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4-HYDROXY-2-QUINOLONES. 3.* SYNTHESIS AND PHYSICOCHEMICAL PROPERTIES OF 1-R-3-CARBETHOXY-4-HYDROXY-2-QUINOLONES

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1-R-3-Carbethoxy-4-hydroxy-2-quinolones were synthesized by intramolecular cyclization of N-R-2-carbalkoxymalonanilic acids by the Dieckmann reaction. The possibility and advantages of conducting this reaction in aqueous medium were demonstrated. The mutually perpendicular orientation of the heterocyclic and aryl fragments was demonstrated for the 1-phenyl derivative by ESR spectroscopy.

There are now several versions of synthesis of 4-hydroxy-2-quinone-3-carboxylic acids and their derivatives, used to create many antimalarials [2-4]. 3-Carbethoxy-4-hydroxy-2-quinolone (Ia) was first prepared by heating methyl anthranilate with malonic ester in the presence of sodium ethylate in 1927 [5]. Compounds of this class were later synthesized by reducing cyclization of 2-nitrobenzoylmalonic esters [6] and by the reaction of cyanoacetic ester with an excess of anthranilic acid in dry pyridine [7].

Acylation of esters of the corresponding anthranilic acids with ethoxymalonyl chloride with subsequent intramolecular condensation of anilides (II) formed by the Dieckmann reaction, which takes place in the presence of basic catalysts in

*See [1] for Communication 2.

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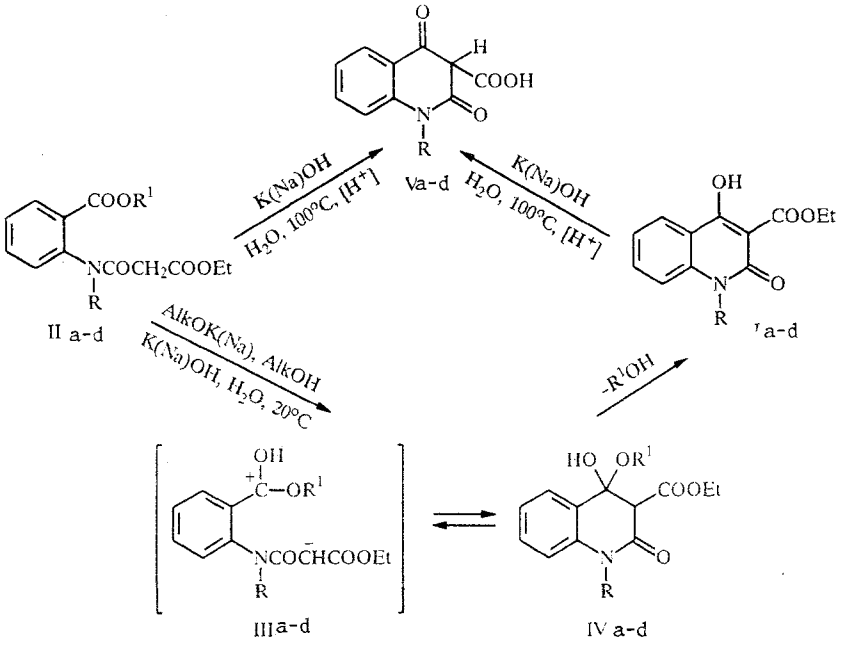
nonaqueous solvents during prolonged boiling of the reaction mixture, is probably the most convenient method of preparation of quinolones I, especially the N—R-substituted analogs [2, 5].

We found that esters II are cyclized into the corresponding quinolones I with high yields at room temperature (scheme). This reaction also takes place in aqueous medium with no complications, especially those related to hydrolysis of ester groups. In this case, the solvent effect plays an important role, since conversions take place more rapidly (by 10^4-10^9 times) with catalysts of interphase transfer in aqueous-organic two-phase systems than the corresponding "classic" reactions conducted in homogeneous medium. Substitution of the organic solvent by water increases the degree of solvation of intermediates (III) and consequently also the rate of ring closure with formation of intermediate hydroxy esters (IV).

The existence of five tautomeric forms is theoretically possible for esters I and the products of their saponification (V) due to realization of lactam—lactam and keto—enol tautomerism. Such compounds are either characterized as 4-hydroxy-2-quinolone [5, 6] or 2,4-dihydroxyquinoline derivatives [2, 7] in the literature. The study of the ESR spectra of synthesized esters Ia-d and acids Va-d (Tables 1 and 2) in a solution of DMSO-D_6 showed that the structure of the first corresponds to 4-hydroxy-2-quinolone, while the second exist in the 2,4-dioxo form.



I—V [a] R=H; b R=Me, c R=Et,d R=Ph; II—IV R^1=Me or Et

The signal of one of the aromatic protons in the ESR spectrum of ester Id (see Table 1) is observed in an abnormally strong field (6.47 ppm). The only proton for which such a strong diamagnetic shift is possible is the proton in position 8, which is exposed to the effect of the phenyl substituent at the nitrogen atom. A diamagnetic or a paramagnetic shift relative to the signals of the protons of model compounds having no aryl substituents can be observed for the 8-H signal as a function of the orientation of this substituent. The conformation of the N-aryl substituent can be judged by the magnitude of this shift [8]. A comparison with the ESR spectrum of ester Ib, for example (see Table 1), for which the signal of the 8-H proton is observed at 7.48 ppm, shows that the shift to the strong field for the 8-H signal of ester Id is 1.01 ppm. In constructing a molecular model of ester Id using the tables of Johnson and Bovey [8], it was found that the diamagnetic shift of the 8-H signal is 0.85 ppm, relatively close to the observed shift, when the planes of the heterocyclic fragment and N-aryl substituent have a mutually perpendicular orientation. The diamagnetic shift of this signal decreases in the case of the skewed conformation. For this reason, we can hypothesize that a mutually perpendicular orientation of these fragments occurs in the given case.

TABLE 1. Properties of 1-R-3-Carbethoxy-4-hydroxy-2-quinolones Ia-d

Compound	Empirical formula	Mp, °C	ESR spectrum,							Yield, %
			OH (1H, s)	H_{arom}				OCH_2 (2H, q)	OCH_2CH_3 (3H, t)	R	
				5-H (1H, t.d)	7-H (1H, t.d)	6-H (1H, t.d)	8-H (1H, d)				
Ia	$C_{12}H_{11}NO_4$	203...204**	13,45	7,95	7,63	7,22	7,31	4,37	1,33	11,53 (1H, s, NH)	95
Ib	$C_{13}H_{13}NO_4$	61...62	13,06	8,03	7,73	7,28	7,48	4,34	1,30	3,52 (3H, s, CH_3)	81
Ic	$C_{14}H_{15}NO_4$	66...68	13,05	8,08	7,78	7,30	7,56	4,34	1,25	4,22 (2H, q, NCH_2); 1,19 (3H, t, NCH_2CH_3)	78
Id	$C_{18}H_{15}NO_4$	178...179	13,38	8,10	7,78...7,12 (7H, m., 7-H, 6-H, Ph)		6,47	4,32	1,27	either 7-H or 6-H	98

*Compounds Ia, d were crystallized from ethanol and Ib, c were crystallized from aqueous methanol.

**According to [5], mp = 203-204°C.

TABLE 2. Properties of 1-R-2,4-Dioxo-3H-quinolone-3-carboxylic Acids Va-d

Compound	Empirical formula	Mp, °C	ESR spectrum, δ, ppm							Yield, %
			COOH (1H, s)	H_{arom}				3-H (1H, s)	R	
				5-H (1H, d.d)	7-H (1H, t.d)	6-H (1H, t.d)	8-H (1H, d)			
Va	$C_{10}H_7NO_4$	320...323	11,26	7,81	7,50	7,15	7,29	5,76	11,17 (1H, s, NH)	95
Vb	$C_{11}H_9NO_4$	268...269	11,33	7,90	7,64	7,23	7,46	5,88	3,53 (3H, s, CH_3)	89
Vc	$C_{12}H_{11}NO_4$	266...267	11,34	7,90	7,63	7,22	7,50	5,88	4,21 (2H, q, CH_2); 1,17 (3H, t, CH_3)	90
Vd	$C_{16}H_{11}NO_4$	297...299	11,64	7,93	7,73...7,11 (7H, m, 7-H, 6-H, Ph)		6,49	5,92	either 7-H or 6-H	97

*Compound Va was crystallized from DMF and the others were crystallized from ethanol. All compounds melted with decomposition.

EXPERIMENTAL

The ESR spectra of the synthesized compounds were recorded on a Bruker WP-100 SY (100 MHz) in DMSO-D_6 with TMS as the internal standard.

The data from elemental analysis of the synthesized compounds corresponded to the calculated data.

2-Carbethoxymalonanilic acid ether ester (IIa, $C_{14}H_{17}NO_5$). A solution of 1.66 g (0.011 mole) of ethoxymalonyl chloride [9] in 5 ml of acetone was added to a mixture of 1.65 g (0.01 mole) of ethyl anthranilate and 0.81 ml (0.011 mole) of pyridine in 10 ml of acetone and held for 5 h at room temperature. The solvent was then eliminated, 20 ml of water was added to the residue, and it was acidified with HCl to pH 3-4. The precipitated sediment of ester IIa was filtered off, washed with water, and dried,yielding 2.63 g (94%) of compound IIa. Colorless needles with mp = 53-54°C (diethyl ether). ESR spectrum: 10.80 (1H, s, NH), 8.24 (1H, d, J = 8.0 Hz, 3-H); 7.92 (1H, d. d, J = 7.8 and 1.8 Hz, 6-H); 7.60 (1H, t. d, J = 7.0 and 2.0 Hz, 5-H); 7.20 (1H, t. d, J = 7.8 and 2.0 Hz, 4-H); 4.33 (2H, q, Ar—$COOCH_2$); 4.14 (2H, q, CH_2COOCH_2); 3.58 (2H, s, $COCH_2CO$); 1.32 (3H, t, Ar—$COOCH_2CH_3$); 1.21 ppm (3H, t, $CH_2COOCH_2CH_3$).

N-phenyl-2-carbomethoxymalonanilic acid ethyl ester (IId, $C_{19}H_{19}NO_5$) was prepared analogously. Colorless prisms with mp = 104-105°C (methanol). ESR spectrum: 8.00-7.10 (9H, m, H_{arom}); 4.03 (2H, q, CH_2CH_3); 3.81 (3H, s, OCH_3); 3.31 (2H, s, $COCH_2CO$); 1.16 ppm (3H, t, CH_2CH_3). Yield of 76%.

Esters IIb, c were prepared analogously and were cyclized into the corresponding quinolones without separation from the reaction mixture.

3-Carbethoxy-4-hydroxy-2-quinolone (Ia). A solution of potassium *tert*-butylate (from 0.78 g (0.02 mole) of metallic potassium and 10 ml of *tert*-butanol] was added to a solution of 2.79 g (0.01 mole) of anilide IIa in 10 ml of absolute *tert*-butanol and left for 1 h. Then 100 ml of water was added to the reaction mixture, it was acidified to pH 4 with HCl, and the separated residue of ester Ia was filtered off, washed with water, and dried. Yield of 2.19 g (94%).

Ester Id was prepared analogously (solvent: methanol, basic catalyst: sodium methylate).

B. A solution of 1.12 g (0.02 mole) of KOH in 20 ml of water was added to 2.79 g (0.01 mole) of anilide IIa and stirred until the oily residue had totally dissolved (~30 min). The reaction mixture was subsequently acidified with HCl to pH 4, and the separated sediment of ester Ia was filtered off and dried. Yield of 2.21 g (95%). The mixed sample with ester Ia prepared by method A did not depress the melting point.

Compounds Ib and c were synthesized analogously.

2,4-Dioxo-3H-quinoline-3-carboxylic acid (Va). **A.** Here 2.33 g (0.01 mole) of ester Ia and 1.68 g (0.03 mole) of KOH in 20 ml of water were boiled with a reflux condenser for 10 h. The reaction mixture was treated as described above for method B after cooling, and 1.96 g (96%) of acid Va was obtained.

Compounds Vb-d were prepared analogously.

B. Here 1.90 g (93%) of acid Va was obtained from 2.79 g (0.01 mole) of anilide IIa with the method in the preceding experiment. Mixed samples of acids Va prepared by different methods did not depress the melting point.

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4-HYDROXY-2-QUINOLONES. 4.* SELECTION OF THE OPTIMUM PATH FOR SYNTHESIS OF N—R-SUBSTITUTED 4-HYDROXY-2-QUINOLONE-3-CARBOXYLIC ACID AMIDES

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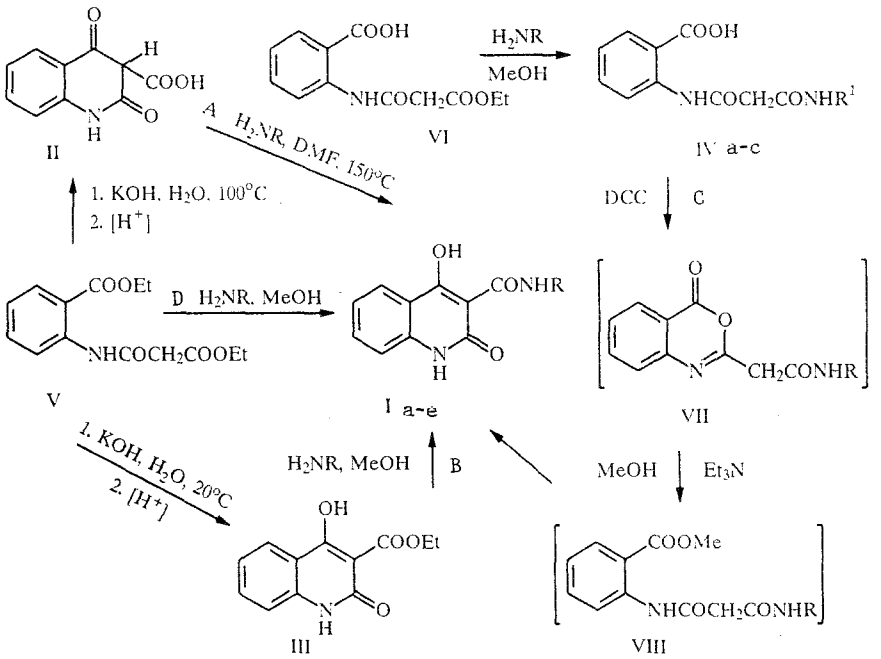
A comparison of several methods of preparation of N—R-substituted 4-hydroxy-2-quinolone-3-carboxylic acid amides showed that intramolecular cyclization of 2-carbalkoxymalonanilic acid ethyl esters with simultaneous amidation is the most rational method.

4-Hydroxy-2-quinolone-3-carboxylic acids and their derivatives are direct analogs of the 3-substituted 4-hydroxy-2-quinolones very common in nature [2]. However, their chemical and pharmacological aspects have virtually not been investigated up to now.

The present study is a continuation of our previous research and concerns N—R derivatives of 4-hydroxy-2-quinolone-3-carboxylic acid amide (I), a promising group for searching for biologically active substances.

Scheme



I—VIIIa R=H, b R=Me, c R=Et, d R=Pr, e R=Bu

*See [1] for Communication 3.

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