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4-HYDROXY-2-QUINOLONES. 180*. SYNTHESIS, CHEMICAL REACTIONS, AND ANALGESIC ACTIVITY OF 1-ALLYL-4-HYDROXY-6,7-DIMETHOXY-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACID ALKYLAMIDES

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A targeted synthesis was carried out of a series of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid alkylamides which show interest for biological study as potential analgesics. It was found that, in the presence of one equivalent of bromine, the compounds indicated undergo halocyclization to the corresponding 2-bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5H-oxa-zolo[3,2-a]quinoline-4-carboxylic acid alkylamides. However, with an excess of bromine the reaction occurs somewhat differently and concludes with the formation of complexes of bromine with 4-alkyl-carbamoyl-2-bromomethyl-5-hydroxy-7,8-dimethoxy-1,2-dihydrooxazolo[3,2-a]quinolinium ditribromides. According to the results of pharmacological screening there are found compounds within the substances discovered with high analgesic activity.

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

The problem of discovering powerful and also safe medicinal preparations which efficiently prevent various kinds of pain has not lost its urgency in the course of mankind's history. In a study of the biological activity of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (dialkylamino)-alkylamide hydrochlorides it was found that, depending on the structure of the amide part of the molecule, these compounds can either show opioid receptor antagonist properties or prove to have a totally opposite effect which marked prolongs the analgesic effect of narcotic analgesics [2]. This observation served as the grounds for carrying out a broader study of a targeted search for 4-hydroxyquinol-2-one substances with a novel form of pharmacological activity on the living organism for this class of compound, *viz.* as potential analgesics.

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* For Communication 179, see [1].

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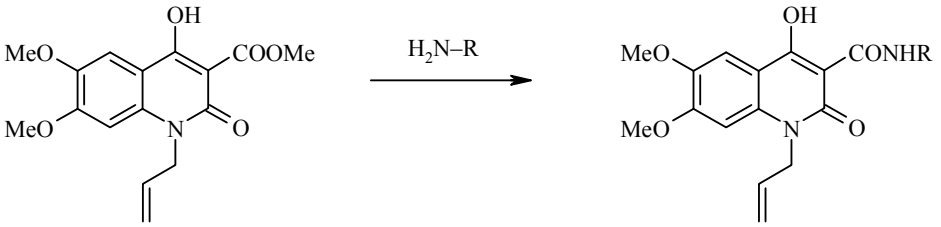
In the first publication connected to this problem the 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [3] were studied. The next step is to their amidated derivatives, and specifically in this report to 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid alkylamides **1a-x**.

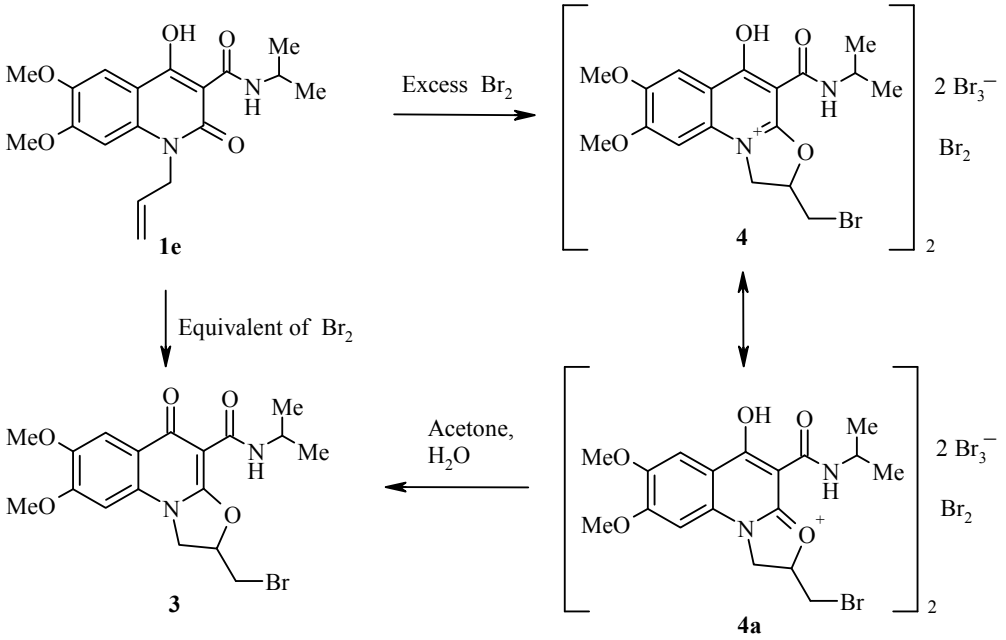
The preparation of these substances was carried out by amidation of the methyl ester **2** by the corresponding alkylamines using a method which was decided by the physical properties of the amines used and their steric structure [4]. All of the alkylamide compounds obtained **1a-x** are colorless, odorless, and tasteless, crystalline materials which are insoluble in water (Table 1). Their structure was confirmed by their ^{1}H NMR spectra, the assignment of whose signals did not cause difficulty (Table 2).



2 **1a–x**

1 a R = Me, **b** R = Et, **c** R = All, **d** R = Pr, **e** R = *i*-Pr, **f** R = Bu, **g** R = *i*-Bu, **h** R = *s*-Bu, **i** R = C_5H_{11}, **j** R = *i*-C_5H_{11}, **k** R = C_6H_{13}, **l** R = C_7H_{15}, **m** R = C_8H_{17}, **n** R = C_9H_{19}, **o** R = $C_{10}H_{21}$, **p** R = $C_{12}H_{25}$, **q** R = –$(CH_2)_2$OH, **r** R = –$(CH_2)_3$OH, **s** R = –$(CH_2)_3$OMe, **t** R = –$(CH_2)_3$OPr-*i*, **u** R = *cyclo*-C_3H_5, **v** R = *cyclo*-C_5H_9, **w** R = *cyclo*-C_6H_{11}, **x** R = *cyclo*-C_7H_{13}

The presence of an N(1)-allyl substituent in the 4-hydroxy-2-oxoquinoline nucleus of amides **1a-x** infers the possible synthesis from them of the corresponding derivatives of 2-bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic acid. As shown by us previously in the case of the isopropylamide **1e**, reaction with an equimolar amount of molecular bromine can very readily cause halocyclization to the oxazolo[3,2-*a*]quinoline **3** [5]. However, the particular structure of the alkylamides **1a-x** evidently makes it impossible to brominate the benzene part of the quinolone nucleus and the amide fragment hence it can reveal yet another interesting aspect of the bromocyclization reaction of the 1-N-allylquinol-2-ones, i.e. their behavior on treatment with an excess of bromine.



The experiment was carried out by us with the same isopropylamide **1e**. It was found that addition of a fivefold excess of bromine to its solution in glacial acetic acid immediately gave an orange, crystalline product which clearly differed in properties from those of the colorless 2-bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic acid isopropylamide (**3**). At the same time, however, the ^{1}H NMR spectra of both samples proved remarkably similar.

TABLE 1. Characteristics of the Alkylamides **1a-x***

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (EtOH)	Yield, %	Analgesic activity*[2]
		C	H	N			
1a	$C_{16}H_{18}N_2O_5$	60.49 60.37	5.81 5.70	8.92 8.80	190-192	97	32.2
1b	$C_{17}H_{20}N_2O_5$	61.53 61.44	6.18 6.07	8.35 8.43	169-171	95	24.0
1c	$C_{18}H_{20}N_2O_5$	62.65 62.78	5.76 5.85	8.20 8.13	162-164	94	31.7
1d	$C_{18}H_{22}N_2O_5$	62.31 62.42	6.33 6.40	7.96 8.09	157-159	91	9.7
1e	$C_{18}H_{22}N_2O_5$	62.34 62.42	6.35 6.40	8.00 8.09	168-170	82	11.5
1f	$C_{19}H_{24}N_2O_5$	63.43 63.32	6.83 6.71	7.85 7.77	151-153	90	11.4
1g	$C_{19}H_{24}N_2O_5$	63.41 63.32	6.80 6.71	7.84 7.77	156-158	93	27.9
1h	$C_{19}H_{24}N_2O_5$	63.26 63.32	6.62 6.71	7.68 7.77	160-162	83	26.0
1i	$C_{20}H_{26}N_2O_5$	64.25 64.16	7.13 7.00	7.59 7.48	147-149	89	26.3
1j	$C_{20}H_{26}N_2O_5$	64.27 64.16	7.11 7.00	7.60 7.48	155-157	90	28.7
1k	$C_{21}H_{28}N_2O_5$	65.04 64.93	7.19 7.27	7.14 7.21	126-128	87	2.2
1l	$C_{22}H_{30}N_2O_5$	65.52 65.65	7.37 7.51	7.08 6.96	113-115	90	20.0
1m	$C_{23}H_{32}N_2O_5$	66.22 66.32	7.83 7.74	6.85 6.73	102-104	85	20.0
1n	$C_{24}H_{34}N_2O_5$	67.07 66.95	8.05 7.96	6.44 6.51	90-92	88	5.6
1o	$C_{25}H_{36}N_2O_5$	67.43 67.54	8.02 8.16	6.41 6.30	85-87	90	7.8
1p	$C_{27}H_{40}N_2O_5$	68.53 68.62	8.40 8.53	5.84 5.93	81-83	92	21.8
1q	$C_{17}H_{20}N_2O_6$	58.72 58.61	5.86 5.79	8.15 8.04	197-199	94	60.7
1r	$C_{18}H_{22}N_2O_6$	59.54 59.66	6.03 6.12	7.84 7.73	164-166	91	31.0
1s	$C_{19}H_{24}N_2O_6$	60.76 60.63	6.55 6.43	7.53 7.44	143-145	89	15.6
1t	$C_{21}H_{28}N_2O_6$	62.47 62.36	7.11 6.98	7.02 6.93	105-107	87	26.9
1u	$C_{18}H_{20}N_2O_5$	62.66 62.78	5.74 5.85	8.05 8.13	167-169	84	14.8
1v	$C_{20}H_{24}N_2O_5$	64.42 64.50	6.39 6.50	7.44 7.52	174-176	85	11.4
1w	$C_{21}H_{26}N_2O_5$	65.38 65.27	6.87 6.78	7.31 7.25	188-190	85	31.7
1x	$C_{22}H_{28}N_2O_5$	66.10 65.98	7.13 7.05	7.10 6.99	171-173	81	30.2

* Analgesic activity of Diclofenac = 34.1, Ketorolac 46.4.

*[2] Increase in the threshold of pain sensation.

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

Compound	Chemical shifts, δ, ppm (*J*, Hz)								
	OH (1H, s)	NH (1H)	H arom	1-N-allyl fragment				2OCH_3	R
			H-5 (1H, s), H-8 (1H, s)	CH (1H, m)	CH=C<u>H</u>-*cis* (1H, d)	CH=C<u>H</u>-*trans* (1H, d)	NCH_2 (2H, d)	(3H, s), (3H, s)	
1	2	3	4	5	6	7	8	9	10
1a	17.43	10.16 (q, *J* = 4.9)	7.39, 6.90	5.92	5.13 (*J* = 10.5)	5.03 (*J* = 17.3)	4.94 (*J* = 4.6)	3.89, 3.82	2.88 (3H, d, *J* = 4.9, CH_3)
1b	17.49	10.29 (t, *J* = 5.6)	7.38, 6.90	5.92	5.15 (*J* = 10.4)	5.03 (*J* = 17.5)	4.93 (*J* = 4.5)	3.89, 3.82	3.36 (2H, quin, *J* = 6.9, NCH_2); 1.15 (3H, t, *J* = 7.1, CH_3)
1c	17.11	10.42 (t, *J* = 5.8)	7.40, 6.91	5.93	See R	See R	4.94 (*J* = 4.7)	3.90, 3.83	5.30-5.00 (4H, m, 2 CH=C<u>H_2</u>); 4.00 (2H, t, *J* = 5.4, NHC<u>H_2</u>)
1d	17.44	10.34 (t, *J* = 5.6)	7.37, 6.89	5.91	5.15 (*J* = 10.6)	5.04 (*J* = 17.3)	4.93 (*J* = 4.5)	3.89, 3.82	3.29 (2H, q, *J* = 6.6, NCH_2); 1.55 (2H, m, NCH_2C<u>H_2</u>); 0.91 (3H, t, *J* = 7.5, CH_3)
1e	17.43	10.27 (d, *J* = 7.4)	7.36, 6.88	5.91	5.14 (*J* = 10.6)	5.04 (*J* = 17.4)	4.92 (*J* = 4.4)	3.89, 3.82	4.08 (1H, m, CH); 1.20 (6H, d, *J* = 6.8, $2CH_3$)
1f	17.43	10.33 (t, *J* = 5.7)	7.38, 6.90	5.91	5.15 (*J* = 10.6)	5.03 (*J* = 17.2)	4.93 (*J* = 4.4)	3.89, 3.82	3.35 (2H, q, *J* = 6.9, NCH_2); 1.53 (2H, quin, *J* = 7.1, C<u>H_2</u>CH_2CH_3); 1.34 (2H, m, C<u>H_2</u>CH_3); 0.90 (3H, t, *J* = 7.2, CH_3)
1g	17.40	10.42 (t, *J* = 5.8)	7.37, 6.89	5.92	5.15 (*J* = 10.5)	5.03 (*J* = 17.4)	4.94 (*J* = 4.4)	3.89, 3.82	3.19 (2H, t, *J* = 6.3, NCH_2); 1.83 (1H, m, CH); 0.91 (6H, d, *J* = 6.7, $2CH_3$)
1h	17.37	10.28 (d, *J* = 7.4)	7.41, 6.92	5.93	5.16 (*J* = 10.6)	5.07 (*J* = 17.6)	4.94 (*J* = 4.2)	3.90, 3.83	3.97 (1H, m, CH); 1.56 (2H, quin, *J* = 7.1, C<u>H_2</u>CH_3); 1.18 (3H, d, *J* = 6.5, NCHC<u>H_3</u>); 0.90 (3H, t, *J* = 7.4, CH_2C<u>H_3</u>)
1i	17.43	10.33 (t, *J* = 5.8)	7.37, 6.89	5.91	5.15 (*J* = 10.6)	5.03 (*J* = 17.6)	4.93 (*J* = 4.2)	3.89, 3.82	3.35 (2H, q, *J* = 6.4, NCH_2); 1.54 (2H, quin, *J* = 6.4, NCH_2C<u>H_2</u>); 1.29 (4H, m, (C<u>H_2</u>)$_2CH_3$); 0.86 (3H, t, *J* = 6.5, CH_3)
1j	17.39	10.31 (t, *J* = 5.5)	7.36, 6.89	5.90	5.14 (*J* = 10.5)	5.02 (*J* = 17.4)	4.93 (*J* = 4.2)	3.88, 3.82	3.36 (2H, q, *J* = 6.7, NCH_2); 1.61 (1H, m, CH); 1.43 (2H, q, *J* = 6.8, NCH_2C<u>H_2</u>); 0.90 (6H, d, *J* = 6.7, $2CH_3$)
1k	17.44	10.31 (t, *J* = 5.6)	7.34, 6.87	5.91	5.14 (*J* = 10.5)	5.03 (*J* = 17.5)	4.92 (*J* = 4.3)	3.88, 3.81	3.35 (2H, q, *J* = 5.8, NCH_2); 1.53 (2H, quin, *J* = 6.0, NCH_2C<u>H_2</u>); 1.27 (6H, m, (C<u>H_2</u>)$_3CH_3$); 0.84 (3H, t, *J* = 6.5, CH_3)
1l	17.45	10.32 (t, *J* = 5.8)	7.36, 6.88	5.91	5.14 (*J* = 10.6)	5.03 (*J* = 17.5)	4.93 (*J* = 4.2)	3.88, 3.81	3.31 (2H, q, *J* = 6.4, NCH_2); 1.52 (2H, quin, *J* = 6.4, NCH_2C<u>H_2</u>); 1.26 (8H, m, (C<u>H_2</u>)$_4CH_3$); 0.83 (3H, t, *J* = 6.5, CH_3)
1m	17.44	10.33 (t, *J* = 5.6)	7.39, 6.91	5.92	5.15 (*J* = 10.4)	5.03 (*J* = 17.2)	4.94 (*J* = 4.3)	3.89, 3.82	3.38 (2H, q, *J* = 6.3, NCH_2); 1.53 (2H, quin, *J* = 6.4, NCH_2C<u>H_2</u>); 1.25 (10H, m, (C<u>H_2</u>)$_5CH_3$); 0.83 (3H, t, *J* = 6.6, CH_3)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10
1n	17.42	10.32 (t, J = 5.7)	7.36, 6.88	5.90	5.14 (J = 10.6)	5.03 (J = 17.5)	4.92 (J = 4.1)	3.88, 3.81	3.31 (2H, q, J = 6.4, NCH_2); 1.52 (2H, quin, J = 6.5, $NCH_2C\underline{H}_2$); 1.24 (12H, m, $(C\underline{H}_2)_6CH_3$); 0.82 (3H, t, J = 6.5, CH_3)
1o	17.39	10.31 (t, J = 5.7)	7.36, 6.88	5.92	5.14 (J = 10.6)	5.04 (J = 17.5)	4.93 (J = 4.1)	3.88, 3.81	3.35 (2H, q, J = 6.4, NCH_2); 1.51 (2H, quin, J = 6.5, $NCH_2C\underline{H}_2$); 1.21 (14H, m, $(C\underline{H}_2)_7CH_3$); 0.80 (3H, t, J = 6.6, CH_3)
1p	17.43	10.32 (t, J = 5.6)	7.36, 6.89	5.91	5.15 (J = 10.6)	5.03 (J = 17.7)	4.93 (J = 4.0)	3.88, 3.81	3.37 (2H, q, J = 6.3, NCH_2); 1.53 (2H, quin, J = 6.5, $NCH_2C\underline{H}_2$); 1.20 (18H, m, $(C\underline{H}_2)_9CH_3$); 0.81 (3H, t, J = 6.5, CH_3)
1q	17.37	10.41 (t, J = 5.4)	7.41, 6.91	5.93	5.16 (J = 10.3)	5.06 (J = 17.2)	4.94 (J = 4.4)	3.90, 3.83	4.80 (1H, t, J = 4.8, OH); 3.56 (2H, q, J = 5.7, NCH_2); 3.42 (2H, q, J = 5.7, $NCH_2C\underline{H}_2$)
1r	17.40	10.30 (t, J = 5.3)	7.39, 6.90	5.92	5.15 (J = 10.4)	5.04 (J = 17.5)	4.93 (J = 4.4)	3.89, 3.82	4.45 (1H, t, J = 4.6, OH); 3.44 (4H, m, $NC\underline{H}_2CH_2C\underline{H}_2O$); 1.69 (2H, quin, J = 6.5, $NCH_2C\underline{H}_2CH_2O$)
1s	17.38	10.32 (t, J = 5.5)	7.40, 6.91	5.91	5.15 (J = 10.5)	5.03 (J = 17.4)	4.93 (J = 4.3)	3.88, 3.81	3.39 (4H, m, $NC\underline{H}_2CH_2C\underline{H}_2O$); 3.25 (3H, s, OCH_3); 1.77 (2H, quin, J = 6.5, $NCH_2C\underline{H}_2CH_2O$)
1t	17.42	10.31 (t, J = 5.6)	7.41, 6.91	5.92	5.14 (J = 10.5)	5.03 (J = 17.5)	4.94 (J = 4.2)	3.89, 3.81,	3.51 (1H, m, CH); 3.41 (4H, m, $NC\underline{H}_2CH_2C\underline{H}_2O$); 1.74 (2H, quin, J = 6.5, $NCH_2C\underline{H}_2CH_2O$); 1.08 (6H, d, J = 6.1, $2CH_3$)
1u	17.03	10.29 (d, J = 4.9)	7.39, 6.90	5.90	5.14 (J = 10.5)	5.01 (J = 17.4)	4.92 (J = 4.4)	3.89, 3.82	2.90 (1H, m, CH); 0.78 (2H, m, CH_2 cyclopropane); 0.60 (2H, m, CH_2 cyclopropane)
1v	17.33	10.37 (d, J = 6.6)	7.39, 6.89	5.91	5.16 (J = 10.6)	5.05 (J = 17.7)	4.91 (J = 4.5)	3.89, 3.83	4.24 (1H, m, CH); 2.02-1.43 (8H, m, $(CH_2)_4$ cyclopropane)
1w	17.40	10.39 (d, J = 7.6)	7.37, 6.90	5.91	5.15 (J = 10.6)	5.03 (J = 17.4)	4.93 (J = 4.1)	3.88, 3.82	3.79 (1H, m, CH); 1.94-1.18 (10H, m, $(CH_2)_5$ cyclopropane)
1x	17.41	10.44 (d, J = 7.8)	7.39, 6.91	5.91	5.15 (J = 10.6)	5.04 (J = 17.8)	4.94 (J = 4.0)	3.89, 3.82	4.02 (1H, m, CH); 1.95-1.44 (12H, m, $(CH_2)_6$ cyclopropane)

The most significant difference between them was the shift to high field and broadening of the signal for the NH group proton. Hence the closure of the oxazole ring may be considered confirmed. Unfortunately no kind of other useful information using NMR spectroscopy could be obtained due to the poor solubility of the sample prepared.

We were able to find an unambiguous solution to the question arising by carrying out an X-ray structural analysis which showed that the compound studied is the di(2-bromomethyl-5-hydroxy-4-isopropyl-carbamoyl-7,8-dimethoxy-1,2-dihydrooxazolo[3,2-*a*]quinolinium) ditribromide (**4**). The independent part of the unit cell of this compound occurs as the two molecules **A** and **B** which differ in several geometric parameters and carrying a positive charge, two Br_3^- anions, and a neutral bromine molecule and randomized in four positions with conformational population densities of 70:15:14:1% (see Figure 1 and Tables 3 and 4).

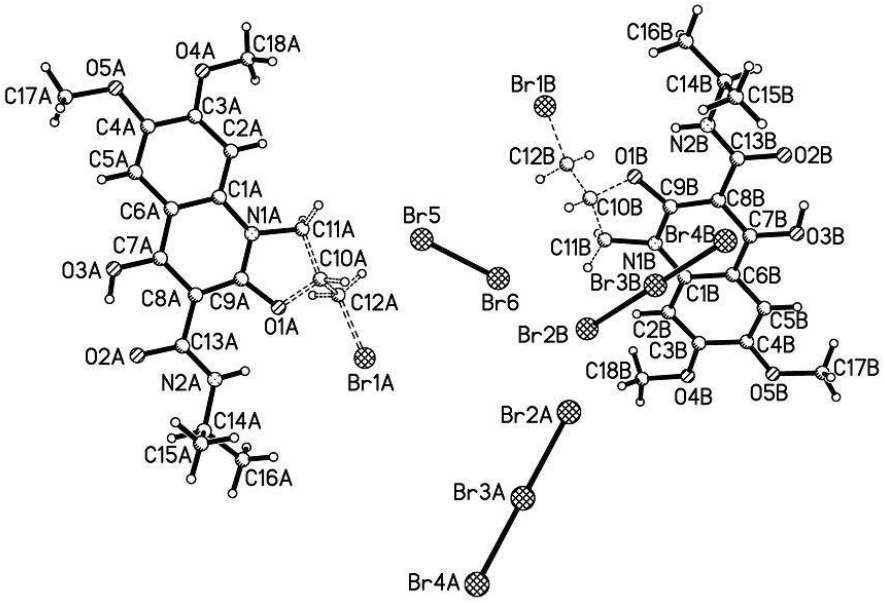


Fig. 1. Two conformers (**A** and **B**) of the diquinolinium ditribromide cation **4** with solvating molecules of bromine and tribromo anions and with atomic numbering. The most populated parts of the randomized fragment are shown.

The quinoline rings with atoms O(1), C(11), O(3), and C(13) in both molecules lie in a single plane to within 0.02 Å despite the presence of shortened intramolecular contacts H(2)···C(11) 2.67 in **A** and 2.65 Å in **B** (sum of van der Waals radii 2.87 Å [6]). The bond lengths N(1)–C(9) 1.33(1) in **A**, 1.34(1) in **B** and O(1)–C(9) 1.34(1) in **A** and 1.33(1) Å in **B** are somewhat shortened when compared with the mean values of 1.355 and 1.370 Å [7], as a result of which the structure of the organic cation can be represented as a resonance hybrid of the two canonical structures **4** and **4a**.

Lengthening of the C(7)–C(8) bonds to 1.41(1) in **A** and 1.40(1) Å in **B** with simultaneous shortening of the C(8)–C(9) bonds to 1.39(1) Å in **A** and **B** when compared with their mean values of 1.340 and 1.455 Å allows us to propose delocalization of electron density in this fragment due to strong conjugative interactions between the π-donor hydroxyl group and the π-acceptor positively charged N(1)–C(9)–O(1) fragment. The five-membered heterocycle in **A** and **B** is randomized in two envelope conformations with population densities of 69:31 in molecules **A** and 66:34% in **B**. The deviations of atom C(10) from the mean square plane of the remaining atoms are 0.23 and -0.47 Å in molecule **A** and 0.23 and -0.43 Å in molecule **B**.

The substituent at atom C(8) is virtually coplanar with the quinoline fragment plane (torsional angle C(7)–C(8)–C(13)–O(2) is 6(1)º in **A** and **B**). Such a substituent conformation is evidently stabilized by the intramolecular hydrogen bonds N(2)–H(2)···O(1) (H···O 2.09 Å, N–H···O 135º in **A** and H···O 2.11 Å, N–H···O 134º in **B**) and O(3)–H(3)···O(2) (H···O 1.72 Å, O–H···O 146º in **A** and H···O 1.71 Å, O–H···O 146º in **B**). The isopropyl group exists in an *ap*-conformation relative to the C(13)–C(8) bond (torsional angle C(14)–N(2)–C(13)–C(8) 177.7(8)º in **A**, 177.5(8)º in **B**) and is twisted relative to the C(13)–N(2) bond (torsional angle C(13)–N(2)–C(14)–H(14) 39º in **A** and 41º in **B**). The substituent on atom C(10) occupies an equatorial position in all conformations (torsional angle C(9)–O(1)–C(10)–C(12) -127(1)º in **A**, 159(2)º in **B**, -127.1(1)º in **C**, and 159(3)º in **D**) and the bromine atom has an *sc*-orientation relative to the O(1)–C(10) bond (torsional angle O(1)–C(10)–C(12)–Br(1) -71.1(1)º, -70(1)º in **A** and 59(3)Å, 64.4(4)º in **B**). The methoxy groups on atoms C(3) and C(4) are virtually coplanar with the plane of the aromatic ring (torsional angles C(18)–O(4)–C(3)–C(2) 6(2)º in **A** and 2(2)º in **B** and C(17)–O(5)–C(4)–C(5) -2(1)º in **A** and -1(1)º in **B**) despite the marked repulsion between the methyl groups and the benzene ring atoms [shortened intramolecular contacts H(2)···C(18) 2.52 in

TABLE 3. Bond Lengths (l) in the Diquinolinium Ditribromide **4** Structure

Bond	*l*, Å	Bond	*l*, Å
Br(5)–Br(6)	2.362(4)	Br(5A)–Br(6A)	2.399(9)
Br(5B)–Br(6B)	1.85(2)	Br(6B)–Br(6C)	1.5(2)
Br(2A)–Br(3A)	2.589(2)	Br(3A)–Br(4A)	2.490(2)
Br(1A)–C(12C)	1.79(3)	Br(1A)–C(12A)	2.00(2)
N(1A)–C(9A)	1.33(1)	N(1A)–C(1A)	1.38(1)
N(1A)–C(11A)	1.49(1)	N(2A)–C(13A)	1.30(1)
N(2A)–C(14A)	1.46(1)	O(1A)–C(9A)	1.34(1)
O(1A)–C(10C)	1.442(5)	O(1A)–C(10A)	1.445(5)
O(2A)–C(13A)	1.26(1)	O(3A)–C(7A)	1.32(1)
O(4A)–C(3A)	1.35(1)	O(4A)–C(18A)	1.44(1)
O(5A)–C(4A)	1.38(1)	O(5A)–C(17A)	1.41(1)
C(1A)–C(2A)	1.39(1)	C(1A)–C(6A)	1.42(1)
C(2A)–C(3A)	1.40(2)	C(3A)–C(4A)	1.39(2)
C(4A)–C(5A)	1.36(1)	C(5A)–C(6A)	1.41(1)
C(6A)–C(7A)	1.43(1)	C(7A)–C(8A)	1.41(1)
C(8A)–C(9A)	1.39(1)	C(8A)–C(13A)	1.47(1)
C(10A)–C(12A)	1.538(5)	C(10A)–C(11A)	1.540(5)
C(10C)–C(12C)	1.539(5)	C(10C)–C(11A)	1.540(5)
C(14A)–C(16A)	1.51(1)	C(14A)–C(15A)	1.55(1)
Br(2B)–Br(3B)	2.596(2)	Br(3B)–Br(4B)	2.491(2)
Br(1B)–C(12D)	1.77(5)	Br(1B)–C(12B)	2.03(2)
N(1B)–C(9B)	1.34(1)	N(1B)–C(1B)	1.37(1)
N(1B)–C(11B)	1.47(1)	N(2B)–C(13B)	1.31(1)
N(2B)–C(14B)	1.47(1)	O(1B)–C(9B)	1.33(1)
O(1B)–C(10D)	1.442(5)	O(1B)–C(10B)	1.442(5)
O(2B)–C(13B)	1.27(1)	O(3B)–C(7B)	1.31(1)
O(4B)–C(3B)	1.35(1)	O(4B)–C(18B)	1.44(1)
O(5B)–C(4B)	1.37(1)	O(5B)–C(17B)	1.43(1)
C(1B)–C(2B)	1.39(1)	C(1B)–C(6B)	1.40(1)
C(2B)–C(3B)	1.38(2)	C(3B)–C(4B)	1.42(2)
C(4B)–C(5B)	1.36(1)	C(5B)–C(6B)	1.42(1)
C(6B)–C(7B)	1.43(1)	C(7B)–C(8B)	1.40(1)
C(8B)–C(9B)	1.39(1)	C(8B)–C(13B)	1.48(1)
C(10B)–C(12B)	1.538(5)	C(10B)–C(11B)	1.540(5)
C(10D)–C(12D)	1.539(5)	C(10D)–C(11B)	1.541(5)
C(14B)–C(16B)	1.51(1)	C(14B)–C(15B)	1.52(1)

A and 2.55 Å in **B** (2.87 Å), H(2)···H(18A) 2.27 in **A** (2.34), H(18A···C(2) 2.70 in **A** and 2.76 Å in **B** (2.87 Å), H(18C)···C(2) 2.80 in **A** and 2.81 Å in **B** (2.87 Å), H(5)···C(17) 2.49 in **A** and 2.52 Å in **B** (2.87 Å), H(5)···H(17A) 2.29 Å in **A** and **B** (2.34 Å), H(5)···H(17C) 2.27 Å in **A** (2.34 Å), H(17A)···C(5) 2.74 in **A** and 2.75 Å in **B** (2.87 Å), and H(17C)···C(5) 2.70 in **A** and 2.76 Å in **B** (2.87 Å)].

TABLE 4. Valence Angles (ω) in the Diquinolinium Ditribromide **4** Structure

Angle	ω, deg	Angle	ω, deg
Br(4A)–Br(3A)–Br(2A)	179.04(7)	Br(4B)–Br(3B)–Br(2B)	179.07(7)
C(9A)–N(1A)–C(1A)	122.9(9)	C(9B)–N(1B)–C(1B)	122.4(9)
C(9A)–N(1A)–C(11A)	111.3(8)	C(9B)–N(1B)–C(11B)	111.1(8)
C(1A)–N(1A)–C(11A)	125.8(8)	C(1B)–N(1B)–C(11B)	126.5(8)
C(13A)–N(2A)–C(14A)	123.3(9)	C(13B)–N(2B)–C(14B)	123.5(8)
C(9A)–O(1A)–C(10C)	106(1)	C(9B)–O(1B)–C(10D)	107(1)
C(9A)–O(1A)–C(10A)	109.3(7)	C(9B)–O(1B)–C(10B)	109.7(8)
C(3A)–O(4A)–C(18A)	118.8(9)	C(3B)–O(4B)–C(18B)	118.9(9)
C(4A)–O(5A)–C(17A)	117.3(8)	C(4B)–O(5B)–C(17B)	117.8(8)
N(1A)–C(1A)–C(2A)	121.7(9)	N(1B)–C(1B)–C(2B)	121.3(9)
N(1A)–C(1A)–C(6A)	117.4(9)	N(1B)–C(1B)–C(6B)	118.3(9)
C(2A)–C(1A)–C(6A)	120.8(9)	C(2B)–C(1B)–C(6B)	120(1)
C(1A)–C(2A)–C(3A)	118.1(9)	C(3B)–C(2B)–C(1B)	119(1)
O(4A)–C(3A)–C(4A)	115(1)	O(4B)–C(3B)–C(2B)	125(1)
O(4A)–C(3A)–C(2A)	123.4(9)	O(4B)–C(3B)–C(4B)	114(1)
C(4A)–C(3A)–C(2A)	121.4(9)	C(2B)–C(3B)–C(4B)	120.6(9)
C(5A)–C(4A)–O(5A)	124(1)	C(5B)–C(4B)–O(5B)	125(1)
C(5A)–C(4A)–C(3A)	121(1)	C(5B)–C(4B)–C(3B)	120(1)
O(5A)–C(4A)–C(3A)	114.8(9)	O(5B)–C(4B)–C(3B)	114.9(9)
C(4A)–C(5A)–C(6A)	119(1)	C(4B)–C(5B)–C(6B)	119(1)
C(5A)–C(6A)–C(1A)	119.4(9)	C(5B)–C(6B)–C(1B)	119.9(9)
C(5A)–C(6A)–C(7A)	121.9(9)	C(5B)–C(6B)–C(7B)	121.1(9)
C(1A)–C(6A)–C(7A)	118.6(9)	C(1B)–C(6B)–C(7B)	119.0(9)
O(3A)–C(7A)–C(8A)	120.8(9)	O(3B)–C(7B)–C(8B)	119.8(9)
O(3A)–C(7A)–C(6A)	117.2(9)	O(3B)–C(7B)–C(6B)	118.9(9)
C(8A)–C(7A)–C(6A)	122.0(9)	C(8B)–C(7B)–C(6B)	121.3(9)
C(9A)–C(8A)–C(7A)	114.8(9)	C(9B)–C(8B)–C(7B)	115.8(9)
C(9A)–C(8A)–C(13A)	125.1(9)	C(9B)–C(8B)–C(13B)	123.9(9)
C(7A)–C(8A)–C(13A)	120.0(9)	C(7B)–C(8B)–C(13B)	120.3(9)
N(1A)–C(9A)–O(1A)	111.6(8)	N(1B)–C(9B)–O(1B)	111.3(9)
N(1A)–C(9A)–C(8A)	124(1)	N(1B)–C(9B)–C(8B)	123.2(9)
O(1A)–C(9A)–C(8A)	124.1(9)	O(1B)–C(9B)–C(8B)	125.4(9)
O(1A)–C(10A)–C(12A)	105(1)	O(1B)–C(10B)–C(12B)	107(1)
O(1A)–C(10A)–C(11A)	105.2(7)	O(1B)–C(10B)–C(11B)	104.6(8)
C(12A)–C(10A)–C(11A)	106(1)	C(12B)–C(10B)–C(11B)	105(1)
C(10A)–C(12A)–Br(1A)	108.6(8)	C(10B)–C(12B)–Br(1B)	107.9(9)
O(1A)–C(10C)–C(12C)	111(2)	O(1B)–C(10D)–C(12D)	109(2)
O(1A)–C(10C)–C(11A)	105.3(8)	O(1B)–C(10D)–C(11B)	104.5(8)
C(12C)–C(10C)–C(11A)	118(2)	C(12D)–C(10D)–C(11B)	122(3)
C(10C)–C(12C)–Br(1A)	116(2)	C(10D)–C(12D)–Br(1B)	117(3)
N(1A)–C(11A)–C(10C)	97(1)	N(1B)–C(11B)–C(10B)	101.0(8)
N(1A)–C(11A)–C(10A)	100.3(7)	N(1B)–C(11B)–C(10D)	98(1)
O(2A)–C(13A)–N(2A)	121.6(9)	O(2B)–C(13B)–N(2B)	121.0(9)
O(2A)–C(13A)–C(8A)	117.3(9)	O(2B)–C(13B)–C(8B)	117.2(9)
N(2A)–C(13A)–C(8A)	121.1(9)	N(2B)–C(13B)–C(8B)	121.8(9)
N(2A)–C(14A)–C(16A)	109.2(8)	N(2B)–C(14B)–C(16B)	108.3(8)
N(2A)–C(14A)–C(15A)	109.6(8)	N(2B)–C(14B)–C(15B)	110.0(8)
C(16A)–C(14A)–C(15A)	111.3(8)	C(16B)–C(14B)–C(15B)	113.2(8)
Br(6C)–Br(6B)–Br(5B)	141(7)	C(10B)–C(11B)–C(10D)	25(2)

The diquinolinium ditribromide **4** forms stacks along the crystallographic [0 0 1] direction due to the intermolecular hydrogen bonds: C(10A)–H(10A)···Br(5B)' H···Br 2.69 Å, C–H···Br 135°; C(10B)–H(10B)···Br (4A)' (*x*, 0.5–*y*, –0.5+*z*) H···Br 2.83 Å, C–H···Br 139°; C(12C)–H(12C)···Br(5B)' H···Br 2.56 Å, C–H···Br 132°; C(12C)–H(12D)···Br(6)' (*x*, 0.5-*y*, -0.5+*z*) H···Br 2.86 Å, C–H···Br 135°; C(11A)–H(11A)···Br(2A)' (*x*, 0.5-*y*, -0.5+*z*) H···Br 2.77 Å, C–H···Br 135°; C(10D)–H(10D)···Br(6B)' H···Br 2.79 Å, C–H···Br 132°; C(12D)–H(12G)···Br(6B)' H···Br 2.73 Å, C–H···Br 121°.

In the crystal studied there are also seen a multisystem series of shortened intermolecular contacts: H(10A)···Br(5)' 3.13 (sum of van der Waal radii 3.23 Å), H(12A)···Br(6)' (*x*, 0.5-*y*, -0.5+*z*) 3.04, H(12B)···Br(4A)' (*x*, 0.5-*y*, -0.5+*z*) 3.16, H(12B)···Br(1A)' (*x*, 0.5-*y*, -0.5+*z*) 2.98, H(12C)···Br(5A)' (*x*, 0.5-*y*, -0.5+*z*) 3.00, H(12D)···Br(5)' (*x*, 0.5-*y*, -0.5+*z*) 2.94, H(12D)···Br(5A)' (*x*, 0.5-*y*, -0.5+*z*) 3.03, H(11A)···Br(2B)' (*x*, 0.5-*y*, -0.5+*z*) 2.90, H(11B)···Br(3A)' (*x*, 0.5-*y*, -0.5+*z*) 2.91, H(11B)···Br(4A)' (*x*, 0.5-*y*, -0.5+*z*) 3.15, H(15A)···Br(4A)' (*x*, 0.5-*y*, -0.5+*z*) 3.14, H(17D)···Br(3A)' (*x*, *y*-1, *z*-1) 2.93, H(18D)···C(3B)' (*x*, 0.5-*y*, -0.5+*z*) 2.77 (2.87), H(18F)···Br(2B)' (*x*, 0.5-*y*, -0.5+*z*) 3.07, H(2BB)···Br(2A)' (*x*, *y*, *z*-1) 2.96, H(10D)···Br(6)' 3.12, H(10D)···Br(5C)' 1.70, H(12E)···Br(5)' (*x*, 0.5–*y*, –0.5+*z*) 2.98, H(12E)···Br(5C)' 2.68, H(12F)···Br(4B)' (*x*, *y*, *z*-1) 3.16, H(12F)···Br(1B)' (*x*, 0.5-*y*, -0.5+*z*) 2.97, H(10C)···Br(4B)' (*x*, *y*, *z*-1) 2.90, H(12G)···Br(5C)' 2.02, H(12H)···Br(5)' (*x*, 0.5-*y*, -0.5+*z*) 2.87, H(12H)···Br(6)' (*x*, 0.5-*y*, -0.5+*z*) 2.93, H(12H)···Br(5A)' (*x*, 0.5-*y*, -0.5+*z*) 3.12, H(12H)···Br(6A)' (*x*, 0.5-*y*, -0.5+*z*) 2.87, H(12H)···Br(6B)' 3.07, H(12H)···Br(5C)' 2.27, H(11E)···Br(5C)' 2.89, H(11E)···Br(3B)' (*x*, *y*, *z*-1) 2.94, H(11E)···Br(4B)' (*x*, *y*, *z*-1) 3.17, H(11F)···Br(2A)' (*x*, *y*, *z*-1) 2.96, H(15D)···Br(4B)' 3.18 Å, H(17A)···Br(3B)' (*x*, 1.5-*y*, -0.5+*z*) 2.90, H(18C)···Br(2A)' (*x*, *y*, *z*-1) 3.06, Br(2A)···Br(5)' (*x*, 0.5-*y*, 0.5+*z*) 2.90 (3.94 Å), Br(2A)···Br(5A)' (*x*, 0.5-*y*, 0.5+*z*) 3.28, Br(2A)···Br(5B)' (*x*, 0.5-*y*, 0.5+*z*) 3.38, Br(2A)···Br(5C)' (*x*, *y*, 1+*z*) 3.56, Br(2B)···Br(6)' 2.89, Br(2B)···Br(6A)' 3.30, Br(2B)···Br(6B)' 3.45, Br(2B)···Br(5C)' 2.96 Å. The Br_3^- anions and the neutral bromine molecules form a 3D net in the crystal.

Hence from the X-ray structural analysis it is clear that two novel features occur in the reaction of molecular bromine with the N(1)-allyl-substituted 4-hydroxyquinol-2-ones. The first of these is the ability of the already formed oxazoloquinolines in the reaction mixture to bind free bromine. An excess amount of bromine is not at all needed to observe this effect since small amounts of orange products insoluble in glacial acetic acid (evidently similar in structure to the diquinolinium ditribromide **4**) have repeatedly been observed by us before when an equimolar ratio of reagents has been closely adhered to.

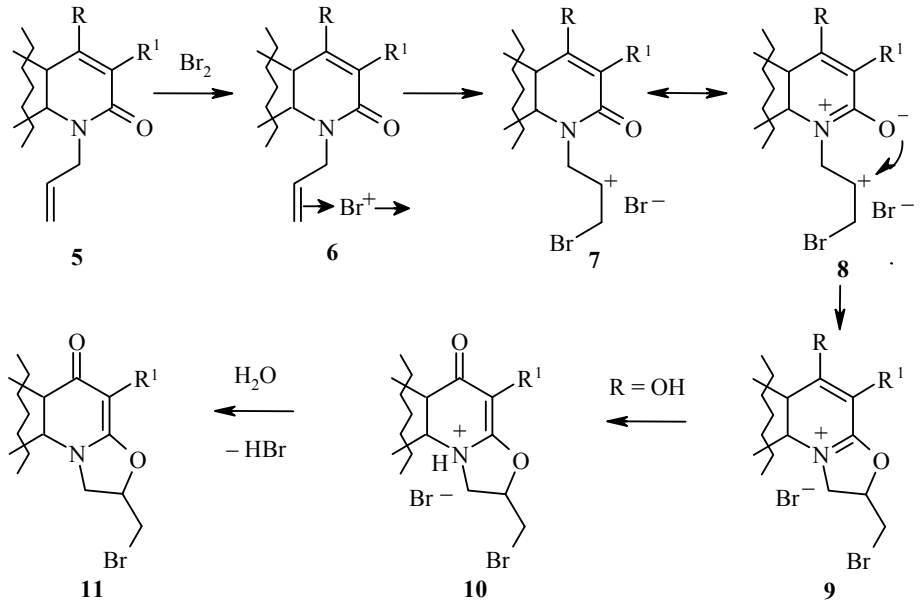
This frequently especially occurs when pure bromine is used and, most probably in such conditions where is the same excess of bromine but only locally. On the other hand, avoiding this side process is simple and for this it is enough to introduce a dilute solution rather than pure bromine into the reaction.

A second feature is more interesting. This is associated with the unusual 5-hydroxy structure of the formed material and permits the introduction of changes to the interpretation of the mechanism of bromocyclization of the N(1)–allylquinol-2-ones. Because exclusively 5-oxo-1,2-dihydrooxazolo[3,2-*a*]quinolines have been obtained from the 4-hydroxy derivatives up to this time it was considered that heterocyclization occurred *via* bipolar 1,4-dihydro forms [8]. It has later become clear that 4-methyl-substituted analogs unable to tautomerize also readily halocyclize similarly. As a result, a separate mechanism has been proposed for such cases involving the formation during the process of an oxazole nucleus of other quite differently structured aromatic, bipolar forms [9]

Indeed the indisputable fact of formation of the 5-hydroxyoxazoloquinoline **4**, practically identical in structure to 2-bromomethyl-4-carboxy-5-methyl-1,2-dihydrooxazolo[3,2-*a*]quinolinium bromide [9], can be considered as the first experimental confirmation that bromocyclization of the 4-hydroxy- and 4-methyl-substituted N(1)-allylquinol-2-ones occurs through the single mechanism **5** → π-complex **6** → secondary carbocation **7** ↔ bipolar aromatic form **8** → oxazoloquinolinium bromide **9**.

The effect of a substituent at position 4 of the starting quinoline **5** only shows up in the final stage. 5-Hydroxyoxazoloquinolinium bromides **9** (R = OH) evidently tautomerize to the more stable 5-oxo forms **10** which are rapidly hydrolyzed to the 5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinolines **11** after dilution of the

reaction mixture with water. Due to its particular structure the diquinolinium ditribromide **4** also proved quite stable in the 5-hydroxy form. None the less, after treatment with acetone (to bind excess bromine) and then water, the typical 4-hydroxyquinolone bromocyclization product 2-bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic acid isopropylamide **3** was obtained. The 5-methyl-substi-tuted oxazoloquinolinium bromides **9** (R = Me) are unable to undergo a similar transformation and remain unchanged after addition of water [9].



The analgesic properties of the 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid alkylamides **1a-x** were studied in non-pedigree, white male rats using the method reported in detail by us before [3] for the standard electric current model of rectal mucosa stimulation [10]. Analysis of the screening results are given in Table 1 and conclusively confirm the correctness of our selection of this set. At a dose of 20 mg/kg and without exception all of the alkylamides **1a-x** demonstrate analgesic activity to some extent. Moreover approximately one half of the studied samples are as active as Diclofenac. However, from all of the group, special mention must be made of one compound (the 2-hydroxyethylamide **1q**) whose analgesic effect markedly exceeds not only diclofenac but also one of the most powerful nonnarcotic analgesics ketorolac [11, 12].

EXPERIMENTAL

The ^{1}H NMR spectra of alkylamides **1a-x** were taken on a Varian Mercury VX-200 instrument (200 MHz) and the oxazoloquinolines **3** and **4** on a Varian Mercury-400 spectrometer (400 MHz). In all cases the solvent was DMSO-d_6 and the internal standard TMS. The starting methyl 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**2**) was prepared by the method reported in [2] and its subsequent amidation using alkylamines was carried out by the method in [4].

2-Bromomethyl-7,8-dimethoxy-5-oxo-1,2-dihydro-5H-oxazolo-[3,2-*a*]quinoline-4-carboxylic Acid Isopropylamide (3). A solution of the diquinolinium ditribromide **4** (1.49 g, 1 mmol) in acetone (15 ml) was heated to reflux, water (10 ml) was added, and the product was left for 5-6 h at about 10ºC. The precipitated isopropylamide **3** was filtered off, washed with cold water, and dried. Yield 0.61 g (72%). Recrystallization

from ethanol gave colorless, triclinic crystals with mp 269-271ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.12 (1H, d, *J* = 7.9, NH); 7.56 (1H, s, H-6); 6.90 (1H, s, H-9); 5.57 (1H, m, CHO); 4.64 (1H, t, *J* = 8.0, NCH); 4.30 (1H, t, *J* = 8.0, NCH); 4.03 (3H, m, CH_2Br + $C\underline{H}(CH_3)_2$); 3.96 (3H, s, OCH_3); 3.87 (3H, s, OCH_3); 1.19 (6H, d, *J* = 7.9, $CH(C\underline{H}_3)_2$).

A sample mixed with the isopropylamide **3** prepared by bromocyclization of the N(1)-allyl derivative **1e** [5] did not give a depression of melting point and the ^{1}H NMR spectra of these compounds were identical.

Di(2-bromomethyl-5-hydroxy-7,8-dimethoxy-4-isopropylcarbamoyl-1,2-dihydrooxazolo[3,2-*a*]quinolinium) Ditribromide (Complex with Bromine) (4). A solution of bromine (2.6 ml, 50 mmol) in glacial acetic acid (10 ml) was added with vigorous stirring to a solution of the 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid isopropylamide **1e** (3.46 g, 10 mmol) in the same solvent (50 ml). The orange precipitate of compound **4** formed was filtered off, washed with glacial acetic acid, and dried. Yield 6.49 g (87%); mp 128-130ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.85 (1H, br. s, NH); 7.56 (1H, s, H-6); 7.13 (1H, s, H-9); 5.77 (1H, m, CHO); 4.87 (1H, t, *J* = 10.0, NCH); 4.58 (1H, t, *J* = 10.0, NCH); 4.16 (1H, m, $C\underline{H}(CH_3)_2$); 4.08 (2H, td, *J* = 8.8 and *J* = 4.0, CH_2Br); 4.04 (3H, s, OCH_3); 3.93 (3H, s, OCH_3); 1.27 (6H, d, *J* = 8.0, $CH(C\underline{H}_3)_2$). Found, %: C 28.74; H 2.72; N 3.60. $(C_{18}H_{22}BrN_2O_5)^+_2.(Br_3^-)_2.Br_2$. Calculated, %: C 28.98; H 2.97; N 3.76.

X-ray Structural Study of the Diquinolinium Ditribromide 4. Crystals are monoclinic (AcOH), at -173ºC: *a* = 31.882(3), *b* = 18.831(2), *c* = 7.897(1) Å, β = 90.14(1)º, *V* = 4741.1(8) Å^3, M_r = 745.93, Z = 8, space group $P2_1/c$, d_{calc} = 2.090 g/cm^3, μ(MoKα) = 8.508 mm^{-1}, *F*(000) = 2872. The unit cell parameters and intensities of 31538 reflections (8345 independent, R_{int} = 0.065) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 50º). Absorption was allowed for analytically (T_{min} = 0.154, T_{max} = 0.778).

The structure was solved by the direct method using the *SHELXTL* program package [13]. In the structure refinement limits were placed on the bond lengths in the randomized molecular cation fragment of O–C_{sp3} 1.44 Å and C_{sp3}–C_{sp3} 1.54 Å. The positions of the hydrogen atoms were calculated geometrically and refined using the "riding" model with $U_{iso} = nU_{eq}$ for a non-hydrogen atom bound to the given hydrogen atom (*n* = 1.5 for methyl groups and *n* = 1.2 for remaining hydrogen atoms). The structure was refined in F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.146 for 8061 reflections (R_1 = 0.085 for 6673 reflections with $F > 4\sigma(F)$, *S* = 1.166). The full crystallographic data has been placed in the Cambridge structural database as deposit CCDC 756719. Interatomic distances and valence angles are given in Tables 3 and 4 respectively.

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