9. P. A. Bezuglyi, V. I. Treskach, I. V. Ukrainets, S. V. Gritsenko, N. V. Garnaya, V. A. Grud'ko, and N. Yu. Bevz, USSR Inventor's Certificate No. 1,474,159; Byull. Izobr., No. 15 (1989).

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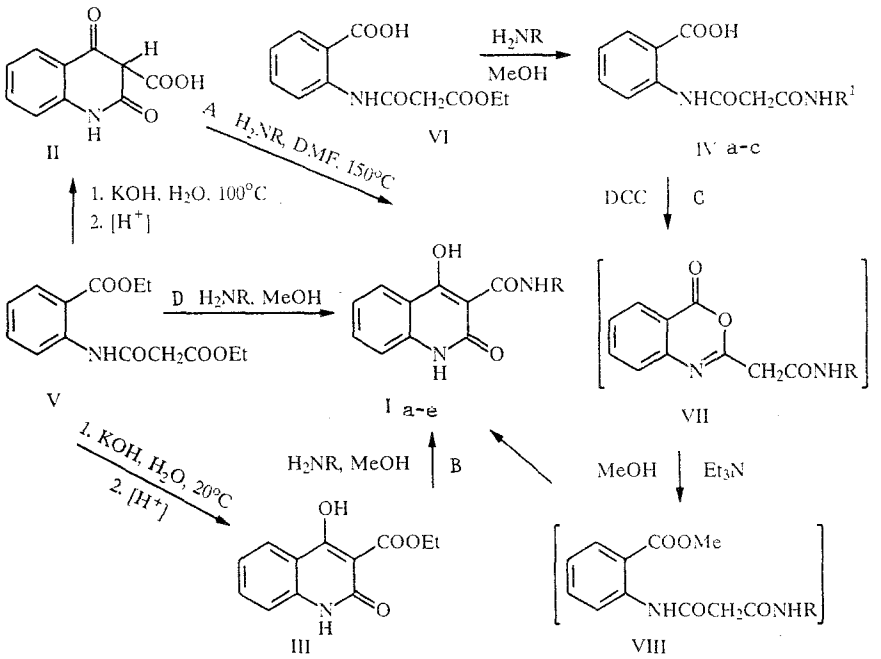
A comparison of several methods of preparation of N—R-substituted 4-hydroxy-2-quinolone-3-carboxylic acid amides showed that intramolecular cyclization of 2-carbalkoxymalonanilic acid ethyl esters with simultaneous amidation is the most rational method.

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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TABLE 1. Properties of Compounds Ia-e

Compound	Empirical formula	Mp, °C (from dioxane)	ESR spectrum, δ, ppm				Yield for methods A-D,** %			
			OH (1H, s)	NHcycl (1H, s)	NH—R (1H)	R	A	B	C	D
Ia	$C_{10}H_8N_2O_3$	306...308	17,71	11,75	9,62s	8,52 (1H, s, NH)	91	93	92	93
Ib	$C_{11}H_{10}N_2O_3$	258...260	17,36	11,82	10,15d	2,94 (3H, d, CH_3)	89	91	90	90
Ic	$C_{12}H_{12}N_2O_3$	250...251	17,37	11,80	10,24t	3,36 (2H, quin CH_2CH_3); 1,18 (3H, t, CH_3)	88	90	78	88
Id	$C_{13}H_{14}N_2O_3$	209...210	17,35	11,80	10,33t	3,37 (2H, q, NCH_2); 1,61 (2H, m, CH_2CH_3); 0,95 (3H, t, CH_3)	92	93	—	94
Ie	$C_{14}H_{16}N_2O_3$	183...184	17,36	11,81	10,31t	3,36 (2H, q, NCH_2); 1,46 (4H, m, $CH_2CH_2CH_3$); 0,92 (3H, t, CH_3)	91	88	—	92

*Signals of 5-H aromatic protons (d. d) in the region of 7.94-7.97; 6-H (t. d): 7.24-7.32; 7-H (t. d): 7.63-7.70; 8-H (d): 7.36-7.41 ppm.

**The yields are reported in conversion to diester V for methods A, B, and D and for acid ester VI for method C.

We investigated several versions of their preparation (scheme) to select the best method of synthesizing the compounds in this group: A: amidation of acid (II), B: amidation of its ethyl ester (III), C: intramolecular cyclization of amides (IV); D: intramolecular cyclization of 2-carbethoxymalonanilic acid ethyl ester (V) with simultaneous amidation.

The analysis of the scheme and results in Table 1 shows that only one of the methods examined, method D, where alkylamines are simultaneously used as the basic catalysts and amidating agents, can be used to synthesize the target substances according to a relatively simple scheme at minimum cost and can be recommended as preparative.

Method C, which eliminates preliminary preparation of anthranilic acid esters with very low yields, is also of definite interest [3]. The use of unavailable dicyclohexylcarbodiimide (DCHC) is the only disadvantage of this method.

Methods A and B, which imply separation of quinolinecarboxylic acid II or its ethyl ester III are only justified when expensive amines are used.

EXPERIMENTAL

The IR spectra of the synthesized compounds were made on a Specord IR-75 in KBr pellets, 1% concentration. The ESR spectra were recorded on a Bruker WP-100 SY (100 MHz) in DMSO-D_6, TMS internal standard.

The data from elemental analysis (C, H, N) of compounds Ia-e correspond to the calculated values.

2,4-Dioxo-3H-quinoline-3-carboxylic acid (II) and 2-carbethoxymalonanilic acid ethyl ester (V) were synthesized by the method in [1], and **2-carboxymalonanilic acid ethyl ester (VI)** was synthesized by the method in [4]. **R-Amides IVa-c** were prepared with the previously elaborated method in [5].

2-Carboxymalonanilic acid ethylamide (IVc, $C_{12}H_{14}N_2O_4$). Mp = 214-215°C (ethanol). IR spectrum: 1685 (C=O); 2400-2660 cm^{-1} (COOH dimer). ESR spectrum: 11.28 (1H, s, AR—NH); 8.51 (1H, d, J = 8.0 Hz, 3-H); 8.20 (1H, t, NH—Et); 7.99 (1H, d.d, J = 7.2 and 1.7 Hz, 6-H); 7.59 (1H, t. d, J = 7.0 and 1.8 Hz, 5-H); 7.16 (1H, t. d, J = 7.0 and 1.4 Hz, 4-H); 3.32 (2H, s, $COCH_2CO$); 3.13 (2H, q, CH_2CH_3); 1.05 ppm (3H, t, CH_3). Yield of 84%.

4-Hydroxy-2-quinolone-3-carboxylic acid R-amides (Ia-e). A. A solution of 2.05 g (0.01 mole) of acid II in 15 ml of DMF was saturated with dry ethylamine, boiled with a reflux condenser for 30 min, then cooled and poured into water acidified with HCl (pH 3-4). The separated sediment of ethylamide Ic was filtered off, washed with water, and dried.

Compounds Ia and b were prepared analogously, and amides Id and e were prepared by the reaction of acid II with an equimolar amount of the corresponding amine.

B. A solution of 2.33 g (0.01 mole) of ester III in 15 ml of methanol was saturated with ethylamine and held for 24 h at room temperature. After the usual treatment, amide Ic was obtained.

Amides Ia and b were prepared analogously, and compounds Id and e were prepared by boiling ester III with the amines in dioxane for 5 h.

C. Here 2.06 g (0.01 mole) of DCHC was added to a solution of 2.50 g (0.01 mole) of amide IVc in 50 ml of dry CH_2Cl_2. The mixture obtained was boiled for 2 h with a reflux condenser, and the solvent was eliminated. Then 30 ml of absolute methanol and 5 ml of triethylamine were added to the residue and boiled with a reflux condenser for 10 h. Then 15 ml of methanol was distilled off, the residue was poured into a solution of 1.12 g (0.02 mole) of KOH in 50 ml of water, the mixture was stirred, and dicyclohexylurea was filtered off. It was washed with water and used in synthesis of DCHC after recrystallization from ethanol [6]. The filtrate was acidified with HCl to pH 3-4, and the precipitated sediment of amide Ic was filtered off, washed with water, and dried.

Compounds Ia and b were synthesized analogously.

D. A solution of 2.79 g (0.01 mole) of diester V in 15 ml of methanol was saturated with ethylamine, and the reaction mixture was held for 50 h at room temperature while stirring periodically. Amide Ic was separated as described above.

Compounds Ia and b were prepared analogously, and amides Id and e were prepared by boiling diester V with the corresponding amines in methanol for 5 h.

The identity of the samples of each product synthesized by the different methods was established with the melting points of mixed samples.

LITERATURE CITED

1. I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, A. V. Turov, and S. V. Slobodzyan, Khim. Geterotsikl. Soedin., No. 5, 636 (1992).
2. M. Lukner, Secondary Metabolism in Microorganisms, Plants, and Animals [Russian translation], Mir, Moscow (1979).
3. A. E. Agronomov and Yu. S. Shabarov, Laboratory Work in Practical Organic Chemistry [in Russian], Khimiya, Moscow (1974), p. 75.
4. P. A. Bezuglyi, V. I. Treskach, and I. V. Ukrainets, USSR Inventor's Certificate No. 1,467,052; Byull. Izobr., No. 11 (1989).
5. P. A. Bezuglyi, B. A. Samura, V. I. Treskach, I. V. Ukrainets, S. V. Shaporenko, and A. I. Maslennikov, KhGFI (Khar'kov State Pharmaceutical Institute) [in Russian], Moscow (1987); submitted to TsBNTIMedprom, No. 4 MP (May 26, 1987).
6. G. Amiard and R. Heymes, Bull. Soc. Chim. France, No. 10, 1360 (1956).