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4-HYDROXY-2-QUINOLONES. 176*. 4-R-2-OXO-1,2-DIHYDROQUINOLINE-3-CARBOXYLIC ACIDS. SYNTHESIS, PHYSICOCHEMICAL AND BIOLOGICAL PROPERTIES

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We have carried out the synthesis and a comparative analysis of the acidic properties of a large group of 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids. Features of the recorded NMR spectra of these compounds are discussed together with their analgesic properties.

Keywords: 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, p*K*a, analgesic activity, hydrolysis.

Even a brief glance at the scientific literature and patent documentation for 4-hydroxy-2-quinolones shows a very broad range of biological properties typifying them. In the series of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids the overwhelming number of publications relate to N-R-amides and the products of their subsequent chemical transformations. Esters have been studied much less frequently and the acids themselves hardly at all. Such a situation becomes fully understandable if one actually takes into account the diverse and well tested arsenal of highly efficient methods for synthesizing the amide derivatives [2-8]. Not least is the unlimited choice and availability of intermediate derivatives available from chemical industry in such syntheses in the form of primary or secondary alkyl-, aryl-, and hetarylamines. Thanks to this there is a real opportunity for a targeted change of properties of the N-R-amides obtained within very broad limits and so for achieving optimum properties. This is of particular value when carrying out work to create novel biologically active materials.

Quite a number of fundamentally different methods of preparing 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids esters are well known [2-6, 9-12]. However, all of these are only effective in relation to the lowest alkyl esters. In the reminder of the examples it is necessary to turn to special methods (e.g., high temperature transesterification [9]) but these are unfortunately characterized by low yields.

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* For Communication 175, see [1].

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TABLE 1. p*K*a Values in 80% Aqueous Dioxane and Biological Properties of 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic Acids **1-32**

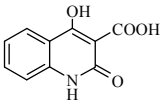
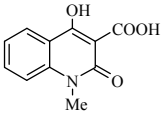
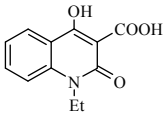
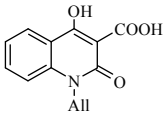
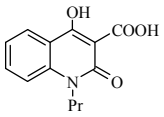
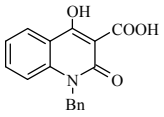
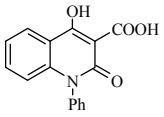
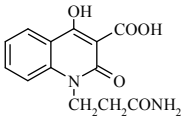
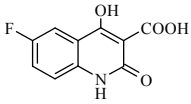
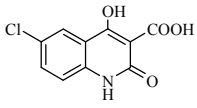
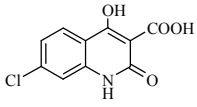
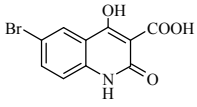
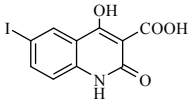
Com-pound*	Structural formula	pKa^{COOH}	pKa$^{4\text{-}OH}$	AE*[2]
1	2	3	4	5
1		7.16 ± 0.03	13.53 ± 0.06	34.1
2		7.49 ± 0.01	13.35 ± 0.08	28.6
3 [15]		7.53 ± 0.05	13.44 ± 0.05	13.9
4 [16]		7.30 ± 0.06	13.51 ± 0.10	14.4
5		7.61 ± 0.02	13.48 ± 0.03	7.8
6		7.15 ± 0.04	13.32 ± 0.08	17.2
7		6.91 ± 0.02	13.24 ± 0.01	17.0
8		7.06 ± 0.05	13.20 ± 0.06	77.3
9		6.87 ± 0.01	13.45 ± 0.11	10.4
10		6.76 ± 0.05	13.25 ± 0.06	7.2
11		Insoluble		13.8
12		6.69 ± 0.02	13.31 ± 0.15	69.1
13		6.63 ± 0.05	13.46 ± 0.11	34.6

TABLE 1 (continued)

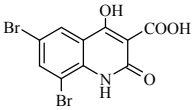
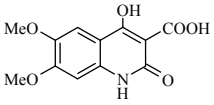
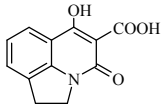
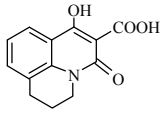
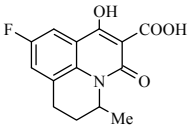
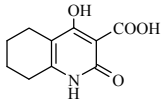
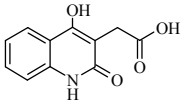
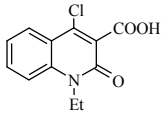
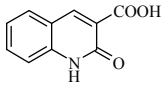
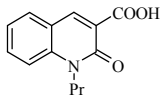
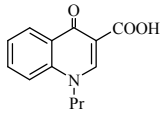
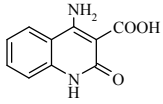
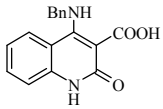
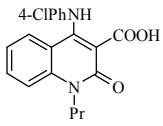
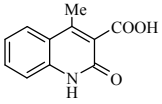
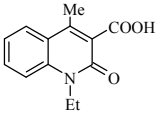
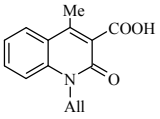
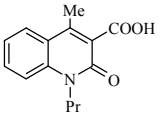
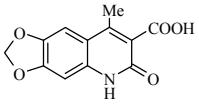
1	2	3	4	5
14		5.69 ± 0.08	13.20 ± 0.11	8.7
15		7.68 ± 0.07	13.60 ± 0.10	10.4
16 [15]		7.20 ± 0.03	13.47 ± 0.06	17.1
17		7.61 ± 0.03	13.48 ± 0.04	8.7
18 [3]		7.32 ± 0.08	13.41 ± 0.03	15.9
19 [17]		8.25 ± 0.01	13.67 ± 0.02	54.9
20 [13]		6.06 ± 0.05	11.65 ± 0.05	30.0
21 [18]		6.29 ± 0.05	—	8.7
22		8.74 ± 0.07	—	30.5
23		8.99 ± 0.01	—	21.2
24		10.92 ± 0.10	—	11.6
25 [19]		p*K*a > 14	—	52.4
26 [14]		p*K*a > 14	—	75.4
27 [14]		10.48 ± 0.05	—	19.6

TABLE 1 (continued)

1	2	3	4	5
28 [20]		7.15 ± 0.01	—	36.7
29 [21]		7.10 ± 0.01	—	33.4
30 [22]		6.95 ± 0.03	—	51.5
31 [21]		7.17 ± 0.03	—	15.6
32		7.70 ± 0.01	—	14.6
	Diclofenac	—	—	34.1
	Ketorolac	—	—	46.4
	Tramadol	—	—	57.2

* The indicated literature sources give the methods of synthesis and ^{1}H NMR spectra of the corresponding quinoline-3-carboxylic acids.

*[2] AE is the analgesic effect (increase in the pain threshold, %).

For the synthesis of the 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid itself only one route has practical value, i.e. ester hydrolysis. In addition, variants of the successful use of this, at first glance, trivial chemical conversion of esters to an acid are quite rare. Thus the generally used alkaline hydrolysis of esters in similar problems is here generally inapplicable. As is known, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids esters show unusually high reactivity towards N-nucleophiles but at the same time are extremely stable to the action of alkali metal hydroxides due to the formation of inert salts at the 4-OH group [13]. Hence base hydrolysis succeeds only after a marked increase in the reaction time and the hydrolysis is invariably accompanied by decarboxylation to give the 3H-derivatives [3, 9].

Acid hydrolysis gives the best results and the target products can be obtained after short heating of 3-ethoxycarbonyl-4-hydroxy-2-oxo-1,2-dihydroquinolines in concentrated HCl. The acids formed in this way are separated from the reaction mixture as crystalline precipitates which allows a visual monitoring of the course of the reaction. This method is, however, difficult to use for large batch sizes.

The reaction of quinoline-3-carboxylic acids esters with the 4-methoxyphenol anion under a nitrogen atmosphere is also not entirely successful [9]. The greatest drawback of this variant is the use of a large excess of NaH for generating the phenolate anion.

Based on the data reported above the most suitable method for the preparation of 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids can, in our opinion, be identified as the hydrolysis of the lowest alkyl esters using an approximately 2.8 M solution of HCl in acetic acid with low water content. This is prepared by mixing the calculated amounts of acetic anhydride and concentrated HCl [2]. The simplicity of the experiment carried out, the availability of the reagents used, the high yields, and the purity of the final products allows us to

recommend this as a preparative method. In fact we have used it in the synthesis of the 4-hydroxy-substituted acids **1-19** (Table 1). The single exception in this group is the 4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl acetic acid (**20**). By contrast with acids **1-19** this is markedly more stable towards decarboxylation and special conditions for its preparation are no longer needed [13]. Similar simple alkaline hydrolysis of esters of the corresponding 2-oxo-1,2-dihydro- or isomeric 4-oxo-1,4-dihydroquinoline-3-carboxylic acids also gave the 4-H-, 4-chloro, 4-oxo-1,4-dihydro, 4-amino-, and 4-methyl-substituted derivatives (Table 1). In the case of the 4-alkyl- and 4-arylamino derivatives **26** and **27** another synthetic scheme was used, i.e. the reaction of the corresponding alkylamines or anilines with 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [14].

The quinoline-3-carboxylic acids given in Table 1 are colorless, crystalline materials. With the exclusion of the quinolin-3-yl acetic acid **20** all of the 4-hydroxy-substituted derivatives **1-19** melt with decomposition (Table 2). These compounds are still less stable in solution and quite rapidly undergo decarboxylation, even at room temperature [16]. This feature must be kept in mind when working with solutions

TABLE 2. Characteristics of Certain 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic Acids

Compound	Empirical formula	Found, % / Calculated, %			mp, °C*	Yield, %
		C	H	N		
1	$C_{10}H_7NO_4$	58.68 / 58.54	3.56 / 3.44	6.75 / 6.83	—	93
2	$C_{11}H_9NO_4$	60.37 / 60.28	4.22 / 4.14	6.50 / 6.39	187 (dec)	88
5	$C_{13}H_{13}NO_4$	63.02 / 63.15	5.41 / 5.30	5.78 / 5.66	154 (dec)	85
6	$C_{17}H_{13}NO_4$	69.24 / 69.15	4.36 / 4.44	4.61 / 4.74	216 (dec)	90
7	$C_{16}H_{11}NO_4$	68.25 / 68.33	4.05 / 3.94	5.10 / 4.98	193 (dec)	94
8	$C_{13}H_{12}N_2O_5$	56.41 / 56.52	4.29 / 4.38	10.02 / 10.14	179 (dec)	96
9	$C_{10}H_6FNO_4$	53.73 / 53.82	2.83 / 2.71	6.35 / 6.28	—	86
10	$C_{10}H_6ClNO_4$	50.22 / 50.13	2.65 / 2.52	5.94 / 5.85	—	93
11	$C_{10}H_6ClNO_4$	50.20 / 50.13	2.66 / 2.52	5.92 / 5.85	—	91
12	$C_{10}H_6BrNO_4$	42.13 / 42.28	2.02 / 2.13	5.06 / 4.93	—	87
13	$C_{10}H_6INO_4$	36.36 / 36.28	1.95 / 1.83	4.10 / 4.23	—	90
14	$C_{10}H_5Br_2NO_4$	32.98 / 33.09	1.27 / 1.39	3.77 / 3.86	257 (dec)	96
15	$C_{12}H_{11}NO_6$	54.46 / 54.34	4.31 / 4.18	5.42 / 5.28	—	95
17	$C_{13}H_{11}NO_4$	63.74 / 63.67	4.63 / 4.52	5.84 / 5.71	141 (dec)	86
22	$C_{10}H_7NO_3$	63.60 / 63.49	3.85 / 3.73	7.33 / 7.40	335-337	93
23	$C_{13}H_{13}NO_3$	67.41 / 67.52	5.60 / 5.67	5.94 / 6.06	156-158	90
24	$C_{13}H_{13}NO_3$	67.44 / 67.52	5.58 / 5.67	5.91 / 6.06	149-151	92
32	$C_{12}H_9NO_5$	58.38 / 58.30	3.79 / 3.67	5.54 / 5.67	300-302	95

* Determination of the melting point in a capillary sealed at both ends the visual moment of decomposition of acids **1**, **9-13**, and **15** could not be observed.

of such compounds, in particular when recording their ^{1}H NMR spectra (Table 3). Thus, for example, many 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids are not very soluble in organic solvents including DMSO. However, heating above 50ºC should not be used for speeding up the solution of the samples. If not, the ^{1}H NMR spectra will identify singlet signals in the region 5.5-5.8 ppm due to the H-3 protons of the quinoline ring and indicate the occurrence of decarboxylation products in the solutions studied.

Of the remaining compounds **21-32** similar precautions would be superfluous in the work with the 4-amino-substituted acids **25-27**. They are rather more stable than the 4-hydroxy analogs and can undergo prolonged refluxing in ethanol without any kind of marked changes. However, in refluxing DMF they do undergo very ready decarboxylation [14].

TABLE 3. ^{1}H NMR Spectra of Certain 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic Acids

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1	15.83 (1H, br. s, 4-OH); 14.39 (1H, br. s, COOH); 12.95 (1H, s, NH); 8.02 (1H, d, *J* = 8.0, H-5); 7.79 (1H, t, *J* = 7.5, H-7); 7.47 (1H, d, *J* = 8.4, H-8); 7.39 (1H, t, *J* = 7.7, H-6)
2	15.80 (1H, br. s, 4-OH); 14.43 (1H, br. s, COOH); 8.17 (1H, d, *J* = 8.0, H-5); 7.91 (1H, t, *J* = 7.7, H-7); 7.81 (1H, d, *J* = 8.4, H-8); 7.47 (1H, t, *J* = 7.5, H-6); 3.63 (3H, s, NCH_3)
5	15.95 (1H, br. s, 4-OH); 14.47 (1H, br. s, COOH); 8.19 (1H, d, *J* = 8.1, H-5); 7.92 (1H, t, *J* = 7.8, H-7); 7.80 (1H, d, *J* = 8.3, H-8); 7.50 (1H, t, *J* = 7.5, H-6); 4.23 (2H, t, *J* = 7.1, NCH_2); 1.55 (2H, m, $NCH_2C\underline{H}_2$); 0.91 (3H, t, *J* = 7.3, CH_3)
6	15.77 (1H, br. s, 4-OH); 14.53 (1H, br. s, COOH); 8.18 (1H, dd, *J* = 7.9 and *J* = 1.5, H-5); 7.81 (1H, td, *J* = 7.8 and *J* = 1.8, H-7); 7.60 (1H, d, *J* = 8.6, H-8); 7.46 (1H, t, *J* = 7.5, H-6); 7.33-7.18 (5H, m, C_6H_5); 5.61 (2H, s, NCH_2)
7	15.53 (1H, br. s, 4-OH); 14.67 (1H, br. s, COOH); 8.28 (1H, dd, *J* = 7.9 and *J* = 1.3, H-5); 7.80 (1H, td, *J* = 7.9 and *J* = 1.5, H-7); 7.70-7.45 (6H, m, H-6 + C_6H_5); 6.76 (1H, d, *J* = 8.6, H-8)
8	15.60 (1H, br. s, 4-OH); 14.42 (1H, br. s, COOH); 8.15 (1H, dd, *J* = 8.1 and *J* = 1.4, H-5); 7.86 (1H, td, *J* = 7.7 and *J* = 1.6, H-7); 7.74 (1H, d, *J* = 8.3, H-8); 7.65 (1H, s, CONH); 7.43 (1H, t, *J* = 7.4, H-6); 7.18 (1H, s, CONH); 4.33 (2H, t, *J* = 7.7, NCH_2); 2.36 (2H, t, *J* = 7.8, $NCH_2C\underline{H}_2$)
9	14.10 (1H, br. s, 4-OH); 13.46 (1H, br. s, COOH); 11.64 (1H, s, NH); 7.79-7.66 (2H, m, H-5,7); 7.51 (1H, d, *J* = 8.3, H-8)
10	14.00 (1H, br. s, 4-OH); 13.12 (1H, br. s, COOH); 11.69 (1H, s, NH); 8.02 (1H, s, H-5); 7.83 (1H, d, *J* = 8.6, H-7); 7.49 (1H, d, *J* = 8.6, H-8)
11	14.32 (1H, br. s, 4-OH); 13.24 (1H, br. s, COOH); 11.66 (1H, s, NH); 8.04 (1H, d, *J* = 8.6, H-5); 7.44 (1H, d, *J* = 1.6, H-8); 7.40 (1H, dd, *J* = 8.6 and *J* = 1.6, H-6)
12	14.25 (1H, br. s, 4-OH); 13.10 (1H, br. s, COOH); 11.73 (1H, s, NH); 8.13 (1H, d, *J* = 1.7, H-5); 7.97 (1H, dd, *J* = 8.5 and *J* = 1.7, H-7); 7.43 (1H, d, *J* = 8.5, H-8)
13	14.20 (1H, br. s, 4-OH); 13.13 (1H, br. s, COOH); 11.68 (1H, s, NH); 8.26 (1H, s, H-5); 8.07 (1H, d, *J* = 8.6, H-7); 7.28 (1H, d, *J* = 8.6, H-8)
14	14.00 (1H, br. s, 4-OH); 13.02 (1H, br. s, COOH); 10.39 (1H, s, NH); 8.32 (1H, d, *J* = 2.0, H-5); 8.13 (1H, d, *J* = 2.0, H-7)
15	14.36 (1H, br. s, 4-OH); 12.61 (1H, br. s, COOH); 11.11 (1H, s, NH); 7.23 (1H, s, H-5); 6.88 (1H, s, H-8); 3.86 (3H, s, OCH_3); 3.82 (3H, s, OCH_3)
17	15.86 (1H, br. s, 1-OH); 14.41 (1H, br. s, COOH); 7.96 (1H, d, *J* = 7.9, H-10); 7.65 (1H, d, *J* = 7.2, H-8); 7.35 (1H, t, *J* = 7.7, H-9); 4.10 (2H, t, *J* = 5.7, NCH_2); 2.96 (2H, t, *J* = 5.9, 7-CH_2); 2.03 (2H, q, *J* = 5.7, 6-CH_2)
22	14.74 (1H, s, COOH); 13.17 (1H, s, NH); 8.96 (1H, s, H-4); 8.03 (1H, dd, *J* = 8.0 and *J* = 1.2, H-5); 7.76 (1H, td, *J* = 7.8 and *J* = 1.4, H-7); 7.49 (1H, d, *J* = 8.4, H-8); 7.38 (1H, td, *J* = 7.7 and *J* = 1.2, H-6)
23	14.54 (1H, s, COOH); 8.92 (1H, s, H-4); 8.08 (1H, dd, *J* = 8.0 and *J* = 1.3, H-5); 7.86 (1H, td, *J* = 7.9 and *J* = 1.3, H-7); 7.77 (1H, d, *J* = 8.2, H-8); 7.45 (1H, td, *J* = 7.3 and *J* = 1.3, H-6); 4.34 (2H, t, *J* = 7.6, NCH_2); 1.72 (2H, m, $NCH_2C\underline{H}_2$); 0.97 (3H, t, *J* = 7.4, CH_3)
24	14.33 (1H, s, COOH); 8.86 (1H, s, H-2); 8.35 (1H, d, *J* = 8.1, H-5); 7.93 (1H, d, *J* = 8.4, H-8); 7.84 (1H, t, *J* = 7.6, H-7); 7.53 (1H, t, *J* = 7.5, H-6); 4.44 (2H, t, *J* = 7.0, NCH_2); 1.78 (2H, m, $NCH_2C\underline{H}_2$); 0.88 (3H, t, *J* = 7.4, CH_3)
32	13.61 (2H, br. s, COOH + NH); 7.40 (1H, s, H-5); 6.85 (1H, s, H-8); 6.14 (2H, s, OCH_2O); 2.65 (3H, s, 4-CH_3)

The ionization constants of the compounds we have synthesized were determined by potentiometric titration and show that the 2-oxo-1,2-dihydroquinoline-3-carboxylic acids **22** and **23** unsubstituted in position 4 have rather weak acid properties although 100 times greater than in the 4-oxo-1,4-dihydro isomer **24** (Table 1). Introduction of a 4-hydroxy group into the molecule of a 4-hydroxy group (acid **1**) is characterized by an increase in the acid properties of the carboxyl group. All of the subsequent structural modifications carried out in the 4-hydroxy-substituted series of quinoline-3-carboxylic acids are basically accompanied by the anticipated effects. In particular, the saturated hydrocarbon radicals of different chain lengths on the nitrogen atom (acids **2**, **3**, **5**) show a weakening of the acidic dissociation with increase in chain length. The acidity with the N-allyl substituent (acid **4**) is also lower but not as markedly as the propyl and this might be explained by a hyperconjugative effect. On the other hand, the N-phenyl ring (acid **7**) which has electron-acceptor properties causes a marked increase in the dissociation of both ionogenic groups whereas this is fully removed by the isolating methylene unit in the N-benzyl-substituted acid **6**. At the same time, the activating effect of a carbamoyl group (acid **8**) cannot be suppressed, even by the length of the ethylene separating unit.

Halogen atoms in position 6 of the quinolone ring (acids **9-13**) increase the acidic properties of the COOH group in agreement with the values of the σ-constant for the substituents: p*K*a (I) < p*K*a (Br) < p*K*a (Cl) < p*K*a (F). An additional bromine atom (acid **14**) still further increases the effect while electron-donor methoxy groups (acid **15**) act in the opposite direction.

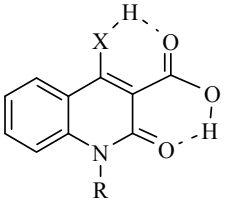
It was interesting to compare the dissociation constants (p*K*a) of the carboxyl group of the tricyclic pyrrolo- and pyrido[3,2,1-*ij*]quinoline carboxylic acids **16** and **17** with their alicyclic analogs containing the same number of carbon atoms in the N-alkyl substituent, i.e. the N-ethyl- and N-propyl-substituted derivatives **3** and **5** respectively. Whereas the reactivity of the carboxyl group with the smaller sized pyrrole ring is increased, the change from propyl derivative **5** to pyridoquinolone **17** has no effect.

Hydrogenation of the benzene part of the quinolone ring (acid **19**) is accompanied by an approximately tenfold lowering of the acidity of the COOH group but has little effect on the 4-OH group. It should be emphasized that the 4-OH group in the studied series of acids **1-19** shows little overall sensitivity to the both the nature and the position of the substituent in the quinolone ring.

Attention was turned in the group of 4-hydroxy-3-carboxylic acids to the anomalously high acidity of both reaction centers in the 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-ylacetic acid (**20**) when compared with its lower homolog **1**. It was found that the methylene unit isolating the carboxylic group from the quinolone ring not only does not lower but, in the opposite sense, actually increases the acidity of the COOH group by more than an order (Δ p*K*a = 1.1) and that of the 4-OH group by almost two orders (Δ p*K*a = 1.88).

As might be expected, a chlorine atom in position 4 (acid **21**) proves to have an effect similar to that of a 4-hydroxyl group whereas a 4-amino group (acid **25**) as an electron-donor group decreases the acidity of the COOH group so strongly that in could no longer be measured by the potentiometric titration method (limit of measurement p*K*a ~ 14). A benzyl substituent in the 4-amino group (acid **26**) does not change this situation and only an aryl fragment (e.g. the 4-chlorophenyl in acid **27**) leads to a marked increase in the acid dissociation of the carboxyl group.

At the same time a 4-methyl group shows a quite unexpected effect since it corresponds to the introduction of a hydroxyl, the acids **28** and **1** showing identical p*K*a values. This effect possibly results from the same kind of intramolecular hydrogen bond systems formed in the 4-methyl- and 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [21, 23] and [24, 25] respectively.



X = CH_2 or O

In the 4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl acetic acid (**20**) formation of a similar system of intramolecular hydrogen bonds is impossible in principle. This factor may be significantly responsible for the increase in acidic properties of both reaction centers of acid **20**, i.e. the ease with which they lose the 4-OH and COOH group protons.

An unusual effect which is difficult to explain unambiguously was found in studying the N-alkyl-substituted 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids **29-31**. By contrast with the 4-hydroxy analogs **3-5** reported above, in the case of N-alkyl substituents there is either observed no effect on the COOH dissociation or (e.g. for the N-allyl derivative **30**) it is anomalously increased. On the other hand, the annelation of the benzene fragment of the quinolone to a dioxole ring (acid **32**) is accompanied by a fully expected lowering of the acidic properties of the carboxyl.

Studies of the analgesic activity of acids **1-32** were carried out on nonpedigree, white, male rats on the model of the electric current stimulation of rectal mucosa (see Experimental). The experimental data obtained in this way indicates that, one hour after intraperitoneal introduction of the investigated compounds at a dose of 20 mg/kg, the pain sensitivity threshold was increased in all of the experimental animals by 7.2-77.3% when compared with the baseline value (Table 1). In other words, despite the marked differences in the strength of the observed effect, all of the acids **1-32** show analgesic effects without exception. Thus the first member of the group of 4-hydroxy derivatives (acid **1**) is no less active than diclofenac and the introduction of N-alkyl, benzyl, or phenyl substituents (acids **2-7**) leads to a marked fall in analgesic activity. At the same time, the carbamoylethyl derivative **8** exceeds in analgesic effect all of the comparators used by us including the narcotic analgesic Tramadol.

Modification of the benzene part of the 4-hydroxy-2-oxo-1,2-dihydroquinoline ring (acids **9-19**) is reflected negatively in biological activity in most cases. None the less, in this series highly active compounds can be found. Thus the 6-bromo-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (**12**) also shows a greater analgesic effect than Tramadol. However, an additional bromine atom at position 8 (acid **14**) eliminates activity almost completely.

The 4-hydroxy-2-oxo-1,2,5,6,7,8-hexahydro- and 1-allyl-4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids (**19** and **30** respectively) exceed the specific activity of the nonnarcotic analgesics Diclofenac and Ketorolac [26] and only fall a little short of Tramadol.

However, in our opinion, the greatest interest in all of the compounds synthesized by us amongst the 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids relates to the 4-amino derivatives **25** and especially **26**. Besides their high activity these compounds are very weak acids. Hence in contrast to Diclofenac and Ketorolac their potential medicinal use should not involve any kind of serious complications with respect to the gastrointestinal tract.

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Varian Mercury-VX-200 instrument (200 MHz) using DMSO-d_6 and with TMS as internal standard. Acid-base equilibria were studied by the method [27] using 80% aqueous dioxane as solvent. Fresh, twice distilled water freed from CO_2 and Labscan UV spectroscopy grade dioxane were used for the preparing of the mixed solvent. The titrant used was a 0.01 M aqueous KOH solution freed from CO_2. The concentration of the titrimetric solutions at half neutralization point was 0.5 mmol·l^{-1}. Potentiometric titration was carried out on a SevenEasy S-20-K Mettler Toledo pH meter using an InLab 4133 combined electrode at 25ºC. Titration for each compound was carried out in triplicate. The accuracy of the results obtained was calculated by mathematical statistics [28].

The starting ethyl 1R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylates were prepared by the methods in [29, 6], esters of quinoline-3-carboxylic acid substituted in the benzene part of the molecule by [11],

and ethyl 1-hydroxy-3-oxo-6,7-dihydro-3H,5H-pyrido[3,2,1-*ij*]quinoline-2-carboxylate by [6]. Synthesis of ethyl 1R-2-oxo-1,2-dihydro- and 4-oxo-1-propyl-1,4-dihydroquinoline-3-carboxylates and also their hydrolysis to acids **22-24** were carried out by a known method [18, 30] and ethyl 8-methyl-6-oxo-5,6-dihydro[1,3]dioxolo-[4,5-*g*]quinoline-7-carboxylate was prepared from the corresponding 2-aminoacetophenone (Aldrich) and then converted to acid **32** by a previously reported method [20].

Analgesic activity in the synthesized compounds was studied on the electric current model of rectal mucosa stimulation in rats [31]. Nonpedigree, white, male rates (six per compound studied) were placed in a narrow cage with a copper plate flooring serving as one electrode. The second electrode was introduced in the rectum and fixed to the tail. The threshold of pain sensitivity is determined as the lowest electric current strength causing pain sensations in the animal as shown by squeaking and/or removal of the foot from the floor. The acids **1-32** studied were introduced intraperitoneally at a dose of 20 mg/kg as a fine aqueous suspension stabilized by Tween-80. The comparator preparations Ketorolac (10 mg/kg) and Tramadol (25 mg/kg) were introduced intraperitoneally and diclofenac (10 mg/kg) orally as aqueous solutions. The starting indicators of pain sensitivity and its changes one hour after test substance administration were compared.

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