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4-HYDROXY-2-QUINOLONES. 20.* SYNTHESIS AND CHEMICAL CONVERSIONS OF ETHYL ESTERS OF CHLORO-SUBSTITUTED QUINOLINE-3-CARBOXYLIC ACIDS

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Preparative methods for the synthesis of ethyl esters of 2,4-dichloro- and 2-oxo-4-chloroquinoline-3-carboxylic acids were developed. The behavior of the compounds indicated was studied under conditions of alkaline and acidic hydrolysis, in reactions with some nucleophilic reagents, as well as in reductive dehalogenation. Results of the study of the antimicrobial and antiinflammatory activity of the synthesized compounds are presented.

Halogen-substituted derivatives of quinoline present significant interest not only as precursors of different derivatives of the quinoline series [2-6], but also as compounds possessing valuable pharmacological properties [7-13]. The given communication involves the development of preparative methods for the synthesis of ethyl esters of 2,4-dichloro- and 2-oxo-4-chloroquinoline-3-carboxylic acids and the study of their reactivity and some pharmacological properties.

Ethyl 2,4-dichloroquinoline-3-carboxylate (II) was obtained by the treatment of 1H-2-oxo-3-ethoxycarbonyl-4-hydroxyquinoline (I) with boiling phosphorus oxychloride. The same compound is formed under analogous conditions from the 4-O-acetyl derivative (III) and the 4-ethoxy derivative (IV) of the ester (I). Consequently, the indicated protective groups are ineffective. In contrast to 4-chloroquinoline-3-carboxylates, which are readily converted to 4-hydroxy derivatives by reaction with DMSO [14], the attempt to replace any chlorine atom (or both) of the ester (II) by the hydroxy group using this method did not give the desired result. Such a substitution was managed using anhydrous sodium acetate. When 2,4-dichloroquinolines react with nucleophilic reagents, the mixture of 2- and 4-substituted isomers is usually formed [13]. The analogous result can probably also be expected in the case of the ester (II). However, this compound forms ethyl 1H-2-oxo-4-chloroquinoline-3-carboxylate (V) with the equimolar amount of sodium acetate, and it forms high yields of 2-benzylamino-3-ethoxycarbonyl-4-chloroquinoline (VI) with the twofold excess of benzylamine. The result obtained indicates the preferred substitution of the chlorine atom at the position 2 of the quinoline nucleus; this is apparently caused by the activating influence both of the ethoxycarbonyl group, and the cyclic nitrogen atom. In order to solve, unambiguously, the problem of the structure of the ester (V) from the method described above using the quinolone (VII) (the reaction of which with $POCl_3$ cannot deliberately lead to a change in the quinolone structure), ethyl 1-ethyl-2-oxo-4-chloroquinoline-3-carboxylate (VIII) was synthesized. Ethyl 1H-2-oxoquinoline-3-carboxylate (IX), obtained (IX), obtained by the condensation of anthranilic aldehyde with diethyl malonate, was utilized as the other model compound. Comparison of the electronic absorption spectra of these compounds indicates the presence of one and the same conjugated system in their structure (Fig. 1).

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Scheme 1

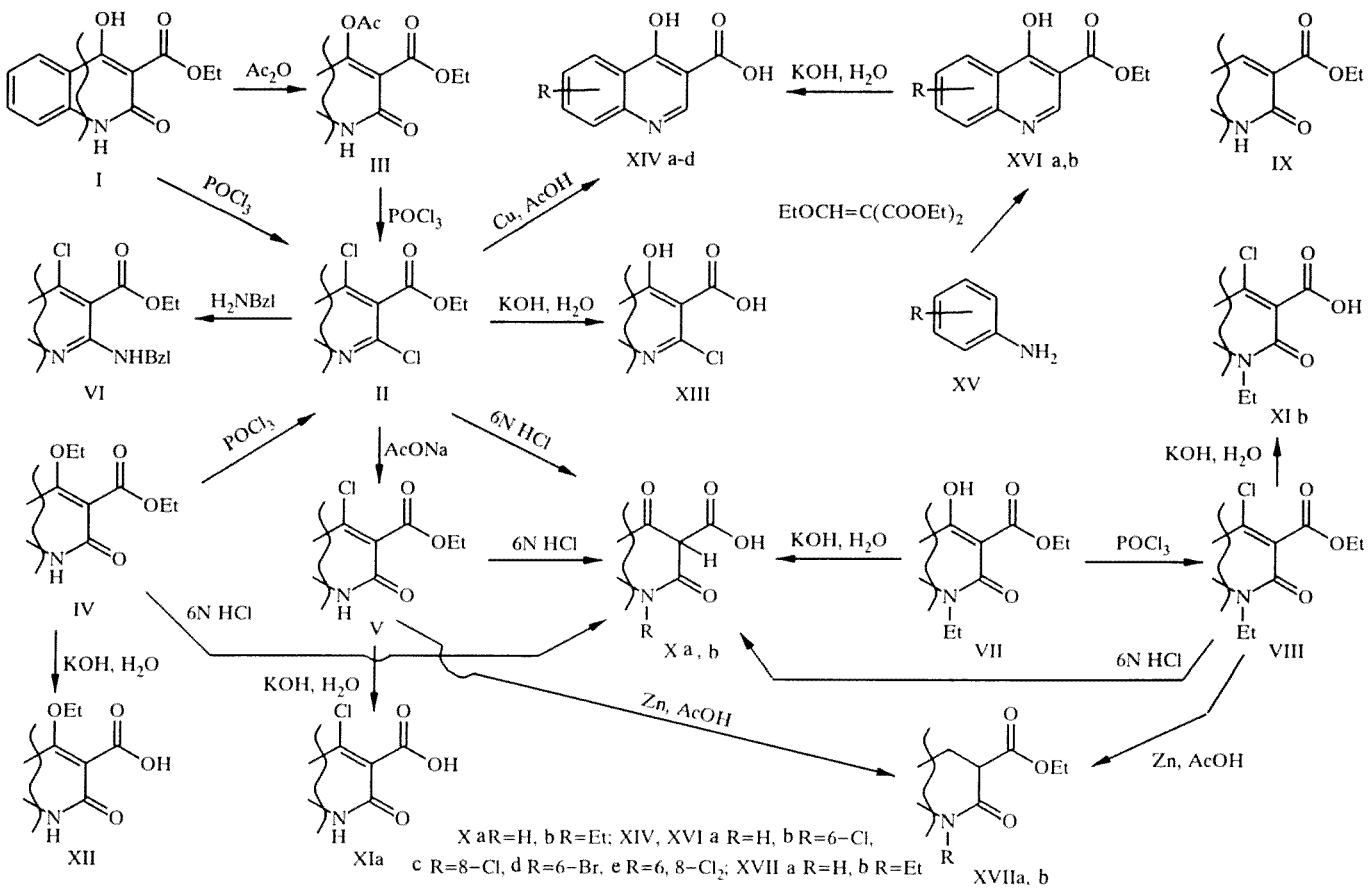
I
III
XIV a-d
XVI a,b
IX
VI
II
XIII
XV
XI b
IV
V
X a, b
VII
VIII
XII
XIa
XVIIa, b
Ac2O
POCl3
Cu, AcOH
KOH, H2O
EtOCH=C(COOEt)2
H2NBzl
AcNa
6N HCl
Zn, AcOH
X a R=H, b R=Et; XIV, XVI a R=H, b R=6-Cl,
c R=8-Cl, d R=6-Br, e R=6, 8-Cl2; XVII a R=H, b R=Et

TABLE 1. Characteristics of 4-Hydroxyquinoline-3-carboxylic Acids (XIV) and Their Ethyl Esters (XVI)

Compound	Empirical formula	mp, °C	PMR spectral parameters, δ, ppm*							Yield, %
			$H_{arom.}$					$COOCH_2CH_3$		
			2-H	5-H	6-H	7-H	8-H	CH_2 (2 H, q)	CH_3 (3 H, t)	
XIVa	$C_{10}H_7NO_3$	262...264*2 (decomp.)	8,38 (1H, s)	8,27 (1H, d)	7,59 (1H, t)	7,91 (1H, t)	7,80 (1H, d)	–	–	97
XIVb	$C_{10}H_6ClNO_3$	260...262*2 (decomp.)	8,85 (1H, s)	8,09 (1H, s)	–	7,81 (2H, d)		–	–	92
XIVc	$C_{10}H_6ClNO_3$	268...270 (decomp.)	8,59 (1H, s)	8,18 (1H, d)	7,53 (1H, t)	8,00 (1H, d)	–	–	–	94
XIVd	$C_{10}H_6BrNO_3$	276...278 (decomp.)	8,38 (1H, s)	8,31 (1H, s)	–	8,00 (1H, d)	7,75 (1H, d)	–	–	90
XIVe	$C_{10}H_5Cl_2NO_3$	273...275 (decomp.)	8,63 (1H, s)	8,20 (1H, s)	–	8,17 (1H, s)	–	–	–	91
XVIa	$C_{12}H_{11}NO_3$	267...269*2	8,35 (1H, s)	8,22 (1H, d)	7,63 (1H, t)	7,92 (1H, t)	7,83 (1H, d)	4,22	1,31	94
XVIb	$C_{12}H_{10}ClNO_3$	303...305*2	8,43 (1H, s)	8,13 (1H, s)	–	7,67 (2H, d)		4,25	1,32	89
XVIc	$C_{12}H_{10}ClNO_3$	253...254	8,43 (1H, s)	8,14 (1H, d)	7,43 (1H, t)	7,88 (1H, d)	–	4,23	1,29	83
XVId	$C_{12}H_{10}BrNO_3$	318...320	8,37 (1H, s)	8,23 (1H, s)	–	7,87 (1H, d)	7,58 (1H, d)	4,22	1,29	90
XVIe	$C_{12}H_9Cl_2NO_3$	280...282	8,44 (1H, s)	8,08 (1H, s)	–	7,95 (1H, d)	–	4,28	1,32	77

*Protons of the 4-OH groups appear in the form of singlet signals at 11.66-13.49 ppm. Protons of the COOH groups in the acids (XIV) appear in the form of singlet signals at 13.91-14.79 ppm.

*2Published data are as follows: melting temperatures are 269°C with decomp. for (XIVa), 261°C with decomp. for (XIVb), 269-270°C with decomp. for (XVIa), and >280°C for (XVIb) [21].

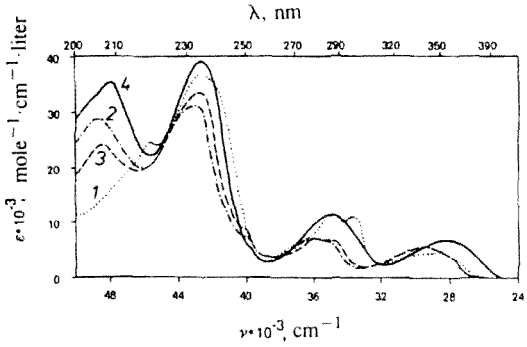

Fig. 1. Electronic absorption spectra in propan-2-ol. 1) Ester (I); 2) ester (V); 3) ester (VIII); 4) ester (IX).

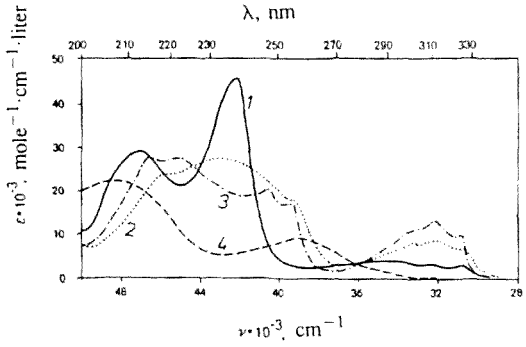

Fig. 2. Electronic absorption spectra in propan-2-ol. 1) Ester (II); 2) acid (XIII); 3) acid (XIVa); 4) ester (XVIIb).

The electronic absorption spectra proved to be most convenient and also sufficiently informative for the analysis of other structural changes presented in Scheme 1, since the spectra of compounds with the quinoline structure differ significantly in their characteristics from the spectra of 2-quinolones. It is known that 2,4-dichloroquinoline is hydrolyzed by 6 N HCl to 4-chlorocarbostyril [13]. Generalizing the data presented in the Scheme and in Figs. 1-3, it can be concluded that the acidic hydrolysis of the ethyl esters of 2,4-dichloro-, 2-oxo-4-chloro-, and 2-oxo-4-ethoxyquinoline-3-carboxylic acids, (II), (V, VIII), and (IV) respectively, leads to 2,4-dioxo derivatives (Xa, b), whereas the alkaline hydrolysis allows the preservation of the substituent at the positions 2 and 4 of the quinoline nucleus [the acids (XI) and (XII)] in most cases. An exception is the ester (II), which is hydrolyzed by the aqueous solution of KOH to the acid (XIII). The mass spectrum of this compound indicates the presence of one chlorine atom in the molecule [15]. The comparison of the data presented with the electronic absorption spectra of the acid (XIII) (Fig. 2) and its isomer — the acid (XIa) (Fig. 3) — allows the reliable interpretation of the product of the alkaline hydrolysis of the ester (II) as 2-chloro-4-hydroxyquinoline-3-carboxylic acid.

The interesting behavior of ethyl 2,4-dichloroquinoline-3-carboxylate (II) under conditions of reductive dehalogenation with copper in glacial acetic acid should also be noted. The resulting formation of 4-hydroxyquinoline-3-carboxylic acid (XIVa) appeared to be somewhat unexpected. A known and well studied method for the synthesis of such molecular systems is the Gould–Jacobs reaction [16], which we also utilized to confirm the structure of the acid (XIVa) by direct synthesis. The wider availability of the substituted anilines (XV) utilized in the synthesis of 3-ethoxycarbonyl-4-hydroxyquinolines (XVI) with the Gould–Jacobs reaction by comparison with the corresponding anthranilic acids allows the result obtained by us only to be considered in its own way as an alternative. At the same time, the reduction of the 1-R-2-oxo-4-chloroquinoline-3-carboxylates (V) and (VIII) by zinc in glacial acetic acid can be recommended as a preparative method for the synthesis of ethyl 1-R-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylates (XVII).

TABLE 2. Electronic Absorption Spectra of Some Quinoline-3-carboxylic Acids and Their Ethyl Esters in Propan-2-ol

Compound	$\nu \cdot 10^{-3}$, cm^{-1}	λ, nm	$\varepsilon \cdot 10^{-3}$, $mole^{-1} \cdot cm^{-1} \cdot liter$	Compound	$\nu \cdot 10^{-3}$, cm^{-1}	λ, nm	$\varepsilon \cdot 10^{-3}$, $mole^{-1} \cdot cm^{-1} \cdot liter$
I	45,7	219	24,4	XIa	48,4	207	27,9
	42,6	235	36,4		43,3	231	30,5
	34,9	287	11,4		40,2	249	8,2*
	33,6	298	10,9		36,3	275	6,7
	29,0	345	4,3		35,3	283	6,6
					29,6	338	5,5
II	47,1	212	29,3	XIb	48,4	207	25,0
	42,2	237	45,6		42,8	234	36,0
	35,2	284	3,8		40,2	249	9,9*
	33,8	296	3,6*		36,0	278	7,5
	32,2	311	2,9		35,0	286	7,2
	30,8	325	2,8		29,6	338	6,2
V	48,8	205	28,8	XIII	45,8	218	24,1
	43,0	233	31,4		43,0	233	27,5
	40,2	249	7,9*		39,4	254	18,2*
	36,3	275	7,3		33,2	301	8,0
	35,2	284	6,6*		32,0	313	8,7
	29,3	341	5,5		30,7	326	6,9
VIII	48,5	206	24,1	XIVa	46,6	216	27,9
	42,7	234	33,6		45,2	221	27,8
	40,2	249	9,0*		40,6	246	20,2
	36,0	278	7,0		39,4	254	17,3
	35,0	286	6,7		32,0	313	12,7
	29,4	340	5,4		30,9	324	9,9
IX	48,0	208	35,2	XVIIb	48,2	207	22,5
	42,7	234	39,0		39,0	256	9,1
	34,9	287	11,3		35,0	286	2,1
	28,2	355	6,6				

*Discontinuities are characterized on the spectrogram.

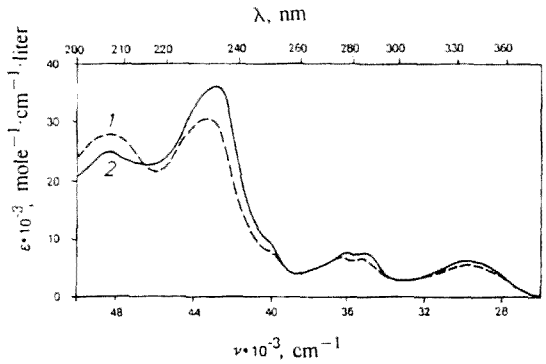

Fig. 3. Electronic absorption spectra in propan-2-ol. 1) XIa; 2) acid (XIb).

The comparison of the electronic absorption spectra presented in Table 2 and in Figs. 1-3 indicates that the conversion from the 2-quinolone system to the quinoline system is accompanied by a hypsochromic shift of the two first long-wave bands, and leads to a significant redistribution of the intensity of the absorption in the short-wave part of the spectrum. In the case of the esters (XVII), the spectra indicate the hydrogenation of the $C_{(3)}-C_{(4)}$ bond since they are essentially very close to the spectra of ethyl esters of malonanilic acids [17]. The mass spectra of the esters (XVII) are characterized by the ease of formation of the $[M-H]^+$ ions, for which the main direction of fragmentation is associated with the cleavage of the ethoxycarbonyl group; this determines the appearance of the $[M-H_2OC_2H_5]^+$ fragment ions and the peaks of maximal intensity due to the $[M-HCOOC_2H_4]^+$.

The s tudy of the antimicrobial activity of the compounds synthesized was performed by the method of twofold serial dilutions in Khottinger broth (pH 7.2-7.4) with the subsequent seeding onto a solid nutrient medium (beef–peptone agar) [18] in relation to the following test strains: *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922), *Pseudomonas aeruginosa* (ATCC 78857), and *Bacillus subtilis* (ATCC 6633). It follows from the results of the investigations carried out that 2-oxo-4-chloro and 2-chloro-4-hydroxyquinoline-3-carboxylic acids exhibit selective antimicrobial action toward *St. aureus*. The minimal concentration of the acids (XI) and (XIII) inhibiting the growth of the indicated test culture comprises 30 μg/ml. In the series of 4-hydroxy derivatives (XIV) and (XVI) (Table 1), higher activity is shown by the ethyl esters (XVI). However, *St. aureus* proved to be practically insensitive to them. The minimal concentration of the dichloro-substituted ester (XVIe) inhibiting growth in relation to *Ps. aeruginosa* comprised 60 μg/ml, and the minimal concentration in relation to the remaining test cultures comprised 30 μg/ml.

The antiinflammatory activity of the compounds synthesized, studied by the method of the work [19] using the model of carragenin edema with the peroral method of introduction, can be classified as weakly marked.

EXPERIMENTAL

The electronic absorption spectra were obtained on the Specord M-40 spectrometer using the solution of propan-2-ol (at 10^{-4}-10^{-3} M). The PMR spectra were recorded on the Bruker WP-100 SY instrument in DMSO-D_6 or $CDCl_3$ with TMS as the internal standard. The mass spectra were obtained on the Finnigan MAT-461 B instrument using the ionizing voltage of 70 eV and the ballistic heating of the sample.

The ethyl 2-oxo-4-hydroxyquinoline-3-carboxylates (I) and (VII) were obtained using the method previously developed by us [20]. The synthesis of the 4-hydroxyquinoline-3-carboxylic acids (XIV) and their ethyl esters (XVI) was accomplished by a known method [21].

The data of the elemental analysis for C, H, N, and halogen correspond with the calculated data.

Ethyl 2,4-Dichloroquinoline-3-carboxylate (II) ($Cl_2H_9Cl_2NO_2$). A. The solution of 2.33 g (0.01 mole) of the ester (I) in 15 ml of $POCl_3$ is boiled for 3 h. The excess of $POCl_3$ is distilled off at decreased pressure, and 20 ml of iced water are added to the residue prior to the neutralization with Na_2CO_3 solution. The residue of the ester (II) is filtered off, washed with water, and dried. The yield is 2.62 g (97%). The mp is 85-86°C (ethanol). The PMR spectrum ($CDCl_3$) is as follows: 8.23 ppm (1H, dd, J = 7.0 and 1.5 Hz, 5-H), 8.05 ppm (1H, dd, J = 7.2 and 1.8 Hz, 8-H), 7.84 ppm (1H, td, J = 6.5 and 1.8 Hz, 7-H), 7.68 ppm (1H, td, J = 7.0 and 1.5 Hz, 6-H), 4.55 ppm (2H, q, J = 7.0 Hz, $COOCH_2$), and 1.46 ppm (3H, t, J = 7.0 Hz, CH_3).

B. The solution of 2.75 g (0.01 mole) of the 4-acetoxy derivative (III) in 20 ml of $POCl_3$ is boiled for 3 h or held for 5 days at room temperature and treated by analogy with the procedure described for the method A. The yield is 2.59 g (96%).

C. By analogy with the method of the first experiment, 2.61 g (0.01 mole) of the 4-ethoxy derivative (IV) yield 2.53 g (93%) of the ester (II).

The identity of the samples of the ester (II), obtained by the different methods, is established by the absence of the depression of the melting temperature of the mixed samples, as well as from the PMR spectra.

2-Oxo-3-ethoxycarbonyl-4-acetoxyquinoline (III) ($C_{14}H_{13}NO_5$). A. To the solution of 11.66 g (0.05 mole) of the ester (I) and 4.05 g (0.05 mole) of pyridine in 30 ml of dry dioxane are added, with cooling and stirring, 3.7 ml (0.051 mole) of acetyl chloride. The mixture is left for 4-5 h. Water (100 ml) is added. The separated residue of the quinoline (III) is filtered off, washed with a solution of $NaHCO_3$ and with water, and dried. The yield is 9.87 g (72%). The mp is 166-168°C (ethanol). The PMR spectrum (DMSO-D_6) is as follows: 12.30 ppm (1H, s, NH), 7.69 ppm (2H, t, 5,7-H), 7.50-7.12 ppm (2H, m, 6,8-H), 4.30 ppm (2H, q, $\underline{CH_2}CH_3$), 2.43 ppm (3H, s, CH_3CO), and 1.28 ppm (3H, t, $CH_2\underline{CH_3}$).

B. The solution of 11.66 g (0.05 mole) of the ester (I) in 30 ml of acetic anhydride is boiled for 30 min. The excess of the Ac_2O is distilled off at reduced pressure. The residue is treated by the procedure given in the method A. The yield is 12.48 g (91%).

The mixed sample with the ester (III), obtained according to the method A, does not give a depression of the melting temperature.

Ethyl 2-Oxo-4-ethoxyquinoline-3-carboxylate (IV) ($C_{14}H_{15}NO_4$). To the solution of 2.51 g (0.01 mole) of ethyl 2-oxo-4-chloroquinoline-3-carboxylate (V) in 10 ml of abs. ethanol is added the solution of sodium ethoxide [from 0.46 g (0.02 mole) of metallic sodium and 10 ml of abs. ethanol], and the mixture is boiled for 2 h. The reaction mixture is cooled and

poured into water acidified with HCl (pH 4). The separated residue of the ester (IV) is filtered off, washed with a solution of Na_2CO_3 and then water, and dried. The yield is 2.04 g (78%). The mp is 174-176°C (ethanol). The PMR spectrum ($CDCl_3$) is as follows: 12.21 ppm (1H, s, NH), 7.92 ppm (1H, d, 5-H), 7.66-7.10 ppm (3H, m, 6,7,8-H), 4.48 ppm (2H, q, $\underline{CH_2}CH_3$), 4.36 ppm (2H, q, $\underline{CH_2}CH_3$), 1.49 ppm (3H, t, $CH_2\underline{CH_3}$), and 1.44 ppm (3H, t, $CH_2\underline{CH_3}$).

Ethyl 2-Oxo-4-chloroquinoline-3-carboxylate (V) ($C_{12}H_{10}ClNO_3$). To the solution of 2.7 g (0.01 mole) of the ester (II) in 15 ml of glacial AcOH is added 0.82 g (0.01 mole) of anhydrous AcONa, and the mixture is boiled for 10 h. The mixture is cooled prior to the addition of 100 ml of water. The residue of the ester (V) is filtered off, washed with water, and dried. The yield is 2.41 g (96%). The mp is 194-196°C (ethanol). The PMR spectrum (DMSO-D_6) is as follows: 12.44 ppm (1H, s, NH), 7.88 ppm (1H, d, J = 8.0 Hz, 5-H), 7.68 ppm (1H, td, J = 7.8 and 1.2 Hz, 7-H), 7.35 ppm (2H, m, 6,8-H), 4.34 ppm (2H, q, $\underline{CH_2}CH_3$), and 1.31 ppm (3H, t, $CH_2\underline{CH_3}$).

Ethyl 2-Benzylamino-4-chloroquinoline-3-carboxylate (VI) ($C_{19}H_{17}ClN_2O_2$). To the solution of 2.7 g (0.01 mole) of the ester (II) in 20 ml of methanol are added 2.14 g (0.02 mole) of benzylamine, and the mixture is boiled for 6 h. The mixture is cooled prior to the addition of 100 ml of water. The residue is filtered off, washed with water, and dried before the isolation of 2.35 g (69%) of the ester (VI). The mp is 180-182°C (aqueous ethanol). The R_f is 0.65 (Silufol UV-254, the 16:1 mixture of chloroform–propan-2-ol). The PMR spectrum (DMSO-D_6) is as follows: 8.46 ppm (1H, d, J = 8.0 Hz, 5-H), 8.09 ppm (1H, t, NH, it disappears on the addition of D_2O), 7.78 ppm (1H, d, J = 4.0 Hz, 8-Hz), 7.63 ppm (1H, t, J = 4.0 Hz, 6-H), 7.55 ppm (1H, t, J = 4.0 Hz, 7-H), 7.29 ppm (5H, s, H_{arom}, $CH_2C_6H_5$), 4.58 ppm (2H, s, NCH_2, the splitting of this signal into a doublet is observed in the solution of C_6D_6), 4.05 ppm (2H, q, J = 7.0 Hz, $\underline{CH_2}CH_3$), and 1.07 ppm (3H, t, J = 7.0 Hz, $CH_2\underline{CH_3}$).

Ethyl 1-Ethyl-2-oxo-4-chloroquinoline-3-carboxylate (VIII) ($C_{14}H_{14}ClNO_3$). This compound was synthesized by analogy with the synthesis of the ester (II) (A) with the yield of 83%. The mp is 81-83°C (ethanol). The PMR spectrum (DMSO-D_6) is as follows: 8.05 ppm (1H, d, 5-H), 7.78 ppm (2H, m, 7,8-H), 7.45 ppm (1H, t, 6-H), 4.39 ppm (2H, q, OCH_2), 4.32 ppm (2H, q, NCH_2), 1.31 ppm (3H, t, $OCH_2\underline{CH_3}$), and 1.24 ppm (3H, t, $NCH_2\underline{CH_3}$).

Ethyl 2-Oxoquinoline-3-carboxylate (IX) ($C_{12}H_{11}NO_3$). To the mixture of 1.21 g (0.01 mole) of anthranilic aldehyde and 1.60 g (0.01 mole) of diethyl malonate in 10 ml of propan-2-ol are added a few drops of piperidine, and the mixture is boiled for 2 h, and then it is held at room temperature for 8-10 h. The residue of the ester (IX) is filtered off, washed with ether, and dried. The yield is 1.54 g (71%). The mp is 160-161°C (ethanol); the published value for the mp is 163-164°C [22]. The PMR spectrum (DMSO-D_6) is as follows: 12.04 ppm (1H, s, NH), 8.51 ppm (1H, s, 4-H), 7.80 ppm (1H, d, J = 8.0 Hz, 5-H), 7.60 ppm (1H, t, J = 7.8 Hz, 7-H), 7.31 ppm (1H, d, J = 7.8 Hz, 8-H), 7.20 ppm (1H, t, J = 7.8 Hz, 6-H), 4.24 ppm (2H, q, CH_2), and 1.28 ppm (3H, t, CH_3).

General Method for the Acid Hydrolysis of Ethyl Esters of Quinoline-3-carboxylic Acids. The solution of 0.01 mole of the corresponding ethyl ester (II), (IV), (V), or (VIII) in 30 ml of 6 N HCl is boiled for 3 h. It is cooled prior to the addition of a solution of Na_2CO_3 to the pH ~3.5. The residue of the acid (X) is filtered off, washed with water, and dried. The yields are 74-90%. The known 2,4-dioxoquinoline-3-carboxylic acids (Xa, b) were identified from the melting temperature in mixed tests with known samples, as well as from the data of the PMR spectra [20].

2-Oxo-4-chloroquinoline-3-carboxylic Acid (XIa) ($C_{10}H_6ClNO_3$). The solution of 2.51 g (0.01 mole) of the ester (V) in 20 ml of the 10% aqueous solution of KOH is boiled until the solution of the residue is achieved (~2h). The solution is cooled prior to acidification with HCl to the pH 4. The residue of the acid (XIa) is filtered off, washed with water, and dried. The yield is 2.17 g (90%). The mp is 243°C (decomp., ethanol).

The following compounds were synthesized by analogous methods.

1-Ethyl-2-oxo-4-chloroquinoline-3-carboxylic Acid (XIb) ($C_{12}H_{10}ClNO_3$). The yield is 84%. The mp is 174-175°C (ethanol). The PMR spectrum (DMSO-D_6) is as follows: 14.70 ppm (1H, broad s, COOH), 8.07 ppm (1H, d, 5-H), 7.96-7.65 ppm (2H, m, 7,8-H), 7.44 ppm (1H, t, 6-H), 4.33 ppm (2H, q, $\underline{CH_2}CH_3$), and 1.24 ppm (3H, t, CH_3).

2-Oxo-4-ethoxyquinoline-3-carboxylic Acid (XII) ($C_{12}H_{11}NO_4$). The yield is 91%. The mp is 212-214°C (ethanol). The PMR spectrum (DMSO-D_6) is as follows: 13.74 ppm (1H, broad s, COOH), 12.07 ppm (1H, s, NH), 7.91 ppm (1H, dd, J = 7.9 and 1.8 Hz, 5-H), 7.64 ppm (1H, td, J = 7.2 and 1.7 Hz, 7-H), 7.38 ppm (1H, d, J = 7.9 Hz, 8-H), 7.28 ppm (1H, td, J = 7.2 and 1.3 Hz, 6-H), 4.32 ppm (2H, q, OCH_2), and 1.41 ppm (3H, t, CH_3).

2-Chloro-4-hydroxyquinoline-3-carboxylic Acid (XIII) ($C_{10}H_6ClNO_3$). The yield is 89%. The mp is 197°C (decomp., ethanol). The PMR spectrum (DMSO-D_6) is as follows: 12.41 ppm (1H, s, OH), 8.19 ppm (1H, d, J = 8.0 Hz, 5-H), and 7.90-7.20 ppm (3H, m, 6,7,8-H). The mass spectrum [m/z (relative intensity, %)] is as follows: 223 (29) $[M]^+$,

205 (100) $[M - H_2O]^+$, 179 (25) $[M - CO_2]^+$, and 170 (74) $[M - H_2OCl]^+$. Values of the m/z are only presented for the isotope ^{35}Cl.

4-Hydroxyquinoline-3-carboxylic Acid (XIVa). The mixture of 2.7 g (0.01 mole) of the ester (II) and 5 g of copper powder in 30 ml of glacial AcOH is boiled for 5 h. The mixture is cooled and filtered, and the residue is washed with alcohol. To the filtrate are added 50 ml of water, and the solution of KOH to the pH 8-8.5. The mixture is stirred and filtered. The filtrate is acidified with HCl to the pH ~ 3.5. The residue of the acid (XIVa) is filtered off, washed with water, and dried. The mass spectrum is as follows: 189 (33) $[M]^+$, 171 (56) $[M - H_2O]^+$, 145 (100) $[M - CO_2]^+$, and 117 (58).

The mixed test with the sample of the acid (XIVa) obtained by the method of the work [21] does not give a depression of the melting temperature. The electronic absorption spectra of these compounds were identical.

Ethyl 2-Oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (XVIIa) ($Cl_{12}H_{13}NO_3$). The mixture of 2.51 g (0.01 mole) of the ester (V) and 5 g of zinc dust in 30 ml of glacial AcOH is boiled with stirring for 5 h. The mixture is cooled and filtered, and the residue on the filter is washed with alcohol. The filtrate is evaporated to dryness under reduced pressure. The yield is 1.47 g (67%). The mp is 210-211°C (ethanol). The PMR spectrum (DMSO-D_6) is as follows: 10.36 ppm (1H, s, NH), 7.09 (1H, td, J = 7.0 and 1.3 Hz, 7-H), 6.85 ppm (1H, dd, J = 8.0 and 1.6 Hz, 5-H), 6.62 ppm (1H, td, J = 7.2 and 1.8 Hz, 6-H), 6.36 ppm (1H, dd, J = 7.4 and 1.5 Hz, 8-H), 3.93 ppm (2H, q, $COOCH_2$), 3.72 ppm (1H, s, 3-H), 3.25 ppm (2H, d, CH_2), and 0.93 ppm (3H, t, CH_3). The mass spectrum is as follows: 219 (38) $[M]^+$, 218 (92) $[M - H]^+$, 172 (73) $[M - H_2OC_2H_5]^+$, and 146 (100) $[M - HCOOC_2H_4]^+$.

Ethyl 1-Ethyl-2-oxo-1,2,3,4-tetrahydroquinoline-3-carboxylate (XVIIb) ($C_{14}H_{17}NO_3$). This compound was synthesized analogously with the yield of 63%. The mp is 127-129°C (hexane). The PMR spectrum (DMSO-D_6) is as follows: 7.21 ppm (1H, td, J = 6.8 and 1.3 Hz, 7-H), 6.96 ppm (1H, d, J = 8.0 Hz, 5-H), 6.78 ppm (1H, t, J = 7.0 Hz, 6-H), 6.47 ppm (1H, dd, J = 7.2 and 1.6 Hz, 8-H), 3.99 ppm (4H, q, $NCH_2{}^+COOCH_2$), 3.76 ppm (1H, s, 3-H), 3.31 ppm (2H, d, CH_2), 1.26 ppm (3H, t, $NCH_2\underline{CH_3}$), and 0.98 ppm (3H, t, $COOCH_2CH_3$). The mass spectrum is as follows: 247 (18) $[M]^+$, 246 (80) $[M - H]^+$, 200 (29) $[M - H_2OC_2H_5]^+$, and 174 (100) $[M - HCOOC_2H_4]^+$.

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