4-HYDROXY-2-QUINOLONES. 6.* SYNTHESIS, CHEMICAL TRANSFORMATIONS, AND BIOLOGICAL PROPERTIES OF DIALKYLAMINO-, HYDROXY-, AND HALODIALKYLAMIDES OF 4-HYDROXY-2-QUINOLONE-3-CARBOXYLIC ACIDS

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We suggest a preparative method for the synthesis of dialkylaminoalkylamides of 4-hydroxy-2-quinolone-3-carboxylic acids, their hydrochlorides, and haloalkylates. We developed a simple and effective means of obtaining the halopropylamides of the indicated acids. Data on biological studies of the synthesized compounds is provided.

Earlier [2], we showed the possibility of making new anesthetic materials based upon the hydrochlorides of dialkylaminoalkylamides of 1-R-4-hydroxy-2-quinolone-3-carboxylic acids. However, it was found that the method of isolation and purification of these compounds given in the indicated work has a series of significant deficiencies, the foremost of which is a significant decrease in yield of 1-alkyl-4-hydroxy-2-quinolone-3-carboxylic acid derivatives because of their high solubility in aqueous alcohol and the presence of water of crystallization in the products.

In the present study we suggest other means of purifying compounds of this type and propose the preliminary isolation of dialkylaminoalkylamides — structure I, which then may be transformed into the hydrochloride II or the haloalkylates III under conditions excluding the formation of crystalline hydrates.

Taking into account the high stability of the dialkylaminoalkylamides, we undertook the synthesis of amide I with the use of more low-cost and accessible reagents. However, the aminolysis of the chloralkylamide IV, easily obtainable from the corresponding hydroxyalkylamide V did not give a satisfactory result. Instead of the expected amide I we obtained the oxazocyclo-fused quinoline VI, which proved to be an extremely valuable intermediate in the synthesis of bromo- and iodopropylamides of the 4-hydroxy-2-quinolone-3-carboxylic acids (VIIa, b). In contrast to the Finkelstein reaction [3], which did not produce the expected result of generating amide VII, the indicated procedure achieved the substitution of chlorine in amide IV by bromine or iodine in practically quantitative yields.

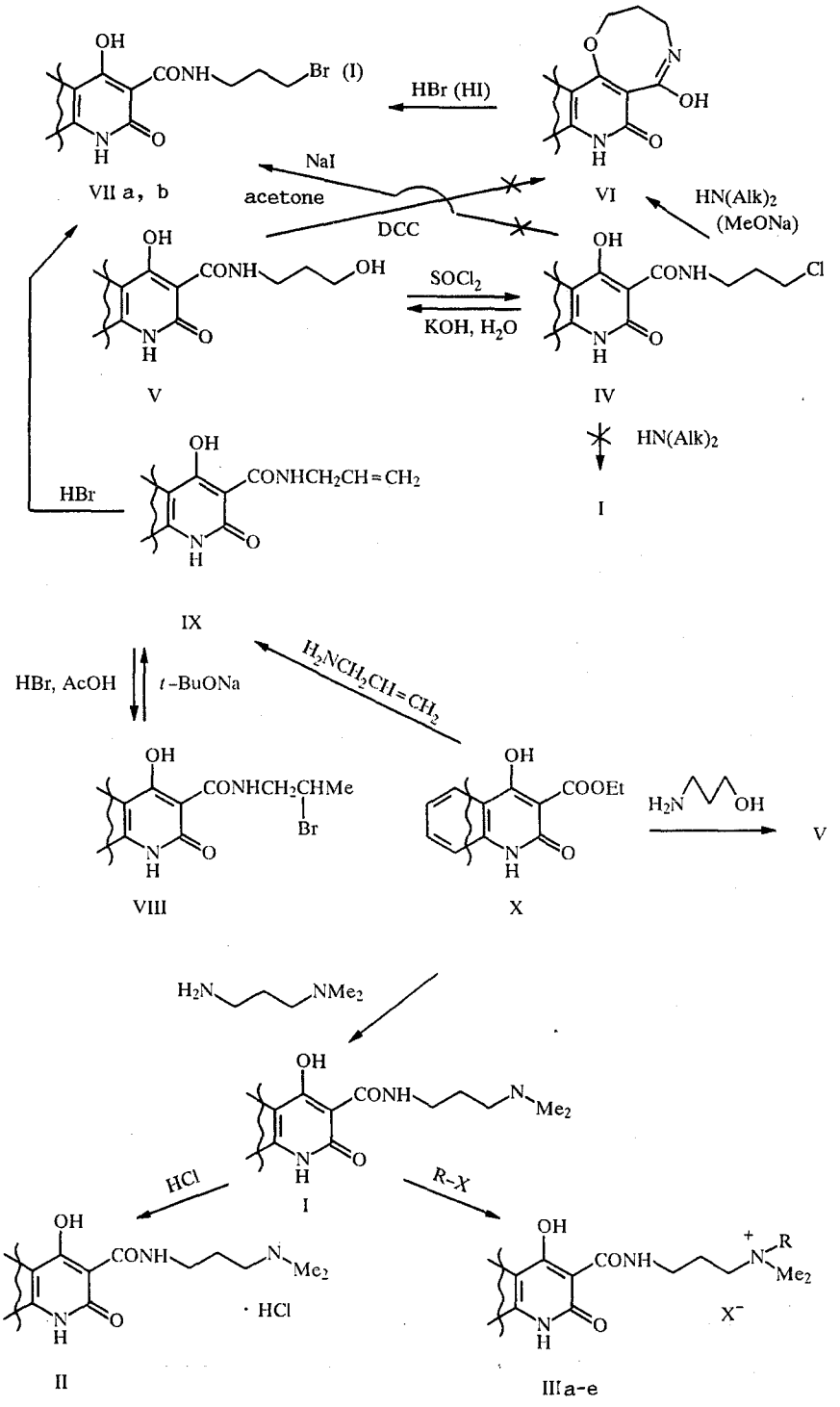
It is of interest that upon treatment of chloroamide IV with equimolar quantity of potassium hydroxide in water, the oxazocyclo-fused quinoline VI was not formed. The ineffectiveness of dicyclohexylcarbodiimide for the synthesis of this material also was shown (See Scheme).

The 2-bromopropylamide of 4-hydroxy-2-quinolone-3-carboxylic acid (VIII), obtained by the ionic addition of HBr to the allylamide IX, did not form the corresponding oxazocyclo-fused quinoline. Treatment of this compound with sodium *tert*-butylate was accompanied by the elimination of HBr in conformation with the Hofmann rule [4], i.e., with the formation of the starting allylamide IX.

*For Communication 5, see [1].

Kharkhov Pharmaceutical Institute, Kharkhov 310002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 100-104, January, 1993. Original article submitted November 29, 1991.

0009-3122/93/2901-0087$12.50



The structural resemblance to the preparations in the 4-hydroxycoumarin series [5] serves as theoretical basis for a study of the influence of the synthesized compounds on the coagulating system of the blood. Investigations conducted according to our earlier-described method [6] indicated the procoagulant effect of allylamide IX, while amides I and III-V manifested weakly significant anticoagulant action. Interesting results have been obtained in an investigation of the influence of the synthesized compounds on the excretory function of the kidneys, carried out according to [7]. Thus, the hydroxypropyl amide V showed diuretic action compared with the activity of hypothiazide (hydrochlorthiazide), presently used in medical practice, which is not characteristic for the given class of compounds. The property of this same material to suppress convulsions elicited by korazole (pentylenetetrazole) [8] is not inferior to Midokalm with lower toxicity. The haloalkylates IIIa-e, showed significant and selective bactericidal action in *in vitro* experiments with respect to *Staphylococcus aureus* (ATCC 25923), discovered in a long-range search for potential antimicrobial drugs.

TABLE 1. Characteristics of the N-R-Derivatives of Amides of 4-Hydroxy-2-quinolone-3-carboxylic Acids

Compound	Empirical formula	mp, °C	^{1}H NMR spectra (signals for the alkylamide residue), ppm*	
I	$C_{15}H_{19}N_3O_3$	142...144	3,40 (2H, q, $NHC\underline{H}_2$); 2,35 (2H, t, $NHCH_2CH_2C\underline{H}_2$); 2,15 (6H, s, CH_3); 1,68 (2H, qv $CH_2C\underline{H}_2CH_2$)	92
II	$C_{15}H_{19}N_3O_3 \cdot HCl$	220...222**	11,03 (1H, s, ^+NH); 3,48 (2H, q., $NHC\underline{H}_2$); 3,11 (2H, qv, $NHCH_2CH_2C\underline{H}_2$); 2,77 (6H, s, CH_3); 2,02 (2H, qv, $CH_2C\underline{H}_2CH_2$)	99
IIIa	$C_{16}H_{22}IN_3O_3$	278...280	3,42 (4H, m, $NC\underline{H}_2CH_2C\underline{H}_2$); 3,08 (9H, s, CH_3); 1,90 (2H, qv, $CH_2C\underline{H}_2CH_2$)	97
IIIb	$C_{17}H_{24}ClN_3O_3$	138...140	3,41 (6H, m, $NC\underline{H}_2CH_2C\underline{H}_2NC\underline{H}_2CH_3$); 3,02 (6H, s, CH_3); 2,04 (2H, qv, $CH_2C\underline{H}_2CH_2$); 1,25 (3H, t, $CH_2C\underline{H}_3$)	84
IIIc	$C_{17}H_{24}BrN_3O_3$	198...200	3,33 (6H, m, $NC\underline{H}_2CH_2C\underline{H}_2NC\underline{H}_2CH_3$); 3,01 (6H, s, CH_3); 1,98 (2H, qv, $CH_2C\underline{H}_2CH_2$); 1,23 (3H, t, $CH_2C\underline{H}_3$)	90
IIId	$C_{17}H_{24}IN_3O_3$	208...210	3,35 (6H, m, $NC\underline{H}_2CH_2C\underline{H}_2NC\underline{H}_2CH_3$); 3,00 (6H, s, CH_3); 2,00 (2H, qv, $CH_2C\underline{H}_2CH_2$); 1,23 (3H, t, $CH_2C\underline{H}_3$)	93
IIIe	$C_{18}H_{26}IN_3O_3$	214...216	3,32 (6H, m, $NC\underline{H}_2CH_2C\underline{H}_2NC\underline{H}_2CH_2CH_3$); 3,01 (6H s, CH3); 2,01 (2H, qv, $CH_2C\underline{H}_2CH_2$); 1,67 (2H, m, $CH_2C\underline{H}_2CH_3$); 0,90 (3H, t, $CH_2CH_2C\underline{H}_3$)	87
IV	$C_{13}H_{13}ClN_2O_3$	200...202	3,54 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$); 2,03 (2H, qv, $CH_2C\underline{H}_2CH_2$)	96
V	$C_{13}H_{14}N_2O_4$	211...212	4,61 (1H, t, $CH_2O\underline{H}$); 3,43 (4H, m, $NC\underline{H}_2CH_2C\underline{H}_2$); 1,73 (2H, qv, $CH_2C\underline{H}_2CH_2$)	96
VIIa	$C_{13}H_{13}BrN_2O_3$	178...179	3,50 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$); 2,12 (2H, qv, $CH_2C\underline{H}_2CH_2$)	97
VIIb	$C_{13}H_{13}IN_2O_3$	144...146	3,37 (4H, m, $C\underline{H}_2CH_2C\underline{H}_2$); 2,07 (2H, qv, $CH_2C\underline{H}_2CH_2$)	98
VIII	$C_{13}H_{13}BrN_2O_3$	217...219	5,93 (1H, m, CH); 5,21 (2H, tq, NCH_2); 4,04 (3H, tt, CH_3)	80
IX	$C_{13}H_{12}N_2O_3$	213...214	5,96 (1H, m, CH); 5,27 (2H, tq, NCH_2); 4,03 (2H, t, CH_2)	98

*Signals for the 4-OH protons are in the form of a singlet in the 17.37-16.92-ppm region; protons of the NH-group of the heterocycle appear as a singlet in the 11.92-11.80-ppm region; protons of the NH-group in the alkylamide residue appear as a triplet in the 10.42-10.33 ppm region. Signals from the aromatic protons 5-H (dd) are found in the 7.98-7.95-ppm region; 7-H(td) at 7.71-7.68 ppm; 8-H(d) at 7.43-7.36 ppm; and 6-H(td) at 7.29-7.27 ppm.

**mp 208-210°C, given in [2], corresponding to the monohydrate of amide II.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker WP-100 SY (100 MHz), dissolved in DMSO-d_6, and with TMS as internal standard.

Elemental analysis data corresponded with the calculated values.

The characteristics of the N-R-derivatives of amides of 4-hydroxy-2-quinolone-3-carboxylic acids are presented in Table 1.

Dimethylaminopropylamide of 4-Hydroxy-2-quinolone-3-carboxylic Acid (I). To a solution of 2.33 g (0.01 mole) of ester X in 15 ml of ethanol was added 1.12 g (0.011 mole) of dimethylaminopropylamine and the solution was boiled under reflux for 5 h. The alcohol was then distilled under reduced pressure, to the residue was added 20 ml of water, and the solution was acidified with HCl to pH 3, after which was added 5 ml of benzene. The mixture was stirred and the organic layer was separated and discarded. The aqueous layer was treated with 0.07 g of sodium hydrosulfide followed by activated charcoal and filtered. To the filtrate was added 10% aqueous KOH to pH 8, the precipitated amide was filtered off, washed with water, and dried to give 2.66 g.

Hydrochloride of Dimethylaminopropylamide of 4-Hydroxy-2-quinolone-3-carboxylic Acid (II). To a solution of 2.89 g (0.01 mole) of amide I in 10 ml of isopropyl alcohol was added a solution of 0.47 g (0.013 mole) of dry HCl in 5 ml of isopropyl alcohol and the mixture was cooled to −5-0°C. The resulting precipitate was filtered off, washed with isopropyl alcohol, cooled to 0°C, and dried to give 3.22 g of product.

Iodomethylate of Dimethylaminopropylamide of 4-Hydroxy-2-quinoline-3-carboxylic Acid (IIIa). To a solution of 2.89 g (0.01 mole) of amide I in 10 ml of acetone was added 1.25 ml (0.02 mole) of methyl iodide, the mixture was boiled under reflux for 4 h, cooled, and treated with 20 ml of diethyl ether. The resulting precipitate was filtered off, washed with diethyl ether, and dried to give 4.18 g of product.

Haloalkylate IIIc-e was obtained analogously, and **compound IIIb** was obtained by reaction of amide I with excess ethyl chloride in acetone in a tightly sealed vessel at room temperature for 20 days.

3-Chloropropylamide of 4-Hydroxyl-2-quinolone-3-carboxylic Acid (IV). A mixture of 2.62 g (0.01 mole) of hydroxyamide V and 1.8 g (0.015 mole) of $SOCl_2$ in 30 ml of $CHCl_3$ was boiled under reflux for 5 h. The solvent and excess $SOCl_2$ were removed under reduced pressure, the residue was treated with 30 ml of water, and, after stirring, the precipitate of 2.68 g of amide IV was filtered off.

3-Hydroxypropylamide of 4-Hydroxy-2-quinolone-3-carboxylic Acid (V). A. To a solution of 2.33 g (0.01 mole) of ester X in 15 ml of dioxane was added 0.83 g (0.011 mole) of 3-aminopropyl alcohol and the mixture was boiled under reflux for 4 h. The reaction mixture was cooled, treated with 50 ml of water, and acidified with concentrated HCl to pH 3. The resulting precipitate was filtered off, washed with water, and dried to give 2.52 g of amide V.

Allylamide IX was obtained analogously.

B. A mixture of 2.81 g (0.01 mole) of chloropropylamide IV and 0.56 g (0.01 mole) of KOH in 20 ml of water was boiled under reflux for 8 h. The mixture was cooled, the precipitated V was filtered off, washed with water, and dried to give 2.21 g (84%) of product.

A sample mixed with material prepared by Method A did not depress the melting point.

6-Hydroxy-3,4-dihydro-2H-1,5-oxazocyclo[3,2-c]-8H-quinolin-7-one (VI, $C_{13}H_{12}N_2O_3$). To 2.80 g (0.01 mole) of chloroamide IV in 30 ml of methanol was added 1.05 g (0.01 mole) of diethylamine or a solution of sodium methylate [from 0.23 g (0.01 mole) of metallic sodium and 5 ml of methanol] and the mixture was boiled under reflux for 10 h. The reaction mixture was cooled, the precipitated oxazocycloquinoline VI was filtered off, washed with methanol and dried to give mp 248-250°C (dioxane). ^{1}H NMR spectrum: 13.64 (1H, s, OH); 10.45 (1H, s, NH); 7.91 (1H, dd, J = 8.0 and 2.0 Hz, 12-H); 7.43 (1H, td, J = 7.4 and 1.7 Hz, 10-H); 7.09 (1H, d, J = 7.1 Hz, 9-H); 7.02 (1H, td, J = 7.1 and 1.2 Hz, 11-H); 4.50 (2H, t, J = 5.0 Hz, $C\underline{H}_2CH_2CH_2$); 3.55 (2H, t, J = 5.0 Hz, $CH_2CH_2C\underline{H}_2$); 2.08 md (2H, qd, J = 5.0 and 1.8 Hz, $CH_2C\underline{H}_2CH_2$). Yield 2.43 g (quantitative).

3-Bromopropylamide of 4-Hydroxy-2-quinolone-3-carboxylic Acid (VIIa). A. To a suspension of 2.44 g (0.01 mole) of finely powdered oxazocycloquinoline VI in 10 ml of water was added 2 ml of concentrated HBr and the mixture was intimately mixed for 1 h. The solid was filtered off, washed with water and dried to give 3.15 g.

3-Iodopropylamide VIIb was prepared analogously.

B. To a solution of 2.44 g (0.01 mole) of allyamide IX in 20 ml of dioxane was added a small quantity of finely ground iron and 2 ml of concentrated HBr. After 2 h, the iron was filtered off and to the filtrate was added 100 ml water. The resulting precipitate was filtered off, washed with water and dried to give 2.56 g (79%).

A mixture of this material with a sample of that prepared by route A gave no depression of the melting point.

2-Bromopropylamide of 4-Hydroxy-2-quinolone-3-carboxylic Acid (VIII). To a solution of 2.44 g (0.01 mole) of allylamide IX in 30 ml of glacial acetic acid was added 2 ml of concentrated HBr and the mixture was kept in the dark at room temperature for 10 days. Water (100 ml) was then added and the resulting precipitate was filtered off, washed with water, and dried to give 2.60 g of amide VIII.

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