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4-HYDROXY-2-QUINOLONES. 118*. SYNTHESIS, STRUCTURE, AND CHEMICAL PROPERTIES OF 2-BROMOMETHYL-5-OXO-1,2-DIHYDRO-5H-OXAZOLO-[3,2-*a*]QUINOLINE-4-CARBOXYLIC ACID AND ITS ETHYL ESTER

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Bromination of N-allyl-substituted 4-hydroxy-2-quinolinones with molecular bromine in acetic acid or carbon tetrachloride occurs with closing of a five membered oxazole ring to give 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline.

Keywords: oxazolo[3,2-*a*]quinoline-4-carboxylic acid, bromination, heterocyclization, hydrolysis, X-ray analysis.

The decolorization of bromine is a well known, classical test in organic chemistry for an unsaturated bond [2]. Reactions of this type take place readily and without the use of any kind of catalyst. Ethyl 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) behaves in just this way under these conditions and it was initially suggested that its bromination is simply the usual addition of halogen at the allyl fragment double bond to form the 2,3-dibromopropyl derivative [3]. The basic argument supporting this conclusion was the fact that, after treatment of the compound obtained with excess sodium methylate in methanol and subsequent acidification of the reaction mixture with aqueous hydrochloric acid, the product methyl 1-acetonyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**2**) was formed (whose structure was confirmed by X-ray data [1]). The fully expected transesterification and, mainly, the well established ability of vicinal dibromides to be dehydrobrominated to acetylenes with a terminal triple bond in the presence of strong bases (which, in turn, are hydrated via a Kucherov reaction to the corresponding ketones [4]) could quite logically explain the experimental results.

However, further investigation has cast doubt that the N-allyl substituted ester **1** is actually brominated to 1-(2,3-dibromopropyl)-3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinoline.

In the first place, the bromination product appears to be extremely stable to hydrolysis in a mixture of hydrochloric and acetic acids with a low water content and this is atypical for this class of compound. As is known [5] ethyl 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate is hydrolyzed under these conditions without complication and the example of preparing acid **3** confirms again confirms this. In the second place the reaction with less powerful bases than sodium methylate leads to a totally different compound which is, in fact,

* For Communication 117 see [1].

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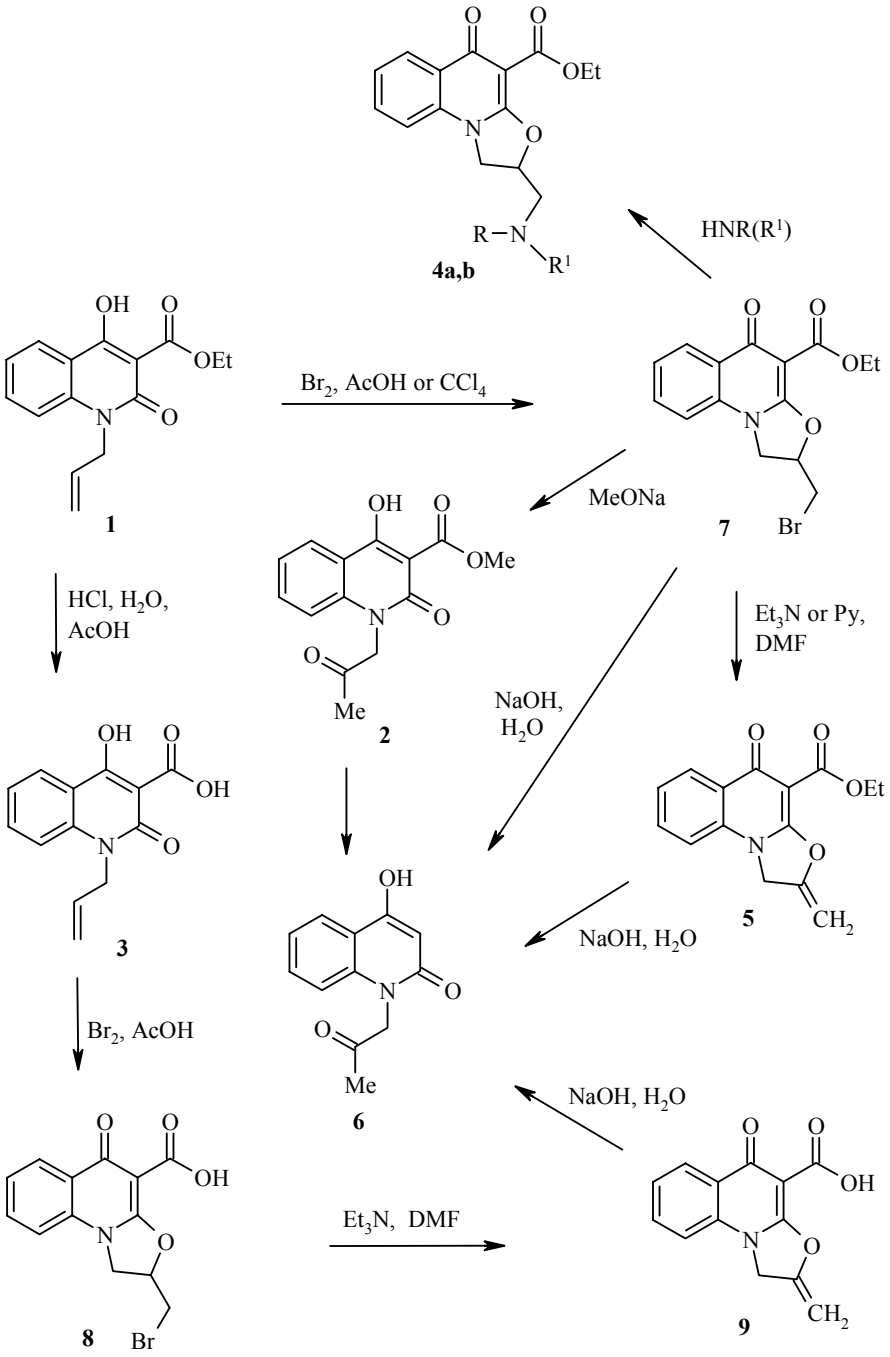
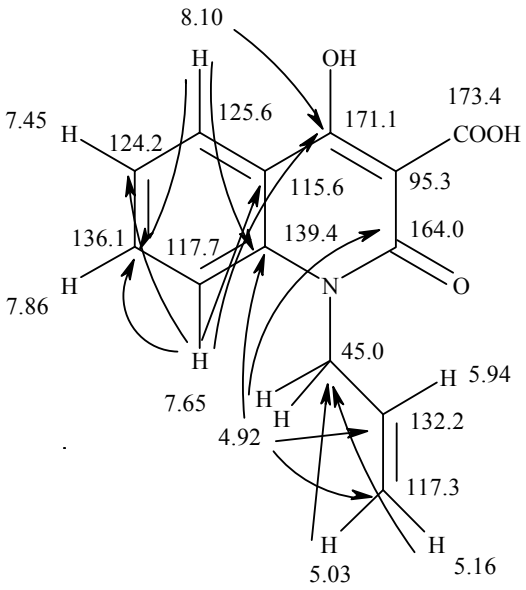
an oxazolo[3,2-*a*]quinoline. When using dialkylamines they were found to be the ethyl 2-dialkylaminomethyl esters **4a,b** and in the case of triethylamine or pyridine the ethyl 2-methylene-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylate (**5**).



4 a R = Me, R^1 = Bu, **b** R = R^1 = Pr

The allyl derivatives of acid **3** and ester **5** were of particular interest when studying the structure of the synthesized materials by NMR spectroscopy. This interest chiefly arises when interpreting the complex olefine proton signals and its resolution needs the use of special NMR procedures. Thus the ^{1}H NMR spectrum of the N-allyl-substituted acid **3** is in good overall agreement with the proposed structure. It contains four aromatic

protons signals in the region 8.10-4.92 ppm corresponding to the 4-hydroxy-2-quinolone ring and four signals for the N-allyl-substituent. For an unambiguous assignment of these proton signals attention was turned both to their multiplicities and to their COSY spectroscopic data in which cross peaks were seen for the doublet at 8.10 and triplet at 7.45 and also the doublet at 7.65 and triplet at 7.86 ppm. The allyl group signals include a singlet for the N-methylene group and three signals for unsaturated protons. One of these (in fact the CH signal) has a complex multiplet structure and is found at 5.94 ppm. The spin related olefinic protons appear as characteristic doublets with spin spin coupling 10 and 17 Hz corresponding to *cis* and *trans* protons at 5.16 and 5.03 ppm. Hence the assignment of the signals in the ^{1}H NMR spectrum of acid **3** is not in doubt. Together with HMQC heteronuclear correlation data this reliably allowed us to assign the signal of the proton bound carbon atoms in the ^{13}C NMR spectrum (Table 1). The assignment of quaternary carbon atoms can be made from correlations take from the HMBC spectrum. Hence the correlation between the benzene ring protons and the carbon atoms allowed us to assign the signals for $C_{(4a)}$ and $C_{(8a)}$ as having chemical shifts of 115.6 and 139.4 ppm respectively.



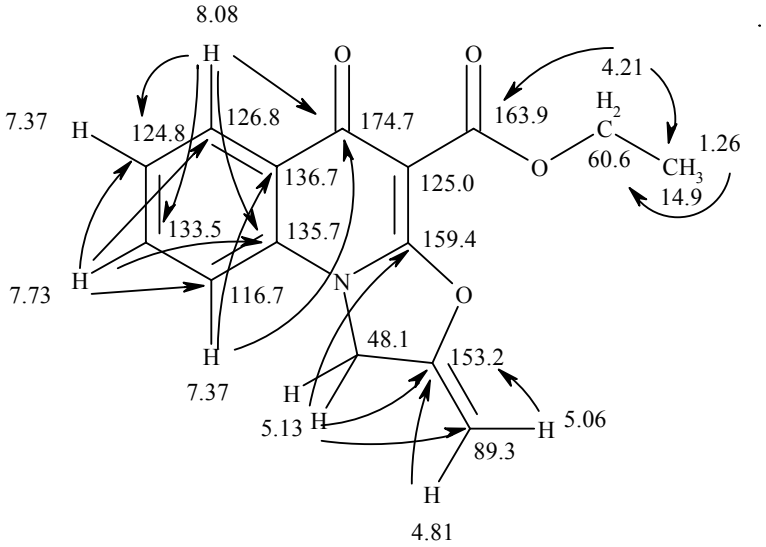
The assignment of the $C_{(4)}$ signal bonded to the hydroxyl group follows from its correlation with proton H-5 and ω interaction with the H-8 proton. The carbonyl atom $C_{(2)}$ can be assigned by correlation with the N–CH_2 protons. The presence of this correlation and also the correlations between the N–CH_2 protons and atom $C_{(8)}$ also

TABLE 1. Complete Correlation List for N-Allyl-substituted Acids **3**

δ, ppm.	HMQC	HMBC
8.10	125.6	139.4; 136.1; 171.1
7.86	136.1	139.4; 125.6; 117.7
7.65	117.7	136.1; 124.2; 115.6; 171.1
7.45	124.2	139.4; 132.2; 125.6; 117.7; 115.6
5.94	132.2	45.0
5.16	117.3	45.0
5.03	117.3	45.0
4.92	45.0	139.4; 132.2; 117.3; 164.0

demonstrates the positioning of the allyl substituent on atom $N_{(1)}$. The only carbon signal for which correlation with protons did not occur was at 95.3 ppm and it can be assigned to the $C_{(3)}$ atom. Attention was drawn to the fact that this signal is found at anomalously high field and this is most likely associated with specific electronic effects in the given molecule. It should be noted that acid **3** is quite unstable in DMSO-d_6 solution. Even after 1 h the spectrum shows signals for a reaction product, the structure of which differs significantly from the starting compound and this can evidently be explained the high tendency of a solution of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids to undergo decarboxylation.

In the ^{1}H NMR spectrum of the 2-methyleneoxazoloquinoline **5** the aromatic doublet for the H-9 proton of the quinoline ring is found at markedly higher field than the signal for the corresponding proton in the preceding compound. This points to a significant change in its chemical surroundings. The allyl group signals also show a different aspect. Hence the spectrum shows only two olefinic signals appearing as doublets at 5.06 and 4.81 ppm. This ^{1}H NMR appearance is typical of 1,1-disubstituted olefins. Hence the compound studied is most likely represented by an oxazolo[3,2-*a*]quinoline structure. The carbon spectrum of this compound is also in agreement. For assignment of the ^{13}C signals we have measured the HMBC and HMQC heteronuclear correlation spectra. From the HMQC spectrum the protonated carbon atoms can be assigned. For the quaternary carbon atom signals we have again used the HMBC correlations. Hence the location of the bridging $C_{(5a)}$ and $C_{(9a)}$ atoms can be made from their correlation with the quinoline benzene ring protons. Assignment of the $C_{(5)}$ carbonyl carbon was possible from its correlation with proton H-6 and ω-correlation with protons H-7 and H-9. The chemical shift of the carbonyl carbon in the ester group follows from its correlation with the methylene protons. Atom $C_{(3a)}$ in the quinoline ring can be assigned by its correlation with the N–CH_2 group protons. The presence of an oxazoline fragment also follows from the ^{1}H to ^{13}C correlation. The full list of correlations found is given in Table 2.



As in the previous case, HMBC correlation was not found for atom $C_{(4)}$ corresponding to $C_{(3)}$ of the quinoline ring in the acid structure **3**. Since the only unassigned signal in the carbon spectrum is the peak at 125.0 ppm this can then be assigned to atom $C_{(4)}$. As is apparent when comparing it with the spectrum of the preceding compound the given signal is found at much lower field and this points to the presence of the conjugated pyridin-4-one ring annelated to the benzene ring.

TABLE 2. Complete Correlation List for 2-Methyleneoxazoloquinoline **5**

δ, ppm	HMQC	HMBC
8.08	126.8	135.7; 133.5; 116.7; 174.7
7.73	133.5	135.7; 126.8; 124.8; 116.7
7.37	124.8; 116.7	124.8; 116.7; 174.7; 136.7; 133.5; 126.8
5.13	48.1	153.2; 159.4; 89.3
5.06	89.3	153.2
4.81	89.3	153.2
4.21	60.6	163.9; 14.9
1.26	14.9	60.6

For confirmation of the steric proximity of the methylene protons on the nitrogen atom and proton H-9 we undertook NOESY-1D type homonuclear Overhauser effect experiments. Saturation of the methylene proton signal at 5.13 ppm led to an increase in the intensity of the H-9 proton signal. It appeared as a sharp doublet. At the same time there was observed an increase in the intensity of the olefine proton signal at 4.81 ppm. This points to its cisoid orientation relative to the methylene protons. Saturation of the aromatic doublet at 7.37 ppm also showed a nuclear Overhauser effect for the $N–CH_2$ protons. Thus the structure of the given compound may be considered as proven.

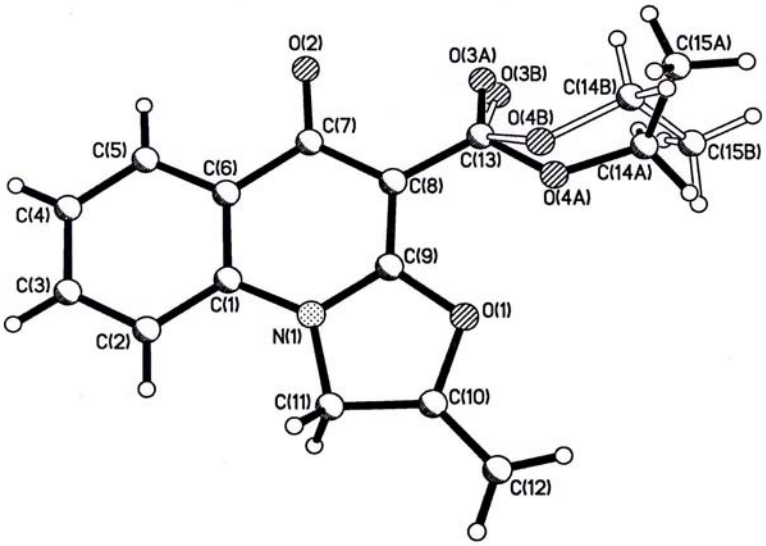


Fig. 1. Structure of the 2-methyleneoxazoloquinoline molecule **5** with atomic numbering.

According to X-ray data (Fig. 1, Tables 3, 4) it was found that all of the non hydrogen atoms of the 2-methyleneoxazoloquinoline molecule **5** lie in a single plane within 0.02 Å (with the exception of the atoms of the ester substituent) despite the shortened intramolecular contact for $H_{(2)}…C_{(11)}$ 2.69 Å (sum of van der Waal radii 2.87 Å [6]). Lengthening of the $O_{(2)}–C_{(7)}$ 1.242(5) and $C_{(8)}–C_{(9)}$ 1.379(6) bonds when compared with their mean values [7] of 1.210 and 1.326 Å is probably due to configurational interactions between the π-acceptor carbonyl group $C_{(7)}–O_{(2)}$ and the π-donor $O_{(1)}$ atom. This proposal also agrees with the marked shortening of the $O_{(1)}–C_{(9\ )}$1.347(5) when compared with the analogous $O_{(1)}–C_{(10)}$ bond 1.407(5) Å.

The ester substituent on atom $C_{(8)}$ is located in two positions (**A** and **B**) as a result of rotation about the $C_{(8)}$–$C_{(13)}$ and $O_{(4)}$–$C_{(14)}$ bonds with a population of **A**:**B** = 48:52%. In both conformations the ester groups are not coplanar with the plane of the pyridine ring (torsional angle $C_{(9)}$–$C_{(8)}$–$C_{(13)}$–$O_{(3)}$ 157(1)º in conformer **A** and 138(1)º in conformer **B**). The ethyl group is found in an *ap*-conformation relative to the $C_{(8)}$–$C_{(13}$ bond and $C_{(14)}$–$C_{(15)}$ is virtually perpendicular to the $C_{(13}$–$O_{(4)}$ [torsional angles $C_{(14)}O_{(4)}$–$C_{(13)}$–$C_{(8)}$ 169(1) in **A** and -179.5(9)º in **B**, $C_{(13)}$–$O_{(4)}$–$C_{(14)}$–$C_{(150}$ 86(2) in **A** and -74(1)º in **B**]. Shortening of the intramolecular contact $O_{(4b)}$…$H_{(14d)}$ 2.41 (2.46 Å) occurs in confrmer **B**. In the crystal the molecules of compound **5** form dimers *via* weak intermolecular hydrogen bonds $C_{(2)}$–$H_{(2a)}$…$O_{(3a)'}$ (1-x, -0.5+y, 0.5-z) H…O 2.39 Å, C–H…O 174º and $C_{(2)}$–$H_{(2a)}$…$O_{(3b)}$ (1-*x*, -0.5+*y*, 0.5-*z*) H…O 2.41 Å, C–H…O 169º.

It was interesting to find that basic hydrolysis of the starting bromo ester, the 2-methylene-oxazoloquinoline **5**, and ketone **2** gave the same product 1-acetonyl-4-hydroxy-1H-2-quinolinone (**6**), moreover in the first two examples the 3-ethoxycarbonyl ketone analog **2** was present through incomplete hydrolysis in the reaction mixture using ^{1}H NMR spectroscopy. It follows that the 2-oxopropyl substituent is formed not from the 2,3-dibromopropyl derivative as proposed before but as a result of base catalyzed opening of the oxazole ring in the 2-methyleneoxazoloquinoline **5**

It should be noted here that the reason for the formation of ketone **2** in the reaction with sodium methylate is likely to be the water. Although present in small amount (otherwise the ester group would also be decomposed) in commercial methanol it appears sufficient to convert sodium methylate to sodium hydroxide which evidently brings about hydrolysis of the oxazole ring. At the same time, reactions with weak bases can also occur in aqueous alcohols without marked hydrolysis of the oxazole ring. In a preparative connection such syntheses are more conveniently carried out in the more solubilizing DMF even though this does not have a theoretical basis.

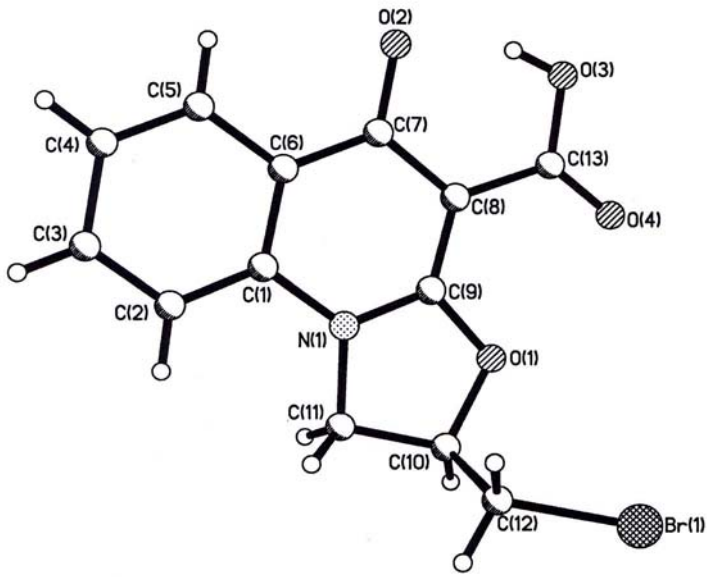


Figure 2. Structure of the 2-bromomethyloxazolo[3,2-a]quinoline-4-carboxylic acid **8.**

From the general results of this investigation we arrived at the conclusion that the product of brominating 1-allyl-3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinoline (**1**) with molecular bromine is the ethyl 2-bromoethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylate (**7**). This structure agrees fully

TABLE 3. Bond Lengths (l) in the Structures of Ester **5** and Acid **8**

Bond	*l*, Å	Bond	*l*, Å
Ester **5**		Acid **8**	
$N_{(1)}$–$C_{(9)}$	1.342(5)	$Br_{(1)}$–$C_{(12)}$	1.96(1)
$N_{(1)}$–$C_{(11)}$	1.453(5)	$N_{(1)}$–$C_{(1)}$	1.41(1)
$O_{(1)}$–$C_{(10)}$	1.407(5)	$O_{(1)}$–$C_{(9)}$	1.36(1)
$O_{(3A)}$–$C_{(13)}$	1.212(9)	$O_{(2)}$–$C_{(7)}$	1.28(1)
$O_{(4A)}$–$C_{(14A)}$	1.449(9)	$O_{(4)}$–$C_{(13)}$	1.21(1)
$O_{(3B)}$–$C_{(13)}$	1.205(8)	$C_{(1)}$–$C_{(6)}$	1.40(1)
$O_{(4B)}$–$C_{(14B)}$	1.449(8)	$C_{(3)}$–$C_{(4)}$	1.43(2)
$C_{(1)}$–$C_{(2)}$	1.400(6)	$C_{(5)}$–$C_{(6)}$	1.43(1)
$C_{(2)}$–$C_{(3)}$	1.363(7)	$C_{(7)}$–$C_{(8)}$	1.46(1)
$C_{(4)}$–$C_{(5)}$	1.378(7)	$C_{(8)}$–$C_{(13)}$	1.48(1)
$C_{(6)}$–$C_{(7)}$	1.476(6)	$C_{(10)}$–$C_{(11)}$	1.50(1)
$C_{(8)}$–$C_{(9)}$	1.379(6)	$N_{(1)}$–$C_{(9)}$	1.33(1)
$C_{(10)}$–$C_{(12)}$	1.341(7)	$N_{(1)}$–$C_{(11)}$	1.49(1)
$N_{(1)}$–$C_{(1)}$	1.377(6)	$O_{(1)}$–$C_{(10)}$	1.47(1)
$O_{(1)}$–$C_{(9)}$	1.347(5)	$O_{(3)}$–$C_{(13)}$	1.32(1)
$O_{(2)}$–$C_{(7)}$	1.242(5)	$C_{(1)}$–$C_{(2)}$	1.35(1)
$O_{(4A)}$–$C_{(13)}$	1.344(8)	$C_{(2)}$–$C_{(3)}$	1.38(2)
$C_{(14A)}$–$C_{(15A)}$	1.50(1)	$C_{(4)}$–$C_{(5)}$	1.37(2)
$O_{(4B)}$–$C_{(13)}$	1.357(7)	$C_{(6)}$–$C_{(7)}$	1.42(2)
$C_{(14B)}$–$C_{(15B)}$	1.504(9)	$C_{(8)}$–$C_{(9)}$	1.36(1)
$C_{(1)}$–$C_{(6)}$	1.409(6)	$C_{(10)}$–$C_{(12)}$	1.47(2)
$C_{(3)}$–$C_{(4)}$	1.380(7)		
$C_{(5)}$–$C_{(6)}$	1.390(6)		
$C_{(7)}$–$C_{(8)}$	1.443(6)		
$C_{(8)}$–$C_{(13)}$	1.490(6)		
$C_{(10)}$–$C_{(11)}$	1.463(6)		

with both the chemical properties of this compound and its spectroscopic properties. In other words, the bromination of N-allyl-substituted 4-hydroxy-2-quinolinones is accompanied by a very ready closing of the five membered oxazole ring. The accuracy of this conclusion was confirmed by X-ray analysis of the reaction product of the N-allyl-substituted acid **3** with bromine and this unambiguously showed it to be the 2-bromomethyl-5-oxo-1.2-dihydro-5H-oxazolo[3,2-*d*]quinoline-4-carboxylic acid (**8**).

The benzopyridone fragment, carboxyl group, and $C_{(11)}$, $O_{(1)}$ atoms of acid **8** (Fig. 2, Tables 3, 4) lie in a single plane to within 0.02 Å despite the shortening of the intramolecular contact $H_{(2)}\ldots C_{(11)}$ 2.64 Å (sum of van der Waal's radii 2.87 Å [6]). The coplanar position of the carboxyl group is additionally stabilized by an intramolecular bond $O_{(3)}$–$H_{(3)}\ldots O_{(2)}$ (H…O 1.69 Å, O–H…O 157º). The five membered heterocycle occurs in an envelope conformation. The deviation of atom $C_{(10)}$ from the mean square plane of the remaining ring atoms is 0.27 Å. The bromomethyl substituent has a pseudoaxial orientation [torsional angle $C_{(9)}$–$O_{(1)}$–$C_{(1)}$–$C_{(12)}$ -106.8(9)º] and occurs in a –*sc*-conformation relative to the $O_{(1)}$–$C_{(10)}$ bond [torsional angle $O_{(1)}$–$C_{(10)}$–$C_{(12)}$–$Br_{(1)}$ -61.9(9)º]. Short intermolecular contacts are found in the molecule **8** crystal: $H_{(2)}$–$Br_{(1)}$ (1-x, -0.5+y, 1-z) 3.19 (3.23), $H_{(4)}\ldots Br_{(1)}$ (1+*x*, *y*, 1+*z*) 3.15 (3.23), $H_{(11a)}\ldots Br_{(1)}$ (1-*x*, -0.5+*y*, 1-*z*) 3.18 (3.23), and $H_{(11b)}\ldots O_{4)}$ (1-*x*, -0.5+*y*, 1-*z*) 2.43 (2.46 Å).

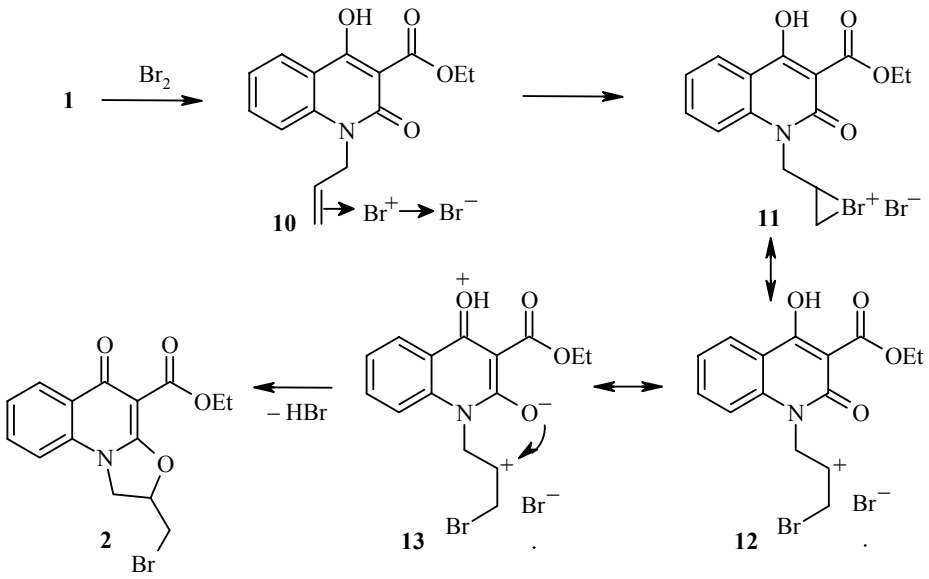
The acid **8** is similar in chemical properties to ester **7** and treatment with triethylamine also readily forms the corresponding 2-methylene derivative **9**, base hydrolysis of which gives 1-acetonyl-4-hydroxy-1H-2-quinolinone (**6**).

TABLE 4. Valence Angles (ω) in the Structures of Ester **5** and acid **8**

Angle of valence	ω, deg	Angle of valence	ω, deg.
Ether **5**		Acid **8**	
$C_{(9)}–N_{(1)}–C_{(1)}$	121.8(3)	$C_{(9)}–N_{(1)}–C_{(1)}$	122.3(7)
$C_{(1)}–N_{(1)}–C_{(11)}$	126.9(4)	$C_{(1)}–N_{(1)}–C_{(11)}$	125.8(8)
$C_{(13)}–O_{(4A)}–C_{(14A)}$	118.1(9)	$C_{(2)}–C_{(1)}–C_{(6)}$	123.4(9)
$C_{(13)}–O_{(4B)}–C_{(14B)}$	115.1(8)	$C_{(6)}–C_{(1)}–N_{(1)}$	115.4(8)
$N_{(1)}–C_{(1)}–C_{(2)}$	121.6(4)	$C_{(2)}–C_{(3)}–C_{(4)}$	118(1)
$C_{(2)}–C_{(1)}–C_{(6)}$	120.3(4)	$C_{(4)}–C_{(5)}–C_{(6)}$	121(1)
$C_{(2)}–C_{(3)}–C_{(4)}$	121.2(5)	$C_{(1)}–C_{(6)}–C_{(5)}$	116.1(9)
$C_{(4)}–C_{(5)}–C_{(6)}$	120.2(4)	$O_{(2)}–C_{(7)}–C_{(6)}$	121.7(8)
$C_{(5)}–C_{(6)}–C_{(7)}$	120.3(4)	$C_{(6)}–C_{(7)}–C_{(8)}$	118.8(8)
$O_{(2)}–C_{(7)}–C_{(8)}$	122.6(4)	$C_{(9)}–C_{(8)}–C_{(13)}$	122.8(8)
$C_{(8)}–C_{(7)}–C_{(6)}$	116.9(3)	$N_{(1)}–C_{(9)}–O_{(1)}$	110.7(8)
$C_{(9)}–C_{(8)}–C_{(13)}$	121.8(4)	$O_{(1)}–C_{(9)}–C_{(8)}$	124.1(9)
$N_{(1)}–C_{(9)}–O_{(1)}$	110.2(3)	$C_{(12)}–C_{(10)}–C_{(11)}$	113.6(9)
$O_{(1)}–C_{(9)}–C_{(8)}$	125.1(4)	$N_{(1)}–C_{(11)}–C_{(10)}$	100.8(7)
$C_{(12)}–C_{(10)}–C_{(11)}$	131.6(4)	$O_{(4)}–C_{(13)}–O_{(3)}$	122(1)
$N_{(1)}–C_{(11)}–C_{(10)}$	101.2(3)	$O_{(3)}–C_{(13)}–C_{(8)}$	114.1(9)
$O_{(3B)}–C_{(13)}–O_{(4B)}$	122.3(8)	$C_{(9)}–N_{(1)}–C_{(11)}$	111.6(7)
$O_{(3A)}–C_{(13)}–C_{(8)}$	120(1)	$C_{(9)}–O_{(1)}–C_{(10)}$	108.1(7)
$O_{(4B)}–C_{(13)}–C_{(8)}$	110.9(5)	$C_{(2)}–C_{(1)}–N_{(1)}$	121.2(8)
$C_{(9)}–N_{(1)}–C_{(11)}$	111.3(4)	$C_{(1)}–C_{(2)}–C_{(3)}$	121(1)
$C_{(9)}–O_{(1)}–C_{(10)}$	108.3(3)	$C_{(5)}–C_{(4)}–C_{(3)}$	121(1)
$O_{(4A)}–C_{(14A)}–C_{(15A)}$	107(2)	$C_{(1)}–C_{(6)}–C_{(7)}$	122.7(8)
$O_{(4B)}–C_{(14B)}–C_{(15B)}$	116(1)	$C_{(7)}–C_{(6)}–C_{(5)}$	121.2(9)
$N_{(1)}–C_{(1)}–C_{(6)}$	118.1(4)	$O_{(2)}–C_{(7)}–C_{(8)}$	119.6(9)
$C_{(3)}–C_{(2)}–C_{(1)}$	119.2(4)	$C_{(9)}–C_{(8)}–C_{(7)}$	115.5(9)
$C_{(5)}–C_{(4)}–C_{(3)}$	120.4(5)	$C_{(7)}–C_{(8)}–C_{(13)}$	121.7(9)
$C_{(5)}–C_{(6)}–C_{(1)}$	118.7(4)	$N_{(1)}–C_{(9)}–C_{(8)}$	125.2(8)
$C_{(1)}–C_{(6)}–C_{(7)}$	120.9(4)	$C_{(12)}–C_{(10)}–O_{(1)}$	109.8(9)
$O_{(2)}–C_{(7)}–C_{(6)}$	120.3(4)	$O_{(1)}–C_{(10)}–C_{(11)}$	105.6(8)
$C_{(9)}–C_{(8)}–C_{(7)}$	117.5(4)	$C_{(10)}–C_{(12)}–Br_{(1)}$	112.3(7)
$C_{(7)}–C_{(8)}–C_{(13)}$	120.6(4)	$O_{(4)}–C_{(13)}–C_{(8)}$	123.5(9)
$N_{(1)}–C_{(9)}–C_{(8)}$	124.8(4)		
$C_{(12)}–C_{(10)}–O_{(1)}$	119.5(4)		
$O_{(1)}–C_{(10)}–C_{(11)}$	108.9(3)		
$O_{(3A)}–C_{(13)}–O_{(4A)}$	126(1)		
$O_{(3B)}–C_{(13)}–C_{(8)}$	126.6(8)		
$O_{(4A)}–C_{(13)}–C_{(8)}$	113.1(5)		

In conclusion we briefly turn to the possible mechanism of such an unusual bromination of N-allyl-substituted 4-hydroxy-2-quinolinones. The first stage of this process evidently appears as a classic formation of a π-complex **10** [2] from the alkene and the polarized bromine molecule. Fission of the π-complex then occurs. Regardless of how this occurs *via* the intermediate cyclic bromonium ion **11** or the alternative secondary (as the more stable) carbocation **12**, the addition would be concluded by nucleophilic attack at one of the two carbon atoms of the initial double bond by the remaining Br^-. However, the presence of a more powerful nucleophile in the structure of this intermediate (the bipolar 1,4-dihydro form **13**, whose formation from 4-hydroxy-2-quinolinones has been noted by us before [8, 9]) leads to the fact that the reaction finishes with heterocyclization. The significant factors responsible for such a reaction course are undoubtedly the size of the ring formed and the extreme convenience of the spatial positioning of the two reaction centers for its closing. For this reason it is

likely that the formation of the 2-bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinolines overall shows only a low sensitivity to change in reaction conditions and is commonly successful both in acetic acid (aqueous or anhydrous) and in anhydrous carbon tetrachloride.



EXPERIMENTAL

^{1}H and ^{13}C NMR spectra for the allyl derivatives **5** and **3**, ^{1}H 2D COSY spectroscopic experiments, the NOESY-1D homonuclear Overhauser effect, and HMQC and HMBC heteronuclear correlation spectra were measured on a Varian Mercury 400 (400 MHz and 100 MHz respectively). All of the 2D experiments were carried out with gradient selection of useful signals. The mixing time in the pulse sequences were $^{1}J_{CH}$ = 140 and $^{2\text{-}3}J_{CH}$ = 8 Hz. The number of increments in the COSY and HMQC spectra was 128 and 400 in the HMBC spectra. The mixing time in the NOESY-1D experiment was 500 ms. The ^{1}H NMR spectra of the remaining compounds were recorded on a Varian Mercury VX-200 (200 MHz) instrument. In all cases the solvent was DMSO-d_6 and the internal standard TMS. The chromatographic mass spectrum of ester **7** was recorded on a Hewlett Packard 5890/5972 instrument in total scanning mode in the range 35-700 *m/z,* electron impact ionization 70 eV, and chromatographic column Hewlett Packard 5MS (length 25 m, internal diameter 0.2 mm, polysiloxane film stationery phase (5% diphenylpolysiloxane, 95% dimethylpolysiloxane) of thickness 0.33 μm and with helium gas carrier. Water was removed from glacial acetic acid and carbon tetrachloride over P_2O_5 and from bromine by shaking with conc. H_2SO_4. Ethyl 1-allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (**1**) can form a crystal hydrate hence in case of need it was dehydrated by prolonged standing over P_2O_5 in a vacuum desiccator.

Ethyl 2-Bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylate (7). Bromine (0.52 ml, 0.01 mol) was added with stirring to a solution of compound **1** monohydrate (2.91 g, 0.01 mol) in acetic acid (50 ml) and it was instantly decolorized. The reaction mixture was diluted with water. The precipitate was filtered off, washed with water, and dried (after carrying out the synthesis with anhydrous reagents in carbon tetrachloride the precipitated ester **7** was simply filtered off). Yield 3.24 g (92%); mp 247-249ºC (from DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.09 (1H, dd, *J* = 7.7 and 1.7, H-6); 7.73 (1H, td, *J* = 7.7 and 1.6, H-8); 7.45 (1H, d, *J* = 8.8, H-9); 7.38 (1H, td, *J* = 7.8 and 1.0, H-7); 5.55 (1H, m, CHO); 4.62

(1H, t, J = 9.6, NCH); 4.23 (1H, t, J = 9.6, NCH); 4.17 (2H, q, J = 7.0, $COOCH_2$); 3.99 (2H, t, J = 4.6, CH_2–Br); 1.24 (3H, t, J = 7.0, $COOCH_2C\underline{H}_3$). Mass spectrum, *m/z* (I_{rel}, %): 271 $[M\text{-}HBr]^+$ (12), 226 $[M\text{-}HBr\text{-}OEt]^+$ (28), 199 $[M\text{-}HBr\text{-}OEt\text{-}CO]^+$ (100), *m/z* values are only given for the ^{79}Br isotope. Found, %: C 51.02; H 3.93; N 3.88. $C_{15}H_{14}BrNO_4$. Calculated, %: C 51.16; H 4.01; N 3.98.

Methyl 1-Acetonyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (2). A mixture of the bromo ester **7** (3.52 g, 0.01 mol) and a solution of sodium methylate prepared from metallic sodium (1.15 g, 0.05 mol) in methanol (70 ml)) was refluxed for 1 h. The product was cooled, diluted with water, and acidified with HCl to pH 4. The precipitated ester **2** was filtered off, washed with water, and dried. Yield 2.20 g (80%); mp 177-179ºC (from ethanol). ^1H NMR spectrum, δ, ppm (*J*, Hz): 13.18 (1H, s, OH); 8.06 (1H, dd, J = 8.0 and 1.6, H-5); 7.66 (1H, td, J = 8.1 and 1.6, H-7); 7.35-7.23 (2H, m, H-8,6); 5.14 (2H, s, NCH_2); 3.83 (3H, s, $COOCH_3$); 2.26 (3H, s, CH_3). Found, %: C 61.17; H 4.64; N 5.01. $C_{14}H_{13}NO_5$. Calculated, %: C 61.09; H 4.76; N 5.09.

1-Allyl-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (3). A solution of compound **1** monohydrate (2.91 g, 0.01 mol) in a mixture of hydrochloric and acetic acids (10 ml) with a low water content as prepared by the method in [6] was held at 60ºC for 5 h. It was left for several hours at room temperature after which the precipitated acid **3** was filtered off, washed with alcohol and then several times with cold water, and dried. Yield 2.23 g (91%); mp 160-162ºC (decomp.). ^1H NMR spectrum, δ, ppm (*J,* Hz); 15.76 (1H, br. s, 4-OH); 14.41 (1H, br. s, COOH); 8.10 (1H, dd, J = 8.2 and 1.4, H-5); 7.86 (1H, td, J = 7.7 and 1.4, H-7); 7.65 (1H, d, J = 8.6, H-8); 7.45 (1H, t, J = 7.4, H-6); 5.94 (1H, m, $C\underline{H}{=}CH_2$); 5.16 (1H, d, J = 10.0, $NCH_2CH{=}CH$-*cis*); 5.03 (1H, d, J = 17.0, $NCH_2CH{=}CH$-*trans*), 4.92 (2H, s, NCH_2). ^{13}C NMR spectrum, δ, ppm: 173.4 (COOH), 171.1 ($C_{(4)}$), 164.0 ($C_{(2)}$), 139.4 ($C_{(8a)}$), 136.1 ($C_{(7)}$), 132.2 ($\underline{C}{=}CH_2$), 125.6 ($C_{(5)}$), 124.2 ($C_{(6)}$), 117.7 ($C_{(8)}$), 117.3 ($=CH_2$), 115.6 ($C_{(4a)}$), 95.3 ($C_{(3)}$), 45.0 (NCH_2). Found, %: C 63.73; H 4.55; N 5.84. $C_{13}H_{11}NO_4$. Calculated, %: C 63.67; H 4.52; N 5.71.

Ethyl 2-[(butylmethylamino)methyl]-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylate (4a). A mixture of the bromo ester **7** (3.52 g, 0.01 mol) and N-butylmethylamine (5.92 ml, 0.05 mol) in ethanol (100 ml) was refluxed for 10 h. The excess amine and solvent were distilled off in *vacuo*. The residue was treated with water (30 ml), acidified to pH 4 with HCl, and filtered. The filtrate was basified with aqueous Na_2CO_3 solution to pH 8. The precipitated butylmethylaminomethyl substituted ester **4a** was filtered off, washed with cold water, and dried. Yield 2.65 g (74%); mp 131-133ºC (from EtOH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.09 (1H, dd, J = 8.0 and 1.4, H-6); 7.71 (1H, td, J = 7.8 and 1.5, H-8); 7.47-7.30 (2H, m, H-7,9); 5.33 (1H, m, $NCH_2C\underline{H}O$); 4.57 (1H, t, J = 9.3, NCH); 4.24-4.09 (3H, m, NCH + $COOCH_2$); 2.79 (2H, dd, J = 5.4 and 1.5, $OCHC\underline{H}_2$–NCH_3); 2.40 (2H, t, J = 7.2, $NC\underline{H}_2CH_2$); 2.26 (3H, s, NCH_3); 1.33 (4H, m, $NCH_2(C\underline{H}_2)_2$); 1.21 (3H, t, J = 7.1, $COOCH_2C\underline{H}_3$); 0.81 (3H, t, J = 7.0, $NCH_2(CH_2)_2C\underline{H}_3$). Found, %: C 66.91; H 7.40; N 7.95. $C_{20}H_{26}N_2O_4$. Calculated, %: C 67.02; H 7.31; N 7.82.

Ethyl 2-dipropylaminomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylate hydrochloride (4b). The dipropylaminomethyl base derivative was obtained by the method above. For conversion to the hydrochloride it was dissolved in 2-propanol (10 ml), diluted with 2-propanol, saturated gaseous HCl added to pH 3, and left for 8-10 h at -25ºC. The crystals formed were filtered off, washed with ether, and dried. Yield 76%; mp 176-178ºC (from ethanol). ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.07 (1H, dd, J = 7.9 and 1.3, H-6); 7.70 (1H, td, J = 7.8 and 1.7, H-8); 745-7.31 (2H, d, H-7,9); 5.30 (1H, m, $NCH_2C\underline{H}O$); 4.53 (1H, t, J = 9.2, NCH); 4.25-4.09 (3H, m, NCH + $COOCH_2$); 2.86 (2H, d, J = 5.0, $C\underline{H}_2$–$N(Pr)_2$); 2.43 (4H, t, J = 7.1, $N(C\underline{H}_2CH_2)_2$; 1.33 (4H, m, $N(CH_2C\underline{H}_2)_2$); 1.22 (3H, t, J = 7.3, $COOCH_2C\underline{H}_3$); 0.76 (6H, t, J = 7.4, $N(CH_2CH_2C\underline{H}_3)_2$. Found, %: C 61.59; H 6.82; N 6.93. $C_{21}H_{28}N_2O_4$.HCl. Calculated, %: C 61.68; H 6.90; N 6.85.

Ethyl 2-methylene-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylate (5). Triethylamine (1.7 ml, 0.012 mol) or pyridine (1.0 ml, 0.01 mol) was added to a solution of the bromo ester **7** (3.52 g, 0.01 mol) in DMF (20 ml) and refluxed for 1 h. After cooling, it was diluted with water (50 ml) and acidified

with HCl to pH 4. the precipitated 2-methyleneoxazoloquinoline **5** was filtered off, washed with water, and dried. Yield 2.52 g (93%); mp 213-215ºC (from ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.08 (1H, dd, *J* = 8.1 and 1.1, H-6); 7.73 (1H, td, *J* = 7.8 and 1.5, H-8); 7.47-7.33 (2H, m, H-7,9); 5.13 (2H, t, *J* = 2.3, NCH_2); 5.06 (1H, s, =CH-*trans*); 4.81 (1H, s, =CH-*cis*); 4.21 (2H, q, *J* = 7.2, OCH_2); 1.26 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$). ^{13}C NMR spectrum, δ, ppm: 174.7 ($C_{(5)}$), 163.9 (COO), 159.4 ($C_{(3a)}$), 153.2 ($C_{(2)}$), 136.7 ($C_{(5a)}$), 135.7 ($C_{(9a)}$), 133.5 ($C_{(8)}$), 126.8 ($C_{(6)}$), 125.0 ($C_{(4)}$), 124.8 ($C_{(7)}$), 116.7 ($C_{(9)}$), 89.3 (=CH_2), 60.6 (OCH_2), 48.1 (NCH_2), 14,9 (CH_3). Found, %: C 66.53; H 4.94; N 5.07. $C_{15}H_{13}NO_4$. Calculated, %: C 66.41; H 4.83; N 5.16.

X-Ray Structural Investigation. Crystals of the 2-methyleneoxazoloquinoline **5** (ethanol) are monoclinic, at 20ºC: *a* = 10.670(1), *b* = 16.571(2), *c* = 7.675(1) Å, β = 107.58(1)º, *V* = 1293.7(3) Å^3, M_r = 271.26. *Z* = 4, space group $P2_1/c$, d_{calc} = 1.393 g/cm^3, μ(MoKα) = 0.102 mm^{-1}, *F*(000) = 568. Crystals of the acid **8** (DMF) are monoclinic, at 20ºC: *a* = 4.612(1), *b* = 11.456(2), *c* = 11.396(2) Å, β = 96.86(2)º, *V* = 597.8(2) Å^3, M_r = 324.13, *Z* = 2, space group $P2_1$, d_{calc} = 1.801 g/cm^3, μ(MoKα) = 3.448 mm^{-1}, *F*(000) = 324. The unit cell parameters and intensities of 7104 reflections (2277 independent with R_{int} = 0.057) for compound **5** and of 3058 reflections (2436 independent with R_{int} = 0.053) for acid **8** were measured on an Xcalibur-3 diffractometer (MoKα, CCD detector, graphite monochromator, ω scanning, $2\theta_{max}$ = 50 and 55º respectively). In the case of acid **8** the absorption was included analytically (T_{min} = 0.273, T_{max} = 0.765).

Both structures were solved by a direct method using the SHELXTL program package [10]. For refinement of the structure of compound **5** limits were set on the bond lengths in the disordered fragment O–C_{sp3} 1.45 and C_{sp3}–C_{sp3} 1.51, C_{sp2}=O 1.21, C_{sp2}–O 1.33 Å. The position of the hydrogen atoms in both cases was calculated geometrically and refined using the "riding" method with $U_{iso} = nU_{eq}$ for the non-hydrogen atom bonded to the given hydrogen (*n* = 1.5 for a methyl group and *n* = 1.2 for the remaining hydrogen atoms). The structure was refined using F_2 full matrix least squares analysis in the anisotropic approximation for non hydrogen to wR_2 = 0.2118 for 2118 reflections (R_1 = 0.088 for 1300 reflections with $F>4\sigma(F)$, *S* = 1.103) for compound **5** and to wR_2 = 0.196 for 2400 reflections (R_1 = 0.082 for 1438 reflections with $F>4\sigma(F)$, *S* = 0.969) for acid **8**. The full crystallographic data has been placed in the Cambridge structural data base (2-methyloxazoloquinoline **5** reference CCDC 296937 and acid **8** reference 296938). The interatomic distances and valence angles are given in Tables 3 and 4.

1-Acetonyl-4-hydroxy-1H-2-quinolinone (6). A mixture of the bromo ester **7** (3.52 g, 0.01 mol) in 10% aqueous NaOH solution (50 ml) was refluxed for 40 h. The product was cooled, diluted with water, and acidified with HCl to pH 4. The precipitated quinolone **6** was filtered off, washed with water, and dried. Yield 1.88 g (87%); mp 258-260ºC (from ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.48 (1H, s, OH); 7.87 (1H, d, *J* = 7.8, H-5); 7.51 (1H, t, *J* = 7.9, H-7); 7.26-7.12 (2H, m, H-8,6); 5.83 (1H, s, H-3); 5.11 (2H, s, NCH_2); 2.22 (3H, s, CH_3). Found, %: C 66.46; H 5.18; N 6.39. $C_{12}H_{11}NO_3$. Calculated, %: C 66.35; H 5.10; N 6.45.

A mixed sample with samples of the quinolone **6** prepared by a similar method from ketone**2**, 2-methylene-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic acid (**9**), and its ethyl ester **5** did not give a depression of melting point. The ^{1}H NMR spectra of these compounds were identical.

2-Bromomethyl-5-oxo-1,2-dihydro-5H-oxazolo[3,2-a]quinoline-4-carboxylic Acid (8) was prepared by bromination of the N-allyl acid **3** in acetic acid using the method for the synthesis of ester **7**. Yield 85%; mp 238-240ºC (with decomp.) (from DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.52 (1H, br s, COOH); 8.25 (1H, dd, *J* = 8.2 and 1.3, H-6); 7.90 (1H, td, *J* = 7.8 and1.6, H-8); 7.63 (1H, d, *J* = 8.2, H-9); 7.54 (1H, t, *J* = 7.9, H-7); 5.71 (1H, m, CHO); 4.73 (1H, t, *J* = 9.9, NCH); 4.36 (1H, t, *J* = 8.6, NCH); 4.04 (2H, t, *J* = 4.1, CH_2Br). Found, %: C 48.11; H 3.03; N 4.40. $C_{13}H_{10}BrNO_4$. Calculated, %: C 48.17; H 3.11; N 4.32.

2-Methylene-5-oxo-1,2-dihydro-5H-oxazolo[3,2-*a*]quinoline-4-carboxylic Acid (9) was prepared from acid **8** using the method for the 2-methyleneoxazoloquinoline **5**. Yield. 90%; mp 254-256ºC (with decomp.) (from DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 15.43 (1H, br. s COOH); 8.24 (1H d, *J* = 8.1, H-6); 7.91 (1H, t, *J* = 7.8, H-8); 7.60-7.48 (2H, m, H-7,9); 5.23 (3H, m, NCH_2 + =CH); 4.93 (1H, m, =CH). Found, %: C 64.26; H 3.80; N 5.66. $C_{13}H_9NO_4$. Calculated, %: C 64.20; H 3.73; N 5.76.

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