (J = 10.4)	5.04 (J = 17.5)	4.94 (J = 4.3)	3.89 3.82	8.58 (1H, d, J = 1.7, H-2'); 8.47 (1H, d. d, J = 4.8, J = 1.6, H-6'); 7.77 (1H, dt, J = 8.0, J = 2.0, H-4'); 7.35 (1H, t, J = 4.8, H-5'); 4.59 (2H, d, J = 6.4, NCH_2)
1o	16.92	10.77 (J = 6.1)	7.39 6.92	6.02-5.82	5.16 (J = 10.6)	5.06 (J = 17.7)	4.95 (J = 4.1)	3.90 3.82	8.51 (2H, d, J = 4.6, H-2',6'); 7.31 (2H, d, J = 4.6, H-3',5'); 4.61 (2H, d, J = 6.1, NCH_2)
1p	17.07	10.80* (J = 7.5)	See R 6.89	6.03-5.83	See R	5.04 (J = 17.3)	4.95 (J = 4.1)	3.89 3.82	7.43-7.22 (6H, m, H-5, H Ph); 5.20-5.13 (2H, m, CH=C<u>H</u>-*cis*, C<u>H</u>Ph); 1.51 (3H, d, J = 6.7, CH_3)
1q	17.33	10.38 (J = 6.0)	7.38 6.91	6.00-5.80	5.14 (J = 10.5)	5.03 (J = 17.7)	4.94 (J = 4.2)	3.89 3.82	7.30-7.19 (5H, m, H Ph); 3.59 (2H, q, J = 6.7, NCH_2); 2.86 (2H, t, J = 7.0, CH_2Ph)
1r	17.29	10.36 (J = 5.6)	7.39 6.91	6.00-5.80	5.15 (J = 10.5)	5.03 (J = 17.7)	4.94 (J = 4.1)	3.89 3.82	7.34 (2H, d, J = 8.6, H-3',5'); 7.27 (2H, d, J = 8.6, H-2',6'); 3.58 (2H, q, J = 6.4, NCH_2); 2.87 (2H, t, J = 6.9, CH_2Ar)
1s	17.35	10.36 (J = 5.9)	7.40 6.91	6.00-5.80	5.15 (J = 10.4)	5.03 (J = 17.6)	4.93 (J = 4.3)	3.89 3.82	7.18 (2H, d, J = 8.5, H-3',5'); 6.85 (2H, d, J = 8.5, H-2',6'); 3.70 (3H, s, OCH_3); 3.55 (2H, q, J = 6.6, NCH_2); 2.79 (2H, t, J = 7.0, CH_2Ar)
1t	17.36	10.38 (J = 5.5)	7.39 6.91	6.01-5.81	5.14 (J = 10.6)	5.02 (J = 17.5)	4.93 (J = 4.2)	3.89 3.82	6.88-6.82 (2H, m, H-2',5'); 6.76 (1H, d, J = 8.3, H-6'); 3.71 (3H, s, OCH_3); 3.69 (3H, s, OCH_3); 3.57 (2H, q, J = 6.6, NCH_2); 2.79 (2H, t, J = 6.9, CH_2Ar)
1u	17.38	10.40 (J = 5.7)	7.40 6.92	6.01-5.81	5.16 (J = 10.4)	5.04 (J = 17.8)	4.95 (J = 4.2)	3.89 3.82	7.33-7.15 (5H, m, H Ph); 3.24 (2H, q, J = 5.9, NCH_2); 2.63 (2H, t, J = 7.7, CH_2Ar); 1.86 (2H, quin., J = 7.5, $NCH_2C\underline{H}_2$)

*Doublet.

possible *ortho* substitution. Whether the bromine atom is in the *para* position to the methoxy group or to the acylaminomethyl group, was determined by NOE. Although the absolute value of the NOE did not exceed 3%, this proved entirely sufficient for making reliable conclusions concerning the spatial proximity of the methoxy groups and the corresponding aromatic protons. The existence of NOE between the methoxy group signal at 3.77 ppm and the doublet at 6.88 ppm proved to be most useful for elucidating the structure of this compound. This finding clearly proves that the indicated methoxy group and aromatic proton are adjacent to each other. Thus, the bromine atom is in *para* position to the methoxy group. Otherwise, the multiplicity of the signal at 6.88 ppm would be completely different. Furthermore, we concurrently solved an additional problem for this structure, which might not be as important for structural characterization, but is nevertheless quite interesting, namely, the specific assignment of the signals of the methoxy groups in the quinolone system.

Thus, there is every reason to believe that the product of the 2-methoxybenzylamide **1g** reaction with a twofold excess of bromine is 2-bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5*H*-oxazolo[3,2-*a*]quinoline-4-carboxylic acid 5-bromo-2-methoxybenzylamide (**4**). This conclusion is supported by the results of our X-ray structural analysis (Fig. 2), which revealed several important features of the three-dimensional structure of the 5-bromo-2-methoxybenzylamide **4** obtained. In particular, it is shown that the quinolone fragment and atoms C(11), O(1), O(2), C(13), O(5), and O(6) in this compound lie in a single plane to within 0.02 Å. The bond length values in the pyridone and oxazole rings are close to those in the previously studied compounds with a similar structure [11-13].

The five-membered heterocycle is disordered between two "envelope" conformations (**A** and **B**); the **A:B** occupancy ratio is 7:3. The carbon C(10) deviates from the mean-square plane of the other ring atoms by 0.45 Å in conformer **A** and -0.40 Å in conformer **B**. In both conformers, the atom C(12) has a pseudo-equatorial orientation (the C(9)–O(1)–C(10)–C(12) dihedral angle is -142.6(7)° in the conformer **A** and 142.8(8)° in the conformer **B**). The bromine atom is not disordered and is found in -*sc* and +*sc* conformations in both conformers relative to the O(1)–C(10) bond (the O(1)–C(10)–C(12)–Br(1) dihedral angle is 59(1)° in the conformer **A** and 79(2)° in the conformer **B**). A shortened H(2)···C(11) intramolecular contact (2.74 Å) is found in the tricyclic fragment (the sum of the van der Waals radii is 2.87 Å [14]).

The methoxy groups at the atoms C(3) and C(4) are coplanar to the aromatic ring plane (dihedral angle C(22)–O(5)–C(3)–C(4) is -177.6(7)° and dihedral angle C(23)–O(6)–C(4)–C(3) is -179.5(6)°) despite the significant repulsion between these groups and the benzene fragment atoms. The following shortened intramolecular contacts are seen: H(2)···C(22), 2.41 Å (sum of the van der Waals radii 2.87 Å); H(2)···H(22b), 2.25 Å (2.34 Å); H(2)···H(22c), 2.19 Å (2.34 Å); H(22b)···C(2), 2.75 Å (2.87 Å); H(22c)···C(2), 2.71 Å (2.87 Å); H(5)···C(23), 2.52 Å (2.87 Å); H(5)···H(23c), 2.25 Å (2.34 Å); H(23c)···C(5), 2.71 Å (2.87 Å); H(23b)···C(5), 2.80 Å (2.87 Å).

The carbamide group of the substituent at the atom C(8) is virtually coplanar to the plane of the bicyclic system (the C(9)–C(8)–C(13)–N(2) dihedral angle is 172.5(6)°), which is apparently a result of formation of the N(2)–H(2N)···O(2) intramolecular hydrogen bond (H···O, 1.94 Å; N–H···O, 136°). The carbon C(14) is in the *ap* conformation relative to the C(13)–C(8) bond (the C(14)–N(2)–C(13)–C(8) dihedral angle is 177.7(6)°), while the bromomethoxyphenyl substituent is oriented virtually perpendicular to the C(13)–N(2) bond and coplanar to the N(2)–C(14) bond (the C(13)–N(2)–C(14)–C(15) dihedral angle is 78.4(8)° and the N(2)–C(14)–C(15)–C(20) dihedral angle is -3(1)°). This conformation of the indicated substitutent apparently is facilitated by the following shortened intramolecular contacts: H(20)···N(2), 2.54 Å (the sum of the van der Waals radii is 2.67 Å) and H(20)···C(13), 2.54 Å (2.87 Å). The methoxy group at the C(16) atom is somewhat non-coplanar to the aromatic ring plane (the C(21)–O(4)–C(16)–C(17) dihedral angle is 11(1)°), probably due to the marked repulsion between the methyl group and benzene ring atoms. The following shortened contacts are seen: H(17)···C(21), 2.52 Å (2.87 Å); H(17)···H(21c), 2.17 Å (2.34 Å); H(21c)···C(17), 2.69 Å (2.87 Å).

Shortened intermolecular contacts between molecules of 5-bromo-2-methoxybenzylamide **4** were found in the crystal: H(22a)···H(12c)' (-1-*x*, 0.5+*y*, -0.5-*z*), 2.17 Å (2.34 Å); H(14a)···H(11c)' (*x*, 0.5-*y*, 0.5+*z*), 2.25 Å (2.34 Å); H(21c)···C(8)' (*x*, 0.5-*y*, 0.5+*z*), 2.71 Å (2.87 Å); H(21a)···Br(1)' (-1-*x*, 0.5+*y*, 0.5-*z*), 3.16 Å (3.23 Å);

H(21b)···Br(1)' (1+*x*, 0.5-*y*, 5+*z*), 3.00 Å (3.23 Å); H(22b)···Br(1)' (*x*, 0.5-*y*, -0.5+*z*), 3.04 Å (3.23 Å); H(11a)···Br(2)' (-1+*x*, 0.5-*y*, -0.5+*z*), 3.17 Å (3.23 Å); H(14b)···Br(2)' (-*x*, 0.5+*y*, 0.5-*z*), 3.15 Å (3.23 Å).

The analgesic activity of all the synthesized 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid arylalkylamides **1a-u** was studied in white non-pedigreed male rats. The standard method involving the irritation of rectal mucosa with electric current was employed [15]. The compounds studied were introduced orally in a fine aqueous suspension stabilized with Tween-80. The dose was 20 mg/kg. Comparison of the experimental data (Table 1) with the results of the previous studies [5] showed that going from the already investigated alkylamide derivatives to the arylalkylamide derivatives examined in this work had no significant effect on biological properties. As previously found, all the compounds without exception have the analgesic activity, the most of which reveal a moderate antinociceptive effect. Two compounds, namely, 4-chlorobenzylamide **1e** and furfurylamide **1k** were found with the specific activity superior to that of the commonly used non-narcotic analgesics, diclofenac and ketorolac [8], and should be subjected to detailed testing. Attention should be also paid to the trend that might be useful in our targeted search for new analgesics, which is clearly seen in all groups of compounds with the same aromatic system in the arylalkylamide fragment, such as going from benzyl derivative **1a** to 2-phenylethyl derivative **1q** to 3-phenylpropyl derivative **1u** and from 4-chlorobenzyl derivative **1e** to 2-(4-chlorophenyl)ethyl derivative **1r**, etc. Removal of the aromatic substituent from the amide nitrogen atom leads to a marked drop in the analgesic activity of the corresponding 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid arylalkylamides.

Thus, in this work, we have proposed a simple method for the preparation of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid arylalkylamides and studied the halocyclization of the resultant amides upon the reaction with bromine. The results of testing the compounds for the analgesic activity suggest that the further search for new analgesics among 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxamides should be concentrated on benzylamides and their heterocyclic analogs.

EXPERIMENTAL

The ^{1}H NMR spectra of arylalkylamides **1a-u** and oxazoloquinoline **3** were recorded on a Varian Mercury VX-200 spectrometer (200 MHz) in DMSO-d_6. The NOE experiments on 5-bromo-2-methoxybenzylamide **4** were carried out on a Varian Mercury VX-400 spectrometer (400 MHz) in 1:1 DMSO-d_6–C_6D_6. TMS served as internal standard in all cases. The starting 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid methyl ester (**2**) was prepared according to our previous procedure [16].

1-Allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid Amides 1a-u (General Method). The corresponding amine (0.011 mol) was added to a solution of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid methyl ester (**2**) (3.19 g, 0.010 mol) in methanol (30 ml) and heated at reflux for 3 h. The reaction mixture was cooled, diluted by adding cold water, and brought to pH ~4 by adding dilute hydrochloric acid (acetic acid was used in the isolation of picolylamides **1m-o**). The precipitate formed was filtered off, washed with cold water, dried, and recrystallized from ethanol.

2-Bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5*H*-oxazolo[3,2-*a*]quinoline-4-carboxylic Acid 2-Methoxybenzylamide (3). A solution of Br_2 (0.52 ml, 0.01 mol) in acetic acid (5 ml) was added with vigorous stirring to a solution of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid 2-methoxybenzylamide (**1g**) (4.24 g, 0.01 mol) in glacial acetic acid (30 ml). The red-brown color of bromine disappeared immediately. The reaction mixture was diluted by adding cold water, the precipitate was filtered off, rinsed with cold water, and dried to give methoxybenzylamide **3**. Yield 4.32 g (86%); mp 135-137°C (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.54 (1H, t, *J* = 5.8, NH); 7.57 (1H, s, H-6); 7.39 (1H, dd, *J* = 8.5, *J* = 2.3, H-6'); 7.24 (1H, t, *J* = 7.5, H-4'); 7.03-6.95 (2H, m, H-9,3'); 6.88 (1H, t, *J* = 8.1, H-5'); 5.63-5.49 (1H, m, $NCH_2C\underline{H}O$); 4.65 (1H, t, *J* = 9.7, NCH); 4.41 (2H, d, *J* = 4.7, $NHC\underline{H}_2$); 4.28 (1H, dd, *J* = 9.7, *J* = 6.7, NCH);

4.01-3.96 (2H, m, CH_2Br); 3.92 (3H, s, OCH_3); 3.82 (6H, s, $2OCH_3$). Found, %: C 54.75; H 4.52; N 5.46. $C_{23}H_{23}BrN_2O_6$. Calculated, %: C 54.88; H 4.61; N 5.57.

2-Bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5*H*-oxazolo[3,2-*a*]quinoline-4-carboxylic Acid 5-Bromo-2-methoxybenzylamide (4). A solution of Br_2 (1.04 ml, 0.02 mol) in acetic acid (5 ml) was added with vigorous stirring to a solution of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid 2-methoxybenzylamide (**1g**) (4.24 g, 0.01 mol) in glacial acetic acid (30 ml) and left for 2 h at room temperature. The reaction mixture was diluted by adding cold water. The yellowish white precipitate was filtered off, washed with cold water, and dried. Yield 4.71 g (81%). Recrystallization from DMF gave the bromomethoxybenzylamide **4** as colorless monoclinic crystals with mp 263-265°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.85 (1H, br. s, NH); 7.78 (1H, s, H-6); 7.51 (1H, s, H-6'); 7.41 (1H, dd, *J* = 8.8, *J* = 2.0, H-4'); 6.98 (1H, s, H-9); 6.88 (1H, d, *J* = 8.8, H-3'); 5.61–5.55 (1H, m, $NCH_2C\underline{H}O$); 4.64 (1H, t, *J* = 9.8, NCH); 4.57 (2H, t with poor resolution, *J* = 4.9, $NHC\underline{H}_2$); 4.34 (1H, dd, *J* = 9.8, *J* = 6.6, NCH); 4.03-3.97 (2H, m, CH_2Br); 3.95 (3H, s, 8-OCH_3); 3.81 (3H, s, 7-OCH_3); 3.77 (3H, s, 2'-OCH_3). Found, %: C 47.53; H 3.77; N 4.87. $C_{23}H_{22}Br_2N_2O_6$. Calculated, %: C 47.45; H 3.81; N 4.81.

X-ray Structural Analysis of Bromomethoxybenzylamide 4. The unit cell parameters of monoclinic crystals of 5-bromo-2-methoxybenzylamide **4** (DMF) at -173°C are as follows: *a* 8.990(3), *b* 14.848(5), *c* 17.068(4) Å, β 105.12(2)°, *V* 2199(1) Å^3, M 582.25, *Z* 4, space group $P2_1/c$, d_{calc} 1.758 g/cm^3, μMoKα 3.730 mm^{-1}, *F*(000) = 1168. The unit cell parameters and intensities of 8049 reflections (3777 independent reflections, R_{int} = 0.080) were measured on an Xcalibur-3 diffractometer using MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ 50°. Absorption was taken into account using a semiempirical method for the ψ-scanning results (T_{min} = 0.194, T_{max} = 0.664).

The structure was solved by a direct method using the SHELXTL software package [17]. In the structure refinement, limits were placed on the bond lengths in the disordered fragment O−C_{sp3} 1.46 Å, C_{sp3}−C_{sp3} 1.54 Å. The positions of the hydrogen atoms were calculated geometrically and refined using the "rider" model with $U_{iso} = nU_{eq}$ for the non-hydrogen atom attached to a given hydrogen atom (*n* = 1.5 for methyl groups and *n* = 1.2 for the other hydrogen atoms). The structure was refined relative to F^2 by the full-matrix least-squares method in anisotropic approximation for the non-hydrogen atoms to wR_2 = 0.145 for 3755 reflections (R_1 = 0.060 for 2320 reflections with $F > 4\sigma(F)$, *S* = 1.018). The complete crystallographic data were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 2155347).

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