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4-HYDROXY-2-QUINOLONES. 92*. REACTION OF 1-R-4-CHLORO-3-ETHOXYCARBONYL-2-OXO-1,2- DIHYDROQUINOLINES WITH ANILINES

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A preparative method is proposed and the synthesis of 4-arylamino-2-oxo-1,2-dihydroquinolines has been effected. An X-ray structural investigation of 4-(4-chlorophenylamino)-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid has been carried out enabling the ease of decarboxylating such compounds to be substantiated. Results are given of a study of the anti-inflammatory activity of the synthesized compounds.

Keywords: 4-arylamino-2-oxo-1,2-dihydroquinolines, decarboxylation, anti-inflammatory activity, X-ray structural analysis.

The ethyl esters of 1-R-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acids react readily with alkylamines forming the corresponding 4-alkylamino derivatives, which possess anti-inflammatory activity [2]. While continuing investigations in this area and with the aim of establishing structure–activity relationships in this series of compounds, we studied the behavior of 1-R-4-chloro-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolines in reactions with aromatic amines.

It turned out that anilines react with chloroquinolines **1** in boiling ethanol similarly to aliphatic amines, i.e. ethyl esters of 1-R-4-arylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **2** are formed. An analogous result was also obtained after conducting the synthesis in DMF at 100°C. However in boiling DMF more profound structural transformations occur, including destruction of the ethoxycarbonyl group, leading finally to 1-R-4-arylamino-2-oxo-1,2-dihydro-quinolines **3**.

It should nevertheless be noted that for complete conversion of the amino esters **2** formed in the first stage into 3H-4-arylaminoquinolines **3** it is necessary to boil the reaction mixture for no less than 20 h, otherwise the product of the studied reaction will consist of a mixture of two substances, ester **2** and the 3H derivative **3**. It is possible to synthesize 1-R-4-arylamino-2-oxo-1,2-dihydroquinolines **3** more smoothly by the interaction of anilines with 1-R-4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **4**. The reaction time is thereby reduced to 2 h, and the 3H-4-aryl-aminoquinolones **3** obtained have a high degree of purity, since the intermediate 1-R-4-arylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acids are so readily decarboxylated that it is impossible to isolate them after carrying out the synthesis in boiling DMF. Nonetheless under milder conditions, such as in boiling ethanol, acids **5** are fairly stable and if necessary may readily be isolated [3]. It

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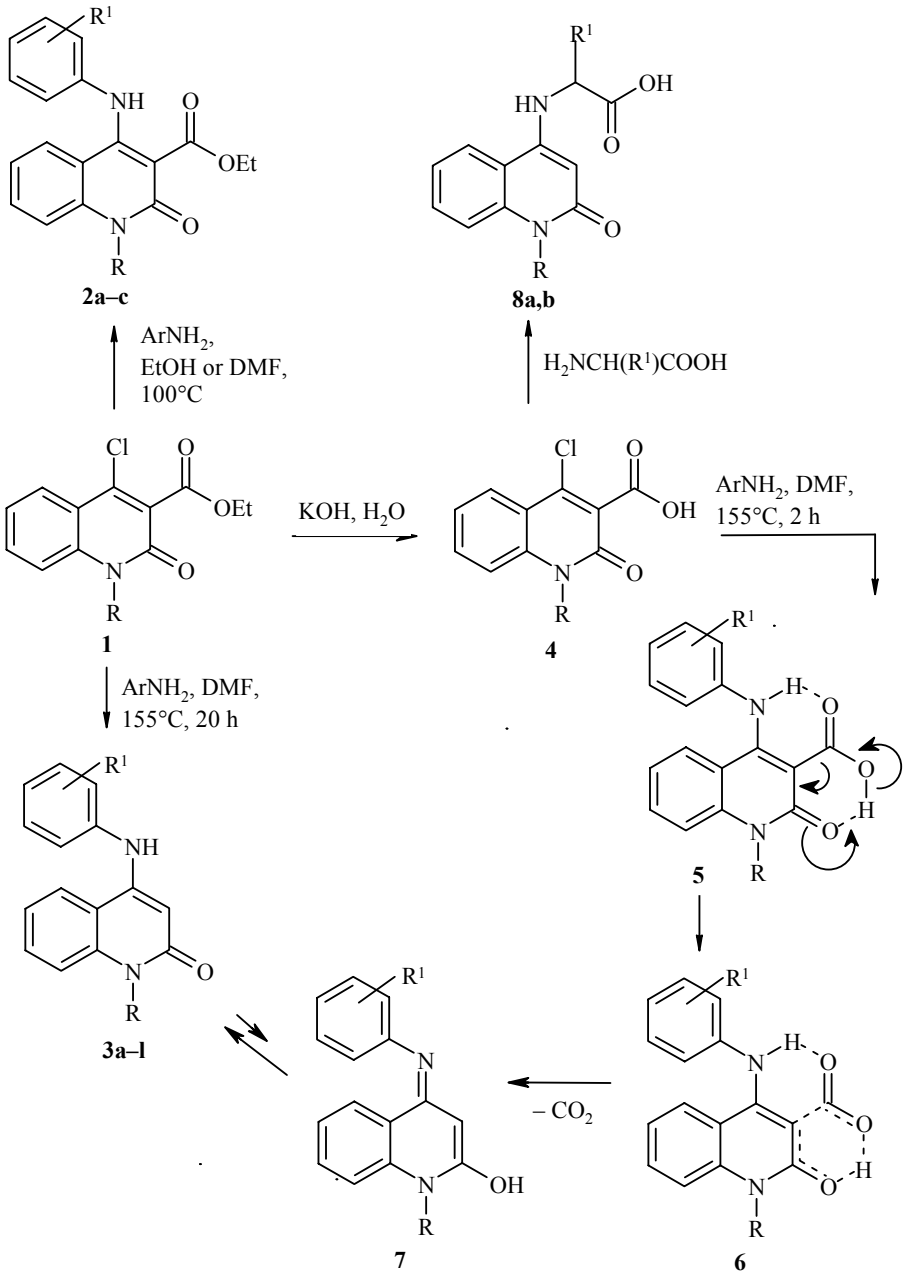
follows from this that fission of CO_2 occurs even after formation of 4-aminoquinoline-3-carboxylic acids **5**, and the activating influence on this process proves to be both the 4-amino and the 2-C=O groups. It is known that β-keto acids, to which acids **5** belong, are decarboxylated very readily. The overall rate of decarboxylation depends on the concentration of the keto acid itself and on the concentration of its anion, but the rapid decarboxylation of such compounds is caused by the transfer of the carboxyl proton to the neighboring C=O group through the formation of a hydrogen bond [4].



2 **a** R = H, R^1 = 4-OEt; **b** R = H, R^1 = 4-Cl; **c** R = Me, R^1 = H; **3, 5** **a–d** R = H, **e–l** R = Pr; **a** R^1 = 4-F; **b** R^1 = 4-Cl; **c** R^1 = 2-OMe-5-Cl; **d** R^1 = 4-OEt; **e** R^1 = 2-F; **f** R^1 = 3-F; **g** R^1 = 4-F; **h** R^1 = 3-CF_3; **i** R^1 = 4-Cl; **j** R^1 = 2-COOH; **k** R^1 = 4-COOH; **l** R^1 = 4-SO_2NH-(4,6-dimethyl-2-pyrimidinyl); **8** **a, b** R = Pr, **a** R^1 = H, **b** R^1 = Me

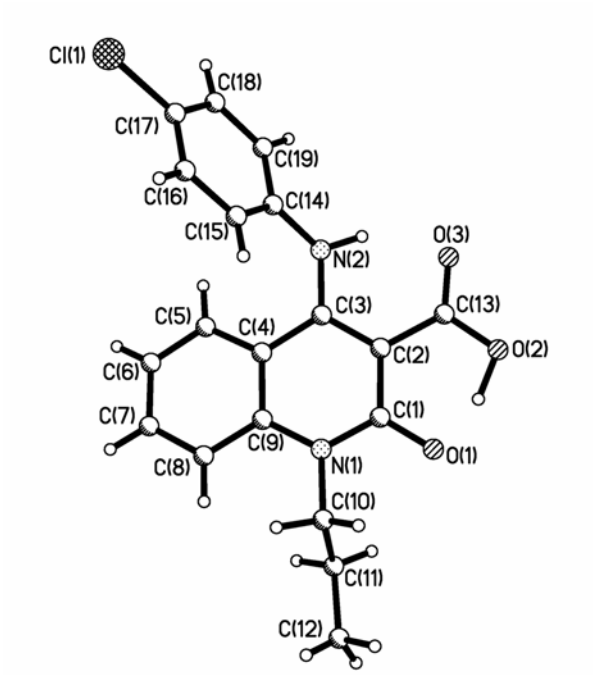


Fig. 1. Structure of the **5i** molecule with numbering of the atoms.

According to the data of X-ray structural analysis (Fig. 1, Tables 1 and 2) the dihydropyridine ring of 4-(4-chlorophenylamino)-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid (**5i**) has the conformation of a very flattened boat (puckering parameters: $S = 0.19$, $\Theta = 79.8°$, $\Psi = 0.8°$ [5]). The deviation of the $N_{(1)}$ and $C_{(3)}$ atoms from the mean-square plane of the remaining atoms of the ring was 0.09 and 0.13 Å respectively. Twisting of the $C_{(2)}$–$C_{(3)}$ double bond was observed [torsion angle $C_{(1)}$–$C_{(2)}$–$C_{(3)}$–$C_{(4)}$ was -12.2(4) °]. The $C_{(2)}$–$C_{(3)}$ double bond at 1.390(4) Å was lengthened compared with the mean value of 1.334 Å [6], and the $N_{(2)}$–$C_{(3)}$ at 1.361(4) and the $C_{(2)}$–$C_{(13)}$ at 1.482(4) Å were shortened (mean values of 1.416 and 1.502 Å respectively). The reason for such electron density redistribution may either be the formation of an intramolecular hydrogen bond (IMHB) $N_{(2)}$–$H_{(2N)}$···$O_{(3)}$, H···O 1.84(5) Å, N–H···O 143(4)°, or conjugation interactions between the arylamine substituent and the carboxyl group. The $C_{(13)}$–$O_{(3)}$ bond length at 1.217(4) Å, corresponding to its mean value of 1.210 Å, permits the suggestion that conjugational interactions introduce the main contribution to the electron

TABLE 1. Interatomic Distances (*l*) in the Structure of Acid **5i**

Bond	*l*, Å	Bond	*l*, Å	Bond	*l*, Å
$Cl_{(1)}$–$C_{(17)}$	1.747(3)	$C_{(8)}$–$C_{(9)}$	1.411(5)	$C_{(1)}$–$C_{(2)}$	1.447(4)
$N_{(1)}$–$C_{(9)}$	1.384(4)	$C_{(11)}$–$C_{(12)}$	1.504(5)	$C_{(2)}$–$C_{(13)}$	1.482(4)
$N_{(2)}$–$C_{(3)}$	1.361(4)	$C_{(14)}$–$C_{(19)}$	1.392(4)	$C_{(4)}$–$C_{(5)}$	1.402(5)
$O_{(1)}$–$C_{(1)}$	1.259(4)	$C_{(16)}$–$C_{(17)}$	1.376(5)	$C_{(5)}$–$C_{(6)}$	1.371(5)
$O_{(3)}$–$C_{(13)}$	1.217(4)	$C_{(18)}$–$C_{(19)}$	1.386(5)	$C_{(7)}$–$C_{(8)}$	1.370(5)
$C_{(2)}$–$C_{(3)}$	1.390(4)	$N_{(1)}$–$C_{(1)}$	1.355(4)	$C_{(10)}$–$C_{(11)}$	1.519(5)
$C_{(3)}$–$C_{(4)}$	1.452(4)	$N_{(1)}$–$C_{(10)}$	1.476(4)	$C_{(14)}$–$C_{(15)}$	1.380(5)
$C_{(4)}$–$C_{(9)}$	1.413(4)	$N_{(2)}$–$C_{(14)}$	1.419(4)	$C_{(15)}$–$C_{(16)}$	1.386(5)
$C_{(6)}$–$C_{(7)}$	1.378(5)	$O_{(2)}$–$C_{(13)}$	1.319(4)	$C_{(17)}$–$C_{(18)}$	1.382(5)

TABLE 2. Valence Angles (ω) in the Structure of Acid **5i**

Angle	ω, deg.	Angle	ω, deg.	Angle	ω, deg.
$C_{(1)}$–$N_{(1)}$–$C_{(9)}$	122.0(3)	$O_{(3)}$–$C_{(13)}$–$C_{(2)}$	123.2(3)	$C_{(9)}$–$C_{(4)}$–$C_{(3)}$	118.9(3)
$C_{(9)}$–$N_{(1)}$–$C_{(10)}$	121.1(3)	$C_{(15)}$–$C_{(14)}$–$C_{(19)}$	119.5(3)	$C_{(5)}$–$C_{(6)}$–$C_{(7)}$	120.2(3)
$O_{(1)}$–$C_{(1)}$–$N_{(1)}$	118.8(3)	$C_{(19)}$–$C_{(14)}$–$N_{(2)}$	119.5(3)	$C_{(7)}$–$C_{(8)}$–$C_{(9)}$	120.2(3)
$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	119.6(3)	$C_{(17)}$–$C_{(16)}$–$C_{(15)}$	119.1(3)	$N_{(1)}$–$C_{(9)}$–$C_{(4)}$	119.6(3)
$C_{(3)}$–$C_{(2)}$–$C_{(13)}$	121.5(3)	$C_{(16)}$–$C_{(17)}$–$Cl_{(1)}$	119.4(2)	$N_{(1)}$–$C_{(10)}$–$C_{(11)}$	112.8(3)
$N_{(2)}$–$C_{(3)}$–$C_{(2)}$	120.9(3)	$C_{(17)}$–$C_{(18)}$–$C_{(19)}$	119.0(3)	$O_{(3)}$–$C_{(13)}$–$O_{(2)}$	120.4(3)
$C_{(2)}$–$C_{(3)}$–$C_{(4)}$	118.6(3)	$C_{(1)}$–$N_{(1)}$–$C_{(10)}$	116.8(3)	$O_{(2)}$–$C_{(13)}$–$C_{(2)}$	116.4(3)
$C_{(5)}$–$C_{(4)}$–$C_{(3)}$	122.2(3)	$C_{(3)}$–$N_{(2)}$–$C_{(14)}$	125.2(3)	$C_{(15)}$–$C_{(14)}$–$N_{(2)}$	120.9(3)
$C_{(6)}$–$C_{(5)}$–$C_{(4)}$	120.9(3)	$O_{(1)}$–$C_{(1)}$–$C_{(2)}$	121.6(3)	$C_{(14)}$–$C_{(15)}$–$C_{(16)}$	120.6(3)
$C_{(8)}$–$C_{(7)}$–$C_{(6)}$	120.9(3)	$C_{(3)}$–$C_{(2)}$–$C_{(1)}$	119.4(3)	$C_{(16)}$–$C_{(17)}$–$C_{(18)}$	121.4(3)
$N_{(1)}$–$C_{(9)}$–$C_{(8)}$	121.5(3)	$C_{(1)}$–$C_{(2)}$–$C_{(13)}$	118.9(3)	$C_{(18)}$–$C_{(17)}$–$Cl_{(1)}$	119.1(3)
$C_{(8)}$–$C_{(9)}$–$C_{(4)}$	118.8(3)	$N_{(2)}$–$C_{(3)}$–$C_{(4)}$	120.4(3)	$C_{(18)}$–$C_{(19)}$–$C_{(14)}$	120.2(3)
$C_{(12)}$–$C_{(11)}$–$C_{(10)}$	111.5(3)	$C_{(5)}$–$C_{(4)}$–$C_{(9)}$	118.8(3)		

density redistribution in the $N_{(2)}\cdots C_{(3)}\cdots C_{(2)}\cdots C_{(13)}$ fragment. The formation of a very strong IMHB at $O_{(2)}$–$H_{(20)}\cdots O_{(1)}$ [H···O 1.37(7) Å, O–H···O 160(5)°] leads to a lengthening of the $O_{(1)}$-$C_{(1)}$ bond to 1.259(4) Å (mean value is 1.210 Å). The $C_{(13)}$–$O_{(2)}$ bond length at 1.319(4) Å corresponds to the mean value of the bond length in a carboxyl group, and the distance between the $O_{(2)}$ atom and the $H_{(20)}$ atom is 1.117 Å. This permits the suggestion that only one minimum exists on the potential energy surface corresponding to the location of the proton on the $O_{(2)}$ atom.

The steric repulsion between the aromatic ring $C_{(14)}\cdots C_{(19)}$ and the quinolone fragment {shortened contacts of $H_{(5)}\cdots C_{(14)}$ (sum of van der Waals radii 2.87 Å [7]), $H_{(5)}\cdots C_{(15)}$ 2.85 (2.87), $C_{(5)}\cdots C_{(14)}$ 3.01 (3.42), $C_{(5)}\cdots C_{(15)}$ 3.09 (3.42), $C_{(15)}\cdots C_{(4)}$ 3.15 Å (3.42 Å)} causes a pyramidal configuration for the $N_{(2)}$ atom (sum of valence angles 355°). This also probably explains the *sc* orientation of the chlorophenyl substituent relative to the $C_{(3)}$–$C_{(4)}$ bond [torsion angle $C_{(14)}$–$N_{(2)}$–$C_{(3)}$–$C_{(4)}$ is 42.9(4)°] and the turn of the plane of the aromatic ring relative to the $C_{(3)}$–$N_{(2)}$ bond [torsion angle $C_{(3)}$–$N_{(2)}$–$C_{(14)}$–$C_{(15)}$ is 25.3(5)°].

The repulsion between the substituent at the $N_{(1)}$ atom and the neighboring carbonyl group and the hydrogen atom in the *peri* position of the benzene ring [intramolecular contacts $H_{(8)}\cdots C_{(10)}$ 2.52 (2.87), $H_{(8)}\cdots H_{(10a)}$ 1.93 (2.34), $H_{(10a)}\cdots C_{(8)}$ 2.48 (2.87), $H_{(10b)}\cdots O_{(1)}$ 2.35 Å (2.46 Å)] leads to a lengthening of the $N_{(1)}$–$C_{(9)}$ bond to 1.384(4) Å compared with a mean value of 1.355 Å. The substituent at the $N_{(1)}$ atom is disposed perpendicular to the plane of the dihydro ring [torsion angle $C_{(9)}$–$N_{(1)}$–$C_{(10)}$–$C_{(11)}$ is 91.3(4)°].

In other words the carboxyl groups of acids **5**, due to intra- and intermolecular hydrogen bonds are oriented in space in a very convenient position for decarboxylation. An important role is evidently also played by the ability of the 4-amino group to undergo amine-imine tautomerism, which must aid the formation of the enolic intermediate **7**. Probably a 4-hydroxy group shows a similar effect (due to keto-enol tautomerism) in 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids which have an analogous system of IMHB [8] and are also inclined towards ready decarboxylation [9].

Aliphatic amino acids also react with 4-chloroquinoline-3-carboxylic acids in boiling DMF, like anilines, forming the corresponding 4-(carboxyalkylamino)quinolones **8** in good yield, which on the whole enables this method to be recommended as preparative.

The 4-aminoquinolones **2**, **3**, **5**, **8** obtained are colorless crystalline substances with sharp melting points, soluble in DMF and DMSO, poorly soluble in alcohols (with the exception of esters **2**), and are practically insoluble in water. Their chemical structures were confirmed by data of elemental analysis and ^{1}H NMR spectroscopy (Tables 3 and 4) , and in individual examples by chromato-mass spectrometry.

TABLE 3. Characteristics of 1-R-4-Arylamino-2-oxo-1,2-dihydroquinolines **3a-l**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (DMF)	Yield, %
		C	H	N		
3a	$C_{15}H_{11}FN_2O$	70.71 / 70.86	4.43 / 4.36	11.14 / 11.02	323-325	87
3b	$C_{15}H_{11}ClN_2O$	66.43 / 66.55	4.22 / 4.10	10.27 / 10.35	296-298	90
3c	$C_{16}H_{13}ClN_2O_2$	63.77 / 63.90	4.26 / 4.36	9.38 / 9.31	329-331	81
3d	$C_{17}H_{16}N_2O_2$	72.96 / 72.84	5.87 / 5.75	9.86 / 9.99	289-291	82
3e	$C_{18}H_{17}FN_2O$	72.90 / 72.96	5.70 / 5.78	9.55 / 9.45	194-196	88
3f	$C_{18}H_{17}FN_2O$	72.82 / 72.96	5.88 / 5.78	9.59 / 9.45	181-183	79
3g	$C_{18}H_{17}FN_2O$	72.80 / 72.96	5.85 / 5.78	9.58 / 9.45	213-215	84
3h	$C_{19}H_{17}F_3N_2O$	65.97 / 65.89	4.86 / 4.95	8.17 / 8.09	185-187	77
3i	$C_{18}H_{17}ClN_2O$	69.24 / 69.12	5.53 / 5.48	8.90 / 8.96	240-242	79
3j	$C_{19}H_{18}N_2O_3$	70.95 / 70.79	5.72 / 5.63	8.57 / 8.69	247-249	81
3k	$C_{19}H_{18}N_2O_3$	70.90 / 70.79	5.77 / 5.63	8.75 / 8.69	294-296	80
3l	$C_{24}H_{25}N_5O_3S$	62.33 / 62.19	5.39 / 5.44	15.02 / 15.11	252-254	75

As a distinguishing feature of the ^{1}H NMR spectra of the ethyl esters of 1-R-4-arylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **2** it is possible to note the significant paramagnetic displacement of the 4-NH group proton signals in comparison with their 4-N-alkyl analogs [2]. It amounts to 1.8 ppm on average and is caused by the proximity of the aromatic ring. The proton in position 3 of the quinoline nucleus in the ^{1}H NMR spectra of 3H-4-arylaminoquinolines **3** is displayed by just one characteristic signal, a singlet of intensity 1H at 5.05-6.24 ppm (Table 4).

The cation radicals (molecular ions), formed on ionization of neutral molecules in the mass spectra of aminoquinolones **3,** containing an alkoxy group in the N-aryl fragments, are characterized by high stability, as indicated by their maximal intensity peaks. A specific characteristic of the spectrum of chloro-substituted compound **3c** is the duplicate signal of the molecular ion* peak $[M]^+$ at 300/302 and of the $[M\text{-}OMe]^+$ fragment at 269/271 with a signal intensity ratio of 3:1 in each case. This is caused by the presence in the molecule of one chlorine atom, the natural abundance of the two isotopes of which (^{35}Cl and ^{37}Cl) is 75.53 and 24.47% respectively [10].

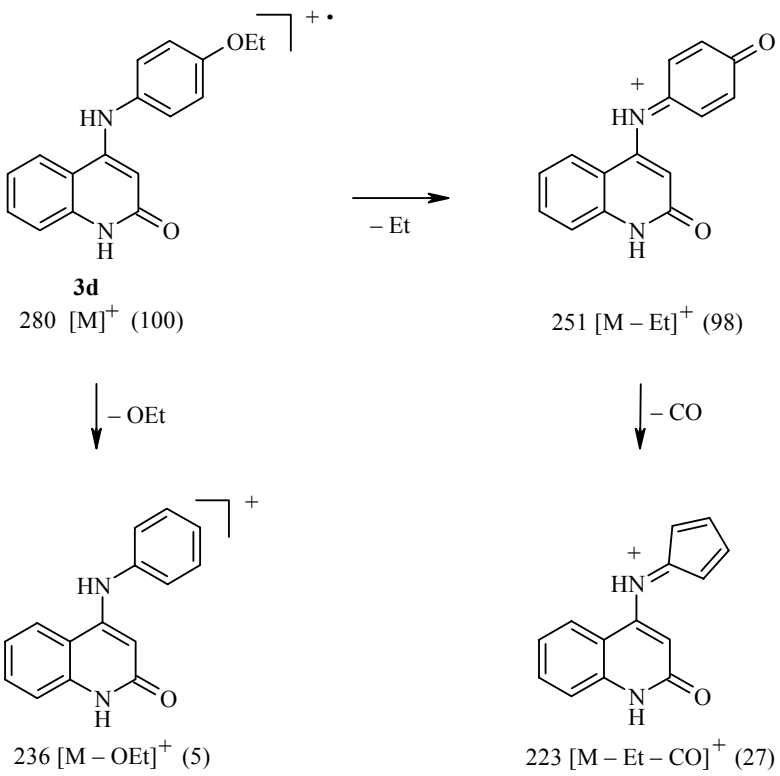
The typical decomposition of aromatic compounds of the type of Ar–O–Alk under the action of electron impact proceeds by the preferred dissociation of the Ar–O bond with the formation of $[M\text{-}OAlk]^+$ ions, while the intensity of $[M\text{-}Alk]^+$ ions is usually significantly less [10]. In reality, fragmentation of the molecular ion of methoxy-substituted quinolone **3c** proceeds by just this scheme (intensity of the $[M\text{-}OMe]^+$ peak at 269 was 77%, but that of the $[M\text{-}Me]^+$ peak at 285 was 12%) after which the sequential loss of chlorine atom and phenyl substituent follows. The elimination of CH_2O, which is characteristic of *meta* and *para* methoxyarenes, in the case of quinolone **3c** was depressed to a significant extent (the intensity of the $[M\text{-}CH_2O]^+$ peak at 270 was 14% in all), which may serve as additional confirmation of precisely *ortho*-methoxy-substitution.

* Here and subsequently values of *m/z* are given for ion peaks in the mass spectra.

TABLE 4. ^{1}H NMR Spectra of 1-R-4-Arylamino-2-oxo-1,2-dihydroquinolines **3a-l**

Compound	Chemical shifts, δ, ppm. (*J*, Hz)*					
	4-NH (1H, s)	H-5 (1H, d)	H-7 (1H, t)	H arom. (m, H-6,8 + 4-N–Ar)	H-3 (1H, s)	R[1]
				7		
3a	8.64	8.19 (*J* = 8.0)	7.63 (*J* = 7.2)	7.50-7.18 (6H)	5.56	—
3b	8.70	8.17 (*J* = 8.0)	7.64 (*J* = 7.5)	7.52-7.17 (6H)	5.74	—
3c	8.32	8.07 (*J* = 8.1)	7.48 (*J* = 7.5)	7.35-7.18 (5H)	5.05	3.77 (3H, s, OCH_3)
3d	8.23	8.05 (*J* = 8.2)	7.38 (*J* = 7.4)	7.26-6.90 (6H)	5.51	4.06 (2H, q, *J* = 6.9, OCH_2); 1.40 (3H, t, *J* = 6.9, CH_3)
3e	8.53	8.19 (*J* = 8.0)	7.62 (*J* = 7.3)	7.55-7.21 (6H)	5.28	—
3f	8.75	8.13 (*J* = 8.0)	7.63 (*J* = 7.2)	7.56-6.85 (6H)	5.96	—
3g	8.61	8.16 (*J* = 8.0)	7.61 (*J* = 7.3)	7.54-7.16 (6H)	5.17	—
3h	8.87	8.14 (*J* = 7.9)	7.68 (*J* = 7.1)	7.60-7.23 (6H)	5.95	—
3i	8.55	8.13 (*J* = 7.8)	7.62 (*J* = 7.1)	7.51-7.18 (6H)	5.88	—
3j	10.20	8.00 (*J* = 8.0)	7.66 (*J* = 7.5)	7.95 (1H, d, *J* = 8.1, H-3'); 7.52-7.05 (5H)	6.24	12.60 (1H, s, COOH)
3k	8.79	8.13 (*J* = 7.9)	7.64 (*J* = 7.4)	7.93 (2H, d, *J* = 8.1, H-3',5'); 7.52 (1H, d, *J* = 8.0, H-8); 7.35 (2H, d, *J* = 8.1, H-2',6'); 7.27 (1H, t, *J* = 7.4, H-6)	6.16	12.42 (1H, s, COOH)
3l	8.83	8.09 (*J* = 8.0)	7.63 (*J* = 7.5)	7.95 (2H, d, *J* = 8.6, H-3',5'); 7.51 (1H, d, *J* = 8.1, H-8); 7.40 (2H, d, *J* = 8.6, H-2',6'); 7.25 (1H, t, *J* = 7.5, H-6)	6.13	11.41 (1H, s, SO_2H); 6.73 (1H, s, H-5 pyrimidine); 2.25 (6H, s, $2CH_3$)

* Signals of the 1-NH group protons of quinolones **3a-d** have the form of singlets at 10.92-11.18 ppm; the 1-N-propyl fragment of quinolones **3e-l** gives rise to three signals at 4.10 (2H, t, NCH_2), 1.56 (2H, m, $NCH_2\underline{CH_2}$), and 0.91 ppm (3H, t, CH_3).



On the other hand the primary decomposition process of the molecular ion in the mass spectrum of 4-ethoxy derivative **3d** was linked with loss of the ethyl group and the formation of a fragment ion (251) having a quinonoid structure, and subsequent ejection of a CO molecule. A second fragmentation pathway, *viz*. fission of the R–OEt bond, for 4-ethoxyphenylaminoquinolone **3d** may be considered to be uncharacteristic, since the intensity of the corresponding $[M\text{-}OEt]^+$ peak at 236 was only 5% in all.

The anti-inflammatory properties of the synthesized compounds were studied in white rats of both sexes of weight 180-200 g in the carrageenan paw edema model by the known method of [11]. Inflammation was caused by the subplantar injection into one of the rear paws of 0.1 ml 1% carrageenan solution. The substances being investigated and the reference compound (voltaren) were administered intra-peritoneally at a dose of 8 mg/kg (ED_{50} of voltaren) 1 h before injection of carrageenan. The development of edema was assessed by the change of paw volume, which was measured dynamically after 1, 2, 3, 4, and 5 h oncometrically. Analysis of the experimental data obtained showed that the ethyl esters of 1-R-4-arylamino-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **2** did not in practice show any effect on the course of the inflammatory reaction. Of the group of 3H-4-arylamino-2-oxo-1,2-dihydroquinolines **3** only the *ortho*-fluoro-substituted derivative **3e** merited attention with a level of antiexudative activity (50%) almost as high as voltaren (65%). It is interesting that the remaining substances of this group were characterized by proinflammatory properties, i.e. they enhanced the inflammatory reaction, and this effect was displayed maximally (by 250-300%) again in the case of monofluoro-phenylaminoquinolones but just for the *meta*- and *para*-substituted derivatives **3f,g**. 4-(Carboxyalkylamino)-quinolones **8a,b** displayed moderate (30-32%) antiexudative action for 1 h after injecting the phlogogen, however in the second hour the activity was sharply reduced and became a weakly expressed anti-inflammatory action.

EXPERIMENTAL

The ^{1}H NMR spectra of the synthesized compounds were recorded on a Varian Mercury VX 200 (200 MHz) instrument in DMSO-d_6, internal standard was TMS. Chromato-mass spectra were recorded on a Kratos MS 890 A magnetic mass spectrometer, ionization was by electron impact at 70 eV with direct insertion of samples, heating the coupling for direct insertion with a heating chamber at 250°C.

4-Chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **4**, their esters **1**, and 4-(4-chlorophenylamino)-1-propyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**5i**) were obtained by known procedures [12, 13, and 3 respectively].

Ethyl Ester of 4-(4-Ethoxyphenylamino)-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (2a). A mixture of 4-chloro-2-oxoquinoline-3-carboxylic acid ethyl ester (**1**, R = H) (2.51 g, 0.01 mol), *p*-phenetidine (1.50 g, 0.01 mol), and triethylamine (1.4 ml, 0.01 mol) in ethanol (30 ml) was boiled for 5 h. Triethylamine was not added when carrying out the synthesis in DMF, but the reaction mixture was maintained at 100°C for 4-5 h . At the end of the reaction the mixture was diluted with water. The precipitated solid was filtered off, washed with water, and dried. Yield 3.13 g (89%); mp 190-192°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.12 (1H, s, CONH); 8.53 (1H, s, 4-NH); 8.02 (1H, d, *J* = 8.0, H-5); 7.50 (1H, t, *J* = 7.5, H-7); 7.27 (1H, d, *J* = 8.1, H-8); 7.14 (1H, t, *J* = 7.5, H-6); 7.00 (2H, d, *J* = 8.4, H-3′,5′); 6.83 (2H, d, *J* = 8.4, H-2′,6′); 4.00 (2H, q, *J* = 6.9, Ar-OCH_2); 3.51 (2H, q, *J* = 7.0, $COOCH_2$); 1.16 (3H, t, *J* = 6.9, Ar-$OCH_2C\underline{H}_3$); 1.00 (3H, t, *J* = 7.0, $COOCH_2C\underline{H}_3$).

Compounds 2b,c and 3i were obtained by an analogous procedure.

Ethyl Ester of 4-(4-Chlorophenylamino)-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (2b). Yield 92%; mp 222-224°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.41 (1H, s, CONH); 8.68 (1H, s, 4-NH); 7.94 (1H, d, *J* = 7.9, H-5); 7.53 (1H, t, *J* = 7.4, H-7); 7.27 (1H, d, *J* = 8.0, H-8); 7.32 (1H, t, *J* = 7.4, H-6); 7.26 (2H, d, *J* = 8.4, H-3′,5′); 6.99 (2H, d, *J* = 8.4, H-2′,6′); 3.68 (2H, q, *J* = 7.0, $COOCH_2$); 1.00 (3H, t, *J* = 7.0, $COOCH_2C\underline{H}_3$).

Ethyl Ester of 1-Methyl-2-oxo-4-phenylamino-1,2-dihydroquinoline-3-carboxylic Acid (2c). Yield 83%; mp 149-151°C (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.73 (1H, s, 4-NH); 8.12 (1H, d, *J* = 8.0, H-5); 6.95-7.78 (8H, m, H-7,8,6 + C_6H_5); 3.57 (3H, s, N–CH_3); 3.49 (2H, q, *J* = 7.0, $COOCH_2$); 0.99 (3H, t, *J* = 7.0, $COOCH_2C\underline{H}_3$).

4-(4-Chlorophenylamino)-2-oxo-1-propyl-1,2-dihydroquinoline (3i). A. *p*-Chloroaniline (1.27 g, 0.01 mol) was added to a solution of the ethyl ester of 4-chloro-2-oxo-1-propylquinoline-3-carboxylic acid (**1**, R = Pr) (2.93 g, 0.01 mol) in DMF (20 ml), the mixture was boiled under reflux for 20 h, after which the reaction mixture was cooled, and diluted with water. The precipitated solid aminoquinolone **3i** was filtered off, washed with alcohol, and dried. Yield 1.98 g (63%).

B. *p*-Chloroaniline (1.27 g, 0.01 mol) was added to a solution of 4-chloro-2-oxo-1-propylquinoline-3-carboxylic acid (**4**, R = Pr) (2.65 g, 0.01 mol) in DMF (10 ml) and the mixture was boiled under reflux for 2 h. The reaction mixture was then treated by the procedure of the previous experiment. Yield 2.46 g (79%).

A mixing test on the samples of aminoquinolone **3i** obtained by the different methods gave no depression of melting point. Their ^{1}H NMR spectra were identical.

The remaining 1-R-4-arylamino-2-oxo-1,2-dihydroquinolones **3** (Table 3) and also compounds **8a,b** were obtained by an analogous procedure.

2-Oxo-1-propyl-1,2-dihydro-4-quinolylaminoacetic Acid (8a). Yield 80%; mp 255-257°C (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.56 (1H, s, COOH); 7.94 (1H, d, *J* = 8.0, H-5); 7.57 (1H, t, *J* = 7.6, H-7); 7.43 (1H, d, *J* = 8.1, H-8); 7.20 (1H, t, *J* = 7.6, H-6); 7.10 (1H, t, *J* = 6.0, 4-NH); 5.29 (1H, s, H-3); 4.10 (2H, t, *J* = 7.7, $NC\underline{H}_2CH_2$); 3.89 (2H, d, *J* = 6.9, $NC\underline{H}_2COOH$); 1.54 (2H, m, $NCH_2C\underline{H}_2$); 0.92 (3H, t, *J* = 7.4, $NCH_2CH_2C\underline{H}_3$). Found, %: C 64.43; H 6.33; N 10.61. $C_{14}H_{16}N_2O_3$. Calculated, %: C 64.60; H 6.20; N 10.76.

2-(2-Oxo-1-propyl-1,2-dihydro-4-quinolylamino)propionic Acid (8b). Yield 75%; mp 212-214°C (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 12.60 (1H, s, COOH); 8.15 (1H, d, *J* = 8.0, H-5); 7.59 (1H, t, *J* = 7.6, H-7); 7.44 (1H, d, *J* = 8.1, H-8); 7.20 (1H, t, *J* = 7.6, H-6); 6.88 (1H, d, *J* = 6.4, 4-NH); 5.30 (1H, s, H-3); 4.03 (3H, m, NCH_2 + C<u>H</u>–CH_3); 1.51 (5H, m, $NCH_2C\underline{H}_2$ + CH_3); 0.90 (3H, t, *J* = 7.4, $NCH_2CH_2C\underline{H}_3$). Found, %: C 65.77; H 6.48; N 10.11. $C_{15}H_{18}N_2O_3$. Calculated, %: C 65.68; H 6.61; N 10.21.

X-Ray Structural Investigation. Crystals of 4-(4-chlorophenylamino)-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid (**5i**) were monoclinic. At 20°C *a* = 11.062(5), *b* = 10.678(4), *c* = 14.290(6) Å; β = 104.03(3)°; *V* = 1638(1) Å^3; M_r = 356.80; *Z* = 4; space group $P2_1/c$; d_{calc} = 1.447 g/cm^3; μ(MoKα) = 0.255 mm^{-1}; *F*(000) = 744. The parameters of the unit cell and the intensities of 2740 reflections (2588 independent, R_{int} = 0.023) were measured on an automatic Siemens P3/PC four-circle diffractometer (MoKα, graphite monochromator, 2θ/θ scanning, $2\theta_{max}$ = 50°). The structure was solved by the direct method with the SHELXTL set of programs [14]. The positions of hydrogen atoms were made apparent from an electron density difference synthesis and refined isotropically. The structure was refined anisotropically according to F^2 with a full-matrix least squares method for the nonhydrogen atoms to wR_2 = 0.136 for 2531 reflections (R_1 = 0.052 for 1925 reflections with $F > 4\sigma(F)$, *S* = 1.050). The complete crystallographic information has been deposited in the Cambridge structural data bank (deposit No. CCDC 250566). Interatomic distances and valence angles are given in Tables 1 and 2.

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