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4-HYDROXY-2-QUINOLONES. 24.* IMPROVED SYNTHESIS AND BIOLOGICAL PROPERTIES OF HYDROCHLORIDES OF β-DIALKYLAMINOALKYLAMIDES OF 1-ALKYL-2-OXO-4-HYDROXYQUINOLINE-3-CARBOXYLIC ACIDS

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High-purity hydrochlorides of β-dialkylaminoalkylamides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids have been obtained from N-alkyl-2-carbalkoxyanilides of malonic acid. The synthesized compounds have been tested for certain forms of pharmacological activity.

The need for constant improvement of drug therapy, in particular by developing more active and (particularly important) harmless substances is quite obvious and does not need any special justification. There is still an urgent need for new local anesthetic preparations. We had reported previously [2-6] on a number of studies dealing with this theme and devoted to the development of methods for synthesis and investigation of the biological properties of derivatives of the dialkylaminoalkylamides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids. In those studies, we found experimental confirmation of favorable effects on the extended action of local anesthetics as a result of increasing the level of lyophilic properties of the test compounds by introducing alkyl substituents into position 1 of the quinolone ring [2].

It is known that the special features of medical applications of local anesthetics (here we refer mainly to the injectable forms) impose extremely rigid requirements on the purity of such preparations. At the same time, in tests to determine the purity of the amides I by HPLC, it has been established that they often contain as impurities the corresponding derivatives of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid. N-Alkylanthranilic acids obtained by alkylating potassium or sodium anthranylate by iodoalkanes or bromoalkanes [7, 8] usually contain the unalkylated product as an impurity that is difficult to eliminate by recrystallization. As a result, this impurity persists in the esters II-IV and ultimately in the amides V and hydrochlorides Ia-s.

This problem can be solved quite simply by carrying out the Dieckmann condensation of ethyl esters of N-alkyl-2-carbalkoxyanilides of malonic acid II in an aqueous medium [9]. In contrast to 1H-2-oxo-3-carbethoxy-4-hydroxyquinoline, salts of the N-alkyl-substituted esters III are poorly soluble in alkalis, so that these compounds can be readily separated. The salts III, according to [10], are extremely inert to the action of nucleophilic reagents. Subsequently, therefore, the synthesis scheme proposes that they should be treated with a mineral acid in order to recover the esters IV, which are then subjected to amidation. It must be noted that, along with the additional costs involved because of the low melting points and high lyophilicities of the esters IV, the whole operation is extremely laborious. We were able to avoid this problem as a result of treating the salts III with glacial acetic acid in an alcoholic medium, followed by amidation in the same reaction vessel. While an equivalent quantity of acetic acid is sufficient when the synthesis is performed in 96% ethanol, a twofold excess is required for the reaction is absolute ethanol (probably because of the formation of acidic potassium acetate [11]).

*For Communication 23, see [1].

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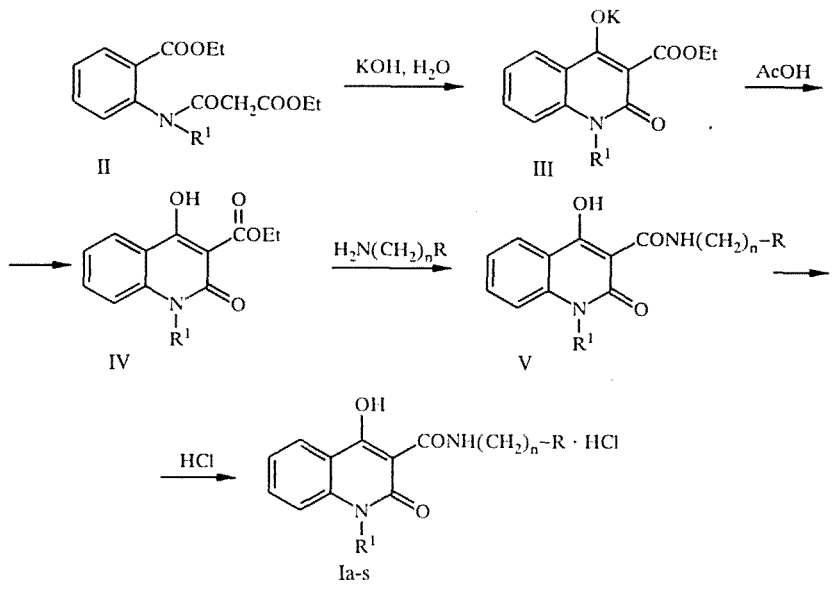

I) $R^1 = CH_3$: a) R = $N(C_2H_5)_2$, n = 2; b) R = 4-morpholyl, n = 2; c) R = 1-piperidyl, n = 2; d) R = 4-morpholyl, n = 3; e) R = 1-piperidyl, n = 3; $R^1 = C_2H_5$: f) R = $N(CH_3)_2$, n = 2; g) R = $N(C_2H_5)_2$, n = 2; h) R = 4-morpholyl, n = 2; i) R = 1-piperidyl, n = 2; j) R = 4-morpholyl, n = 3; k) R = 1-piperidyl, n = 3; $R^1 = C_3H_7$: *l*) R = $N(CH_3)_2$, n = 2; m) R = 4-morpholyl, n = 2; $R^1 = C_4H_9$: n) R = $N(C_2H_5)_2$, n = 2; $R^1 = C_5H_{11}$: o) R = $N(CH_3)_2$, n = 2; p) R = $N(C_2H_5)_2$, n = 2; $R^1 = C_6H_{13}$: q) R = $N(CH_3)_2$, n = 2; r) R = $N(C_2H_5)_2$, n = 2; $R^1 = C_8H_{17}$: s) R = $N(CH_3)_2$, n = 2

The dialkylaminoalkylamides (bases) V are also low-melting substances (see Table 1), and hence they are difficult to segregate in crystalline form. For preparative operations, it is more rational to extract these compounds from the reaction mixture by an appropriate water-immiscible organic solvent and only then subject the compounds to further chemical conversion, either directly in the solvent or after driving off the solvent.

On the whole, this procedure for obtaining the amides Ia-s is quite simple; moreover, it offers a means for synthesizing the final products in a high degree of purity. According to HPLC data, the content of the principal substance is 99.1-99.4%, which is entirely acceptable for the preparation of injection solutions.

Evaluation of the local anesthetic activity of the amides Ia-s was performed by the use of a procedure given in [2] in the model of infiltration anesthesia. Of the entire group of substances, we should single out two compounds: the hydrochlorides of diethylamino- (Ig) and morpholino- (Ih) ethylamides of 1-ethyl-2-oxo-4-hydroxyquinoline-3-carboxylic acid. In comparing their anesthetic effects with that of the local anesthetic most widely used in current medical practice – lidocaine [12], we find that compound Ig is equal in this respect and compound Ih is somewhat better. An especially valuable property of the amide Ih is that, along with its high activity, the compound has a comparatively low toxicity: LD_{50} = 300 mg/kg (0.5% aqueous solution, white mice, intra-abdominally), considerably better in this respect than lidocaine (LD_{50} = 125 mg/kg).

Along with their specific activity, many local anesthetics have very definite antiarrhythmic properties [12]. Therefore, we studied the antiarrhythmic action of the most active compounds (Ig,h) in the model of potassium chloride arrhythmia (white rats). Here it was established that on the basis of the number of surviving animals and the time before the onset of ventricular fibrillation, these substances are as good as lidocaine.

An important criterion for anesthetics is the absence of stimulating effects. Studies performed by various methods [13] showed that the amides Ig,h manifest a stimulating effect only at concentrations 7-9 times the nominal therapeutic concentrations.

Many papers are published every year describing searches for new antimicrobial substances in the series of 4-hydroxy(oxo)quinoline-3-carboxylic acids [4, 14, 15]. Almost all of the amides that we have synthesized (Ia-s) manifest a high level of antimicrobial and fungicidal activities for *Staphylococcus aureus* (209-P), *Bacillus subtilis* (ATCC 6633), *Bacillus cereus* (ATCC-8035), *Escherichia coli* (M-17), *Proteus vulgaris* (HX19, N222), *Candida albicans* (ATCC 10261), and *Saccha-*

TABLE 1. Characteristics of Hydrochlorides of β-Dialkylaminoalkylamides of 1-Alkyl-2-oxo-4-hydroxyquinoline-3-carboxylic Acids Ia-s

Compound	Empirical formula	mp*, °C	PMR spectrum,† δ, ppm	Yield, %
1	2	3	4	5
Ia	$C_{17}H_{23}N_3O_3 \cdot HCl$	208...210 (64...66)	10,62 (1H, s, N^+H); 10,44 (1H, t, CONH); 3,74 (2H, q, $NHCH_2$); 3,61 (3H, s, CH_3); 3,50...3,00 (6H, m, $N(CH_2)_3$); 1,25 (6H, t, $NCH_2CH_3 \times 2$	78
Ib	$C_{17}H_{21}N_3O_4 \cdot HCl$	268...270 (128..130)	11,08 (1H, s, N^+H); 10,48 (1H, t, CONH); 3,88 (4H, m, NCH_2CH_2N); 3,65 (3H, s, CH_3); 3,37 (8H, m, $(CH_2)_4$ morpholyl)	97
Ic	$C_{18}H_{23}N_3O_3 \cdot HCl$	270...272	10,71 (1H, s, N^+H); 10,52 (1H, t, CONH); 3,83 (2H, q, $NHCH_2$); 3,60 (3H, s, CH_3); 3,37 (6H, m, $N(CH_2)_3$); 2,90 (2H, q, $NCH_2CH_2CH_2$ piperidyl); 1,77 (4H, s, $NCH_2CH_2CH_2CH_2$ piperidyl)	94
Id	$C_{18}H_{23}N_3O_4 \cdot HCl$	240...242	10,68 (1H, s, N^+H); 10,46 (1H, t, CONH); 3,90 (4H, m, $NCH_2CH_2CH_2N$); 3,61 (3H, s, CH_3); 3,42 (4H, m, $N(CH_2)_2$ morpholyl); 3,10 (4H, m, $O(CH_2)_2$ morpholyl); 2,03 (2H, q, $NCH_2CH_2CH_2N$)	92
Ie	$C_{19}H_{25}N_3O_3 \cdot HCl$	248...250	10,70 (1H, s, N^+H); 10,53 (1H, t, CONH); 3,63 (3H, s, CH_3); 3,39 (6H, m, $N(CH_2)_2$ piperidyl + $NHCH_2$); 3,00 (4H, m, $NHCH_2CH_2CH_2N$ + $NCH_2CH_2CH_2$ piperidyl); 2,05 (2H, q, $NHCH_2CH_2CH_2N$); 1,74 (4H, s, $NCH_2CH_2CH_2CH_2$ piperidyl)	90
If	$C_{16}H_{21}N_3O_3 \cdot HCl$	236...238 (70...72)	10,72 (1H, s, N^+H); 10,57 (1H, s, CONH); 4,32 (2H, q, NCH_2CH_3); 3,79 (2H, q, $NHCH_2$); 3,40 (2H, t, $NHCH_2CH_2$); 2,85 (6H, s, $CH_3 \times 2$); 1,24 (3H, t, NCH_2CH_3)	93
Ig	$C_{18}H_{25}N_3O_3 \cdot HCl$	210...212	10,49 (2H, t, N^+H + CONH); 4,31 (2H, q, $CONCH_2CH_3$); 3,81 (2H, q, $NHCH_2$); 3,24 (6H, m, $N(CH_2)_3$); 1,26 (9H, t, $CH_3 \times 3$)	72
Ih	$C_{18}H_{23}N_3O_4 \cdot HCl$	234...236 (76...78)	11,29 (1H, s, N^+H); 10,50 (1H, t, CONH); 4,30 (2H, q, NCH_2CH_3); 3,92 (4H, m, NCH_2CH_2N); 3,37 (8H, m, $(CH_2)_4$ morpholyl); 1,25 (3H, t, CH_3)	94
Ii	$C_{19}H_{25}N_3O_3 \cdot HCl$	258...260 (71...73)	10,46 (2H, t, N^+H + CONH); 4,39 (2H, q, NCH_2CH_3); 3,81 (2H, q, $NHCH_2$); 3,33 (6H, m, $N(CH_2)_3$); 2,91 (2H, q, $NCH_2CH_2CH_2$ piperidyl); 1,79 (4H, s, $NCH_2CH_2CH_2CH_2$ piperidyl); 1,23 (3H, t, CH_3)	91
Ij	$C_{19}H_{25}N_3O_4 \cdot HCl$	204...206	11,20 (1H, t, N^+H); 10,42 (1H, t, CONH); 4,30 (2H, q, NCH_2CH_3); 3,89 (4H, m, $NCH_2CH_2CH_2N$); 3,43 (4H, m, $N(CH_2)_2$ morpholyl); 3,11 (4H, m, $O(CH_2)_2$ morpholyl); 2,05 (2H, q, $NCH_2CH_2CH_2N$); 1,23 (3H, t, CH_3)	89
Ik	$C_{20}H_{27}N_3O_3 \cdot HCl$	238...240	10,63 (1H, s, N^+H); 10,41 (1H, t, CONH); 4,30 (2H, q, NCH_2CH_3); 3,35 (6H, m, $N(CH_2)_2$ piperidyl + $NHCH_2$); 3,01 (4H, m, $NCH_2CH_2CH_2N$ + $NCH_2CH_2CH_2$ morpholyl; 2,06 (2H, q, $NHCH_2CH_2CH_2N$); 1,78 (4H, s, $NCH_2CH_2CH_2CH_2$ piperidyl); 1,24 (3H, t, CH_3)	90
Il	$C_{17}H_{23}N_3O_3 \cdot HCl$	196...198 (102...104)	10,49 (2H, t, N^+H + CONH); 4,24 (2H, t, $NCH_2CH_2CH_3$); 3,76 (4H, m, NCH_2CH_2N); 2,78 (6H, s, $CH_3 \times 2$); 1,53 (2H, m, $NCH_2CH_2CH_3$); 0,97 (3H, t, $NCH_2CH_2CH_3$)	95
Im	$C_{19}H_{25}N_3O_4 \cdot HCl$	242...244 (68...70)	11,43 (1H, s, N^+H); 10,48 (1H, t, CONH); 4,19 (2H, t, $NCH_2CH_2CH_3$); 4,00 (4H, m, NCH_2CH_2N); 3,39 (8H, m, $(CH_2)_4$ morpholyl); 1,63 (2H, m, $NCH_2CH_2CH_3$); 0,96 (3H, t, CH_3)	96
In	$C_{20}H_{29}N_3O_3 \cdot HCl$	156...158	10,82 (1H, s, N^+H); 10,47 (1H, t, CONH); 4,23 (2H, t, $NCH_2C_3H_7$); 3,75 (2H, q, $NHCH_2$); 3,24 (6H, m, $N(CH_2)_3$); 1,80...1,03 (10H, m, $(CH_2)_2CH_3 + NCH_2CH_3 \times 2$); 0,88 (3H, t, $N(CH_2)_3CH_3$)	80

TABLE 1 (continued)

Compound	Empirical formula	mp*, °C	PMR spectrum,† δ, ppm	Yield, %
1	2	3	4	5
Io	$C_{19}H_{27}N_3O_3 \cdot HCl$	216...218 (80...82)	10,50 (2H, t, N^+H + CONH); 4,25 (2H, t, $NCH_2C_4H_9$); 3,77 (2H, q, $NHCH_2$); 3,39 (2H, t, $NHCH_2CH_2N$); 2,88 (6H, s, (CH_3 × 2)); 1,29 (6H, m, $NCH_2(CH_2)_3$); 0,90 (3H, t, $N(CH_2)_4CH_3$)	88
Ip	$C_{21}H_{31}N_3O_3 \cdot HCl$	126...127	10,50 (2H, t, N^+H + CONH); 4,25 (2H, t, $NCH_2C_4H_9$); 3,77 (2H, q, $NHCH_2$); 3,24 (6H, m, $N(CH_2)_3$); 1,80...1,11 (12H, m, $(CH_2)_3CH_3$ + NCH_2CH_3 × 2); 0,94 (3H, t, $N(CH_2)_4CH_3$)	79
Iq	$C_{20}H_{29}N_3O_3 \cdot HCl$	182...183 (58...60)	11,23 (1H, s, N^+H); 10,45 (1H, t, CONH); 4,20 (2H, t, $NCH_2C_5H_{11}$); 3,74 (2H, q, $NHCH_2CH_2N$); 3,38 (2H, t, NCH_2CH_2N); 2,86 (6H, s, CH_3 × 2); 1,28 (8H, m, $NCH_2(CH_2)_4$); 0,83 (3H, t, $N(CH_2)_5CH_3$)	87
Ir	$C_{22}H_{33}N_3O_3 \cdot HCl$	128...130 (37...38)	10,81 (1H, s, N^+H); 10,48 (1H, t, CONH); 4,24 (2H, t, $NCH_2C_5H_{11}$); 3,81 (2H, q, $NHCH_2$); 3,24 (6H, m, $N(CH_2)_3$); 1,84...1,07 (14H, m, $NCH_2(CH_2)_4$ + NCH_2CH_3 × 2); 0,88 (3H, t, $N(CH_2)_5CH_3$)	83
Is	$C_{22}H_{33}N_3O_3 \cdot HCl$	176...178	10,97 (1H, s, N^+H); 10,49 (1H, t, CONH); 4,25 (2H, t, $NCH_2C_7H_{15}$); 3,76 (2H, q, $NHCH_2CH_2N$); 3,40 (2H, t, $NHCH_2CH_2N$); 2,89 (6H, s, CH_3 × 2); 1,26 (12H, m, $NCH_2(CH_2)_6$); 0,89 (3H, t, $N(CH_2)_7CH_3$)	91

*Values shown in parentheses denote the melting points of the corresponding dialkylaminoalkylamides (bases) V.

†The signals of the protons of the 4-OH groups are manifested in the form of a singlet in the 17.11-16.78 ppm region. The signals of the aromatic protons 5-H (dd) are located in the 8.12-7.95 region, 7-H (td) 7.82-7.70, 8-H (d) 7.43-7.40, and 6-H (td) 7.36-7.26 ppm.

romyces cerevisia. However, this effect was the greatest for the 1-hexyl derivatives (Iq,r) and 1-octyl derivative (Ie) of 2-oxo-4-hydroxyquinoline-3-carboxylic acids. It should be noted that the hexyl substituent in position 1 of the quinolone ring is the decisive factor for manifestation of selective antimicrobial action with respect to *Staphylococcus aureus*. In this case, the substituents in the dialkylamine residue and the size of the methylene chain between the amide and quaternary nitrogen atoms are not as important as the position 1 substituent in determining activity. Lidocaine manifests slight antimicrobial activity, confined to intestinal bacilli and yeastlike fungi.

We had previously detected high antioxidant activity for 3-alkyl-2-oxo-4-hydroxyquinolines [16]. Continuing that work, we investigated the influence of the amides Ia-s on the intensity of peroxide oxidation of lipids. Studies performed in a microsomal fraction of the rat liver homogenate by a procedure given in [17] showed that the introduction of the amides Ia-s at concentrations of 0.015-0.195 mg/ml resulted in significant inhibition of enzymatic and nonenzymatic peroxide oxidation of lipids. Lidocaine, even in a dose of 2 mg/ml, did not give any lowering of the intensity of free-radical oxidation of lipids.

In studying the influence of the synthesized compounds on the respiration of mitochondria [18, 19], it was noted that the amides Ia-s have a considerably greater effect than lidocaine on the mitochondrial energetics of the cell. This feature obviously explains their pronounced antimicrobial and fungicidal activities.

On the basis of the results of all of our pharmacological studies, we can conclude that there is promise in the use of hydrochlorides of β-dialkylaminoalkylamides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids as the basis for developing pharmaceutical preparations with a combined type of action.

EXPERIMENTAL

PMR spectra of the synthesized compounds were recorded on a Bruker WP-100 SY instrument (100 MHz), solvent DMSO-d_6, internal standard TMS.

Determination of Chromatographic Purity. The amides Ia-s, in amounts of 0.05-0.07 g, were dissolved in 20 ml of water. A 2-μl quantity of the solution was chromatographed, obtaining at least five chromatograms, in a Milichrom-4 UV chromatograph under the following conditions: ultraviolet detector, wavelength 230 nm, measurement time 0.4 sec; steel column, 2 × 64 mm KAKh 4-64-3, sorbent Separon C 18 with grain size 5.0 μm, column efficiency at least 3800 theoretical plates with respect to anthracene; eluent 50-60% methanol in 0.02 M H_3PO_4 with the addition of 1.0-1.5 mmole sodium pentylsulfonate per 100 ml of eluent; eluent input rate 80 μl/min. We calculated the areas of all chromatogram peaks, determined the fraction of the area of the main peak (amides Ia-s) in the total area of all peaks (internal normalization), and averaged this value on the basis of five chromatograms.

The potassium salts of 1-alkyl-2-oxo-3-carbethoxy-4-hydroquinolines (III) were obtained by a procedure given in [9]. Elemental analyses for C, N, and HCl were in satisfactory agreement with the calculated values.

General Method for Obtaining Hydrochlorides of β-Dialkylaminoalkylamides of 1-R-2-Oxo-4-hydroxyquinoline-3-carboxylic acids (Ia-s). To a solution of 0.01 mole of the potassium salt III in 15 ml of 96% ethanol, 0.58 ml (0.01 mole) of glacial AcOH and 0.011 mole of the appropriate dialkylaminoalkylamine was added, and the mixture was refluxed for 5 h. The alcohol was removed by distillation under reduced pressure. Then 50 ml of water was added to the residue, the solution was acidified with HCl to pH 3.0, 5 ml of benzene was added, and the mixture was stirred. After 30-40 min, the water layer was separated and treated with activated carbon and hydrosulfite (0.07 g). The mixture was then filtered. To the filtrate, while stirring, a 20% NaOH solution was added to bring the pH to 8. The precipitated amide V was filtered off, washed with water, and dried, after which it was dissolved in 2-propanol. A solution of 0.44 g (0.012 mole) of dry HCl in 5 ml of 2-propanol was added, and the mixture was cooled. After 4-5 h, the precipitate of the amide I was filtered off and dried. If the amide V was recovered in the form of an oily residue, it was extracted (3 × 20 ml) with a suitable organic solvent (ether, hexane, benzene). The combined extracts were purified by treatment with carbon, dried with anhydrous $CaCl_2$, and subsequently treated by the method just described, either directly in the solvent or after it had been driven off.

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