4-HYDROXY-2-QUINOLINES. 15.* SYNTHESIS OF N-(2-PYRIDYL)AMIDES OF 1-R-4-HYDROXY-2-QUINOLONE-3-CARBOXYLIC ACIDS AS POSSIBLE NEW NON-STEROIDAL ANTIINFLAMMATORY AGENTS

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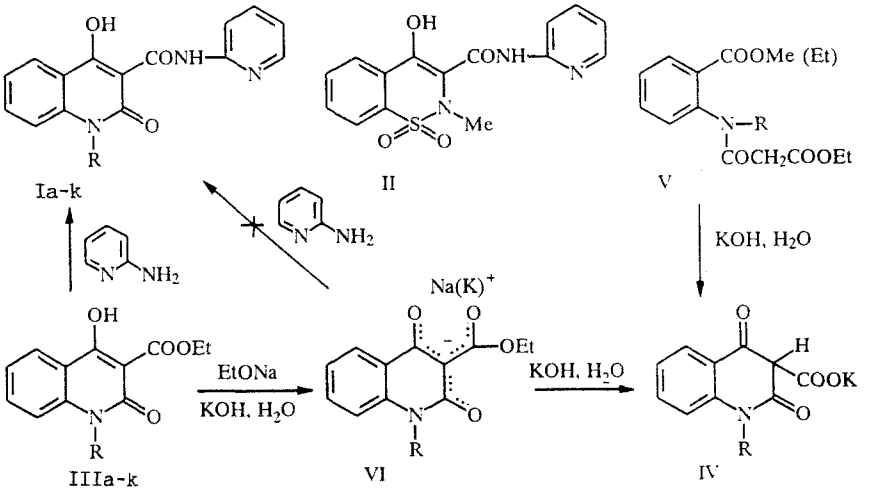
Different approaches to the reaction of ethyl 1-R-4-hydroxy-2-quinolone-3-carboxylates with 2-aminopyridine were studied. It was found that the most rational of them is the thermolysis of equimolar amounts of the amine and the corresponding ester. Data on the analgesic and antiinflammatory activity of the amides synthesized are presented.

Much attention is paid to the production and study of new antiinflammatory preparations and their introduction into medical practice, since inflammatory diseases are widespread, affect people of different ages (often with serious clinical manifestations), and are the cause of the partial or complete loss of the capacity for work [2].

The given communication, which is a continuation of our investigations into the synthesis and study of the biological properties of derivatives of 4-hydroxy-2-quinolones, was dedicated to 1-R-4-hydroxy-2-quinolone-3-carboxylic N-(2-pyridyl)amides (Ia-k) — structural analogs of the highly effective antiphlogistic pyroxikam (II) [2], presenting interest as potential antiinflammatory agents in pharmacological investigations.



Ia—k a R = H, b R = CH, c R = C_2H_5, d R = C_3H_7, e R = C_4H_9, f R = C_5H_{11}, g R = C_6H_{13}, h R = C_7H_{15}, i R = C_8H_{17}, j R = C_9H_{19}, k R = $C_{10}H_{21}$

*For Communication 14, see [1].

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TABLE 1. Characteristics of the Pyridyl-2-amides of 1-R-2-Oxo-4-hydroxyquinoline-3-carboxylic Acids (Ia-k)

Compound	Empirical formula	mp, °C	PMR spectrum, δ, ppm				Yield
			OH (1H, s)	NH (1H, s)	H_{arom} (8H, m)	R	
Ia	$C_{15}H_{11}N_3O_3$	302...304	16,11	12,96	8,48...7,16	12,17 (1H, s, NH)	96
Ib	$C_{16}H_{13}N_3O_3$	160...162	17,17	12,97	8,48...7,15	3,67 (3H, s, CH_3)	92
Ic	$C_{17}H_{15}N_3O_3$	173...174	16,19	13,00	8,46...7,14	4,36 (2H, q, NCH_2); 1,27 (3H, t, CH_3)	90
Id	$C_{18}H_{17}N_3O_3$	178...179	16,13	12,96	8,44...7,10	4,23 (2H, t, NCH_2); 1,67 (2H, m, CH_2CH_3); 0,97 (3H, t, CH_3)	88
Ie	$C_{19}H_{19}N_3O_3$	153...155	16,16	13,09	8,45...7,14	4,23 (2H, t, NCH_2); 1,55 (4H, m, $(CH_2)_2CH_3$); 0,95 (3H, t, CH_3)	89
If	$C_{20}H_{21}N_3O_3$	124...126	16,24	13,08	8,39...7,12	4,30 (2H, t, NCH_2); 1,64 (2H, q, NCH_2CH_2); 1,37 (4H, s, $(CH_2)_2CH_3$); 0,89 (3H, t, CH_3)	76
Ig	$C_{21}H_{23}N_3O_3$	120...121	16,20	13,01	8,40...7,14	4,29 (2H, t, NCH_2); 1,68 (2H, q, NCH_2CH_2); 1,33 (6H, s, $(CH_2)_3CH_3$); 0,87 (3H, t, CH_3)	84
Ih	$C_{22}H_{25}N_3O_3$	117...119	16,16	12,99	8,46...7,15	4,30 (2H, t, NCH_2); 1,65 (2H, q, NCH_2CH_2); 1,31 (8H, s, $(CH_2)_4CH_3$); 0,86 (3H, t, CH_3)	89
Ii	$C_{23}H_{27}N_3O_3$	110...111	16,21	13,04	8,47...7,12	4,31 (2H, t, NCH_2); 1,67 (2H, q, NCH_2CH_2); 1,27 (10H, s, $(CH_2)_5CH_3$); 0,84 (3H, t, CH_3)	90
Ij	$C_{24}H_{29}N_3O_3$	93...95	16,20	13,02	8,45...7,11	4,28 (2H, t, NCH_2); 1,61 (2H, q, NCH_2CH_2); 1,25 (12H, s, $(CH_2)_6CH_3$); 0,84 (3H, t, CH_3)	78
Ik	$C_{25}H_{31}N_3O_3$	102...103	16,13	13,03	8,43...7,10	4,27 (2H, t, NCH_2); 1,61 (2H, q, NCH_2CH_2); 1,24 (14H, s, $(CH_2)_7CH_3$); 0,84 (3H, t, CH_3)	92

In the study of alternative routes for the synthesis of N-R-substituted amides of 1H-4-hydroxy-2-quinolone-3-carboxylic acid [3], we noted that, in the case of the expensive amines, it is the most rational to subject the corresponding acid or its ethyl ester to amidation. However, the esters (III) are hydrolyzed to the corresponding salts of acids (IV) in fairly drastic conditions — the prolonged (up to 20 h) boiling with the aqueous solution of potassium hydroxide [4]. It can be seen that the inclusion of such a prolonged stage in the synthesis, which does not give any advantages subsequently, in the case of the amides (I) can hardly be considered expedient.

It is interesting that the ethyl esters of 2-carbalkoxymalonanilic acids (V) already form salts of quinolone-3-carboxylic acids (IV) after the boiling with aqueous solutions of alkalis for 4-5 h, and their treatment with aqueous ammonia at room temperature leads to 1-R-4-hydroxy-2-quinolone-3-carboxylic amides [5], whereas the esters (III) do not react in an aqueous medium with amines.

The ethyl esters (IIIa-k) may enter into the reaction with 2-aminopyridine under different conditions: the boiling in a suitable organic solvent or the thermolysis of the mixture of the corresponding ester and amine. The analysis of the results of the experiments performed shows that the last method is distinguished by its simplicity and the high yields of the final products (see Table 1), which allows it to be recommended as a preparative method. The accomplishment of the synthesis in alcohol is less effective since it requires the large expenditure of time and gives comparatively low yields.

It should be noted that alcoholates of alkali metals, which are frequently utilized as catalysts of amidation reactions [6], give the opposite effect in the synthesis of 2-oxo-4-hydroxyquinoline-3-carboxylic amides. It was shown that the resulting salts (VI) are quite inert in relation to amines. This is probably caused by the fact that the esters (III) form very stable carbanions by reaction with strong bases, since their anionic center is situated between three carbonyl groups [7]. Additional delocalization

of the charge and, consequently, an increase of stability as well are caused by low-reactive cations of alkali metals [8], as a result of which the carbanions indicated may be isolated in the form of potassium or sodium salts (VI) stable in the crystalline state [4].

In the aqueous solution, there appears one more external factor — the solvent, which also has a significant role in the stabilization of the ionic system (VI). It solvates ions of both signs, thereby leading to the further delocalization of charge [8]. It is probably just the hydration of the resulting carbanions which is the main obstruction to the amidation of the esters (III) in an aqueous medium, since this reaction proceeds without complications in alcohol.

In total, the delocalization of the negative charge in the salts (VI) leads to the situation that the nucleophilic attack at the carbonyl carbon atom of the ester grouping both by OH^- ions during hydrolysis, and by amines in the case of the formation of amides becomes difficult; this is also confirmed experimentally.

Additional evidence for the proposition above is the isolation of the mono- (and not the di-) potassium salt of 1-decyl-2,4-dioxo-3H-quinoline-3-carboxylic acid (IVk), which has low solubility in cold water, as the product of the alkaline hydrolysis of the ester (IIIk) [4]; this is evidently associated with the decrease in the activating influence of the ionized carboxyl group by comparison with the ester group [9].

The study of the analgesic (acetic spasms) and antiinflammatory (carragenin edema) activities of the amides (Ia-k) was conducted using methods of the works [10, 11]. Analysis of the experimental data obtained permitted the most marked antiexudative action to be noted for the amide (Ij), which is not inferior in its activity to pyroxikam and significantly surpasses the last in its analgesic action.

EXPERIMENTAL

The PMR spectra of the synthesized compounds were recorded on the Bruker WP-100 SY instrument (100 MHz) using DMSO-D_6 as the solvent and TMS as the internal standard.

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

General Method for the Synthesis of 1-R-4-Hydroxy-2-quinolone-3-carboxylic Pyridyl-2-amides (Ia-k). The mixture of 0.01 mole of the corresponding ethyl ester (III) and 0.94 g (0.01 mole) of 2-aminopyridine is maintained on a metallic bath at 150-160°C for 10 min. The reaction mixture is cooled and crystallized from DMF.

After the boiling of equimolar amounts of ethyl 1H-2-oxo-4-hydroxyquinoline-3-carboxylate (IIIa) and 2-aminopyridine in ethanol for 5 h, the amide (Ia) was obtained with the yield of 71%.

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