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4-HYDROXY-2-QUINOLONES. 178*. IRREVERSIBLE CHEMICAL MODIFICATION OF CHINOXICAINE AT THE POSITION 4 OF THE QUINOLONE RING

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While continuing our investigation in improving the pharmaceutical activities of the local anesthetic Chinoxicaine we have studied the irreversible replacement of its 4-OH group for bioisosteric fragments. For this purpose the synthesis of a series of 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids 2-(diethylamino)ethylamide hydrochlorides has been carried out. The experimental data of the local anesthetic properties of the compounds obtained are given and discussed.

Keywords: 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acids, amidation, bioisosteric replacement, local anesthetics.

At present chemical modification is one of the most efficient methods for improving of the structural leaders identified during the primary screening and selected for further profound study. It is really this approach that we chose for improving the pharmaceutical properties of Chinoxicaine **1**, which is a novel, promising local anesthetic in the quinolone series [2]. In particular, by a reversible transformation of this medicine to a prodrug we succeeded in increasing of its solubility in water by several times and thus to solve the problem of a solvent for a stable medicinal form for injections [3]. However, the local irritation effect has still remained, even though less clearly expressed. The study of the structurally related 1-R-3-(2-alkylaminoethyl)-1H-quinazoline-2,4-dione hydrochlorides [4] has shown that the most likely source of this drawback is the 4-OH group. Hence, after its blocking one might expect removal of this unwanted side effect. At the same time, alkylation or acylation of the 4-OH group (as the most obvious variant of a further bioreversible modification of Chinoxicaine) was not considered by us. The reason was that, within a rather limited choice of acceptable blocking groups, neither 4-O-alkyl nor 4-O-acyl derivatives of 4-hydroxy-2-quinolonones show high stability and are comparatively readily hydrolyzed. Hence this evidently causes serious problems both in their synthesis and in a subsequent preparation of sterile solutions for injections.

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* For Communication 177, see [1].

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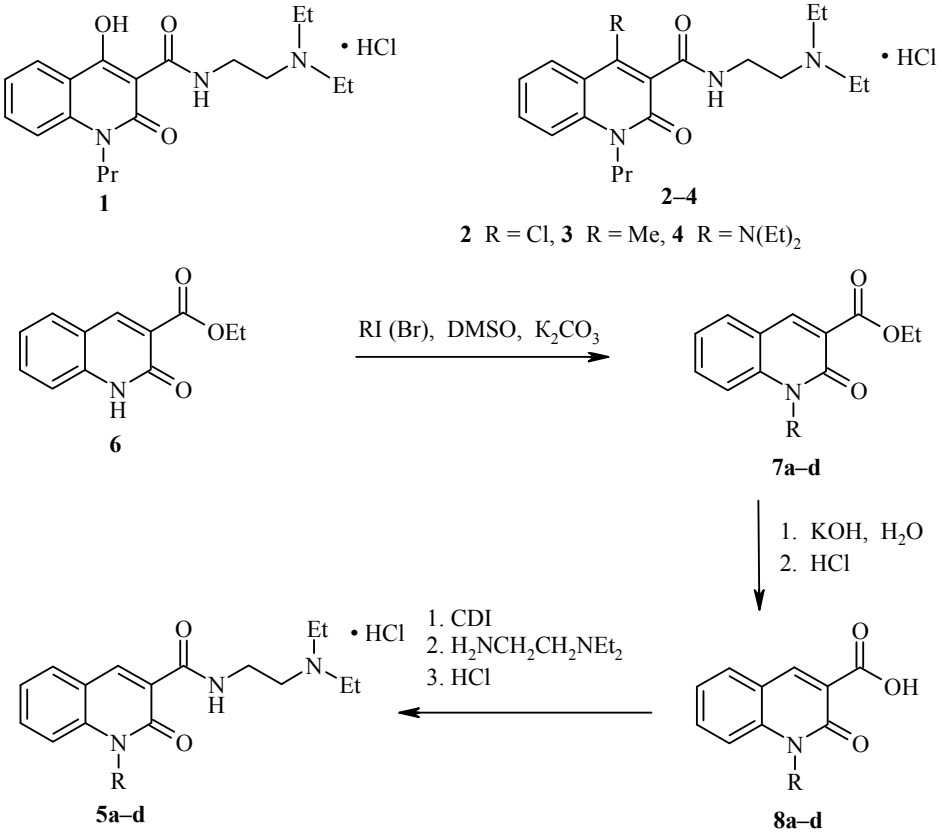
With this in mind we have attempted to modify the 4-OH group of the Chinoxicaine not by the direct formation of a prodrug, but by using the method of bioisosteric replacement, i.e. by an irreversible replacement by groups similar not only in size or volume, but also having similar physicochemical properties and so inducing a closely related pharmacological effect [5].

The first example of such a transformation was 4-chloro-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid 2-(diethylamino)ethylamide hydrochloride (**2**) prepared by acylation of 2-(diethylamino)-ethylamine using the corresponding quinoline-3-carboxylic acid chloride [6].



The high reactivity of the chlorine atom in 1-R-4-chloro-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolines towards nucleophilic reagents allows to transform them readily to 4-methyl-2-oxo-1,2-dihydroquinoline-3-carboxylic acids [7], one of which served as the basis for the synthesis of a Chinoxicaine bioisostere, i.e. the 4-methyl-substituted analogue **3**.

As it is known [6], 2-oxo-1,2-dihydroquinoline-3-carboxylic acid N-R-amides with a primary amino group in position 4 of the quinolone ring exist in the 2-hydroxy-4-imino form rapidly hydrolyzed by mineral acids to 4-hydroxy-2-quinolones. On this basis, as the next subject we deliberately prepared the more stable 4-diethylamino-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid 2-(diethylamino)ethylamide hydrochloride (**4**).

Amides **5** are also undoubtedly of interest for biological study since they do not contain any kind of substituent at position 4 despite the fact that, in the absence of these substituents, they cannot strictly speaking be considered as bioisosteres of Chinoxicaine. Unfortunately, the dehalogenation of 4-chloro-3-ethoxycarbonyl-2-oxo-1,2-dihydroquinolines cannot be achieved [8-11]. That is why the starting ethyl 2-oxo-1,2-di-hydro-quinoline-3-carboxylate (**6**) [12] had to be prepared *via* the difficultly available anthranilic aldehyde. Subsequent

alkylation by alkyl iodides or bromides in the DMSO–K_2CO_3 system gives the esters **7**, which were hydrolyzed to acids **8** without purification, and acids are treated with N,N'-carbonyldiimidazole to give imidazolides, and then converted to the 2-(diethylamino)ethylamides isolated as the target water soluble hydrochlorides **5a-d**.

All of the 1-alkyl-substituted 4-R-2-oxo-1,2-dihydroquinoline-3-carboxylic acid 2-(diethylamino)-ethylamide hydrochlorides obtained are colorless and the crystalline substances, which are readily soluble in water.

The study of their local anesthetic action, ability to cause infiltration anesthesia of the skin and subcutaneous tissue, as well as the assessment of the motor block and the sedative effect were carried out by the standard methods, as described previously in detail [4, 13]. It has been found that none of the compounds studied as 2% aqueous solutions cause any kind of reactive changes or irritation on the skin surface of the experimental animals.

When testing the local anesthetic properties all parameters characterizing the main specific manifestations of this type of biological activity such as the infiltration anesthesia index, the rate of anesthesia onset, duration of the complete anesthetic effect, the motor block, and the sedative effect were considered. From the data presented in Table 1 it is seen that a bioisosteric substitution of the 4-OH group for a chlorine atom (amide **2**) leads to a marked decrease of all parameters and thus it can unambiguously be considered as unsuccessful.

Replacement of the hydroxyl group for the methyl one proved to be more interesting. The activity of the 4-methyl-substituted amide **3** is characterized as the most rapid of all the newly synthesized compounds in the development of the biological effect (less than 2 min after injection). The infiltration anesthesia index reaches the maximum value and the complete anesthesia or the time of absence of pain and the other forms of sensitivity (tactile, temperature, etc.) during which it is possible to carry out surgery (tissue incision, closure of wounds, etc.) lasts for about 55 min. This data indicate a rather high activity of amide **3**, comparable to the activity of the reference medicines – Chinoxicaine and Lidocaine. On the other hand, amide **3** yields greatly to the reference medicines in the overall time for anesthesia duration (i.e. the time when sensitivity gradually increases and then restores completely).

The special attention should be paid to 4-diethylamino derivative **4** not only because of its rather high anesthetic properties, but for its perspective to carry out readily further practically unlimited modifications of a similar type to achieve the desired result.

Amongst the series of amides **5** unsubstituted in position 4 there should be noted only the compounds with a butyl or isobutyl substituent on the cyclic nitrogen atom (compounds **5c** and **5d** respectively). Both of these compounds are characterized by a rather rapid onset of activity and high indexes of infiltration anesthesia. A distinctive feature of the first of them is the fact that after 10-15 min following the injection the animals were drowsy sleeping deeply in 15-20 min. The motor block score of 5 lasted about 20 min after injection of the compound studied. In case of amide **5d**, by 7-10 min after injection the animals had a deep sleep, lying on the side, without reacting to an active needle stimulation (tactile, pain, or temperature sensitivity is absent).

TABLE 1. Biological Properties of the Modified Chinoxicaine Derivatives **2-5**

Compound	Anesthetic penetration				Motor block, score	Sedative effect, score
	Start of anesthesia, min	Index	Full anesthesia, min	Overall anesthesia time, min		
2	3.9 ± 0.42	26.3	14.2 ± 1.11	24.7 ± 2.18	0	0
3	1.9 ± 0.21	36.0	55.3 ± 2.74	68.3 ± 2.68	0	0
4	2.2 ± 0.31	36.0	37.5 ± 2.83	67.8 ± 2.37	0	0
5a	4.5 ± 0.32	19.3	13.2 ± 1.00	21.0 ± 1.67	0	0
5b	4.5 ± 0.36	35.5	27.8 ± 1.89	32.3 ± 2.92	0	0
5c	3.0 ± 0.28	36.0	39.0 ± 2.12	58.2 ± 2.81	5	2
5d	2.7 ± 0.37	36.0	53.7 ± 1.93	83.2 ± 2.05	5	3
Chinoxicaine	1.6 ± 0.13	36.0	74.7 ± 4.71	236.8 ± 9.34	0	0
Lidocaine	2.3 ± 0.20	36.0	51.2 ± 3.45	140.2 ± 6.20	0	0

In 15-20 min the animal awoke but they were without movement in a sleepy state for about 20 min, and only then began to move with paws. Therefore, it is possible to speak of a deep and prolonged motor block with a marked sedative effect and it can appear to be very useful as an anesthetic when carrying out a series of short term surgical operations, particularly when assisting patients with increased nervousness and potential fears before carrying out any kind of surgical manipulations.

EXPERIMENTAL

^{1}H NMR spectra for the compounds synthesized were registered by Varian Mercury VX-200 instrument (200 MHz) using DMSO-d_6 solution as TMS internal standard. Commercial anhydrous DMF for peptide synthesis and N,N'-carbonyldiimidazole (Fluka company) were used in the synthesis of amides **5**.

4-Chloro-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid 2-(Diethylamino)ethylamide Hydrochloride (2). Add 2-popanol saturated with gaseous HCl with vigorous stirring to the cooled solution of the free base of 4-chloro-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid 2-(diethyl-amino)ethylamide (3.63 g, 0.01 mol) [6] in 2-propanol (20 ml) and adjust pH to about 4. A white precipitate of the hydrochloride **2** was produced. Treat the reaction mixture with dry diethyl ethyl (20 ml) and allow it to stand for 3-4 h at -10ºC. Filter the crystalline hydrochloride **2** produced, wash with anhydrous diethyl ether, and dry. The yield is 3.76 g (94%); mp 99-101ºC (acetone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.70 (1H, br. s, NH^+); 8.94 (1H, t, *J* = 5.6, CONH); 8.02 (1H, d, *J* = 8.0, H-5); 7.77 (1H, t, *J* = 7.8, H-7); 7.70 (1H, d, *J* = 8.3, H-8); 7.41 (1H, t, *J* = 7.3, H-6); 4.21 (2H, t, *J* = 7.4, $NC\underline{H}_2CH_2CH_3$); 3.65 (2H, q, *J* = 6-3, $CONHC\underline{H}_2$); 3.18 (6H, m, $N(C\underline{H}_2)_3$); 1.63 (2H, m, $NCH_2C\underline{H}_2CH_3$); 1.25 (6H, t, *J* = 7.2, $N(CH_2C\underline{H}_3)_2$); 0.94 (3H, t, *J* = 7.3, $CH_2CH_2C\underline{H}_3$). Found, %: C 57.14; H 6.92; N 10.41. $C_{19}H_{26}ClN_3O_2 \cdot HCl$. Calculated, %: C 57.00; H 6.80; N 10.50.

4-Methyl-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid 2-(Diethylamino)ethylamide Hydrochloride (3). Add $SOCl_2$ (1.44 ml, 0.02 mol) to the solution of 4-methyl-2-oxo-1-propyl-1,2-di-hydroquinoline-3-carboxylic acid (2.45 g, 0.01 mol) [7] in dry CCl_4 (20 ml) with protection from moisture in the air using a $CaCl_2$ tube and reflux using a reflux condenser until evolving of HCl and SO_2 stops (for about 2 h). Then change the reflux condenser to the descending condenser and distil the solvent with the excess of $SOCl_2$ (finally under reduced pressure). The 4-methyl-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid chloride residue dissolve in dry acetone (10 ml) and add the solution obtained dropwise with stirring and cooling to the mixture of 2-(diethylamino)ethylamine (1.56 ml, 0.011 mol) and triethylamine (1.54 ml, 0.011 mol) in dry acetone (15 ml). Dilute the mixture was with water in 4 h. Filter the precipitate of 4-methyl-2-oxo-1-propyl-1,2-di-hydroquinoline-3-carboxylic acid 2-(diethylamino)ethylamide, wash with cold water, and dry. The yield is 2.77 g (81%); mp 112-114ºC (aqueous ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 8.17 (1H, t, *J* = 5.8, NH); 7.87 (1H, d, *J* = 8.1, H-5); 7.66 (1H, t, *J* = 7.8, H-7); 7.58 (1H, d, *J* = 8.5, H-8); 7.29 (1H, t, *J* = 7.1, H-6); 4.08 (2H, t, *J* = 7.5, $NC\underline{H}_2CH_2CH_3$); 3.26 (2H, q, *J* = 6.6, $NHC\underline{H}_2$); 2.56 (6H, m, $N(CH_2)_3$); 2.37 (3H, s, 4-CH_3); 1.64 (2H, m, $NCH_2C\underline{H}_2CH_3$); 0.95 (9H, m, $N(CH_2C\underline{H}_3)_2$ and $NCH_2CH_2C\underline{H}_3$). Found, %: C 70.05; H 8.60; N 12.35. $C_{20}H_{29}N_3O_2$. Calculated, %: C 69.94; H 8.51; N 12.23. In order to transfer the amide base obtained in this way to the hydrochloride **3** required for biological investigation, weigh it accurately (calculated for the final 2% concentration) into a volumetric flask, add the equivalent amount of the standard titrant of HCl solution and dilute the volume with water.

4-Diethylamino-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid 2-(Diethylamino)ethylamide Hydrochloride (4) was prepared by the method reported above from the free base of the 4-diethylamino-2-oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic acid 2-(diethylamino)ethylamide [6] as 2% aqueous solution.

1-Ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (8a). Finely powdered K_2CO_3 (2.76 g, 0.02 mol) and ethyl iodide (0.96 ml, 0.012 mol) add to the solution of ethyl 2-oxo-1,2-dihydroquinoline-3-carboxylate (**6**) [12] (2.17 g, 0.01 mol) in DMSO (15 ml) and stir for 4 h at 70ºC. Cool the reaction mixture

and dilute with water. Extract the oily ester **7a** produced with dichloromethane (3 x 20 ml). Mix the organic extracts and remove the solvent (finally under reduced pressure). Add 5% aqueous solution of KOH (30 ml) to the residue, boil for 2 h. Acidify the filtrate with dilute HCl (1:1) to pH 3. Filter the precipitate of acid **8a**, wash with cold water, and dry. The yield is 1.84 g (85%); mp 118-120ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 14.57 (1H, br. s, COOH); 8.96 (1H, s, H-4); 8.11 (1H, d, *J* = 8.1, H-5); 7.95 (1H, t, *J* = 7.8, H-7); 7.81 (1H, d, *J* = 8.5, H-8); 7.47 (1H, t, *J* = 7.0, H-6); 4.43 (2H, q, *J* = 7.2, NC$\underline{H}_2$); 1.27 (3H, t, *J* = 7.2, CH_3). Found, %: C 66.23; H 4.98; N 6.36. $C_{12}H_{11}NO_3$. Calculated, %: C 66.35; H 5.10; N 6.45.

Compounds **8b-d** were prepared by the analogous method.

2-Oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid (8b). For characteristics see [14].

1-Butyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (8c). Yield 76%; mp 135-137ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 14.60 (1H, br. s, COOH); 8.95 (1H, s, H-4); 8.11 (1H, dd, *J* = 8.1 and *J* = 1.4, H-5); 7.87 (1H, td, *J* =7.8 and *J* = 1.4, H-7); 7.79 (1H, d, *J* = 8.4, H-8); 7.46 (1H, td, *J* = 7.2 and *J* = 1.4, H-6); 4.37 (2H, t, *J* = 7.5, NCH_2); 1.65 (2H, m, $NCH_2C\underline{H}_2$); 1.41 (2H, m, $NCH_2CH_2C\underline{H}_2$); 0.92 (3H, t, *J* = 7.3, CH_3); Found, %: C 68.69; H 6.27; N 5.65. $C_{14}H_{15}NO_3$. Calculated, %: C 68.56; H 6.16; N 5.71.

1-Isobutyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid (8d). Yield 72%; mp 121-123ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 14.69 (1H, br. s, COOH); 8.98 (1H, s, H-4); 8.11 (1H, d, *J* = 8.0, H-5); 7.86 (1H, t, *J* = 7.7, H-7); 7.79 (1H, d, *J* = 8.3, H-8); 7.47 (1H, t, *J* = 7.1, H-6); 4.29 (2H, d, *J* = 7.4, NCH_2); 2.18 (1H, m, $C\underline{H}(CH_3)_2$); 0.92 (6H, d, *J* = 6.7, $CH(C\underline{H}_3)_2$. Found, %: C 68.70; H 6.24; N 5.82. $C_{14}H_{15}NO_3$. Calculated, %: C 68.56; H 6.16; N 5.71.

1-Ethyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 2-(Diethylamino)ethylamide Hydrochloride (5a). Add N,N'-carbonyldiimidazole (1.78 g, 0.011 mol) to the solution of acid **8a** (2.17 g, 0.01 mol) in anhydrous DMF (15 ml) protecting from the moisture of the air by a $CaCl_2$ tube and keep at 80ºC until the evolving of CO_2 stops (for about 1 h). Then add 2-(dethylamino)ethylamine (1.42 ml, 0.01 mol) and keep at the same temperature for 2 h. Remove the solvent under reduced pressure. Add water (15 ml) to the residue, acidify to pH about 4 using HCl, and then treat with sodium hydrosulphite (0.1 g) and carbon. Filter the product and add NaOH solution to the filtrate adjusting pH ~ 8. Extract the oily precipitate of the amide base with dichloromethane (3×20 ml). Mix the organic extracts, distil the solvent simultaneously removing the water remained as an azeotrope. Transfer the amide base obtained to the target hydrochloride **5a** as described before in the synthesis of the 4-chloro-substituted quinoline-3-carboxylic acid 2-(diethylamino)ethylamide hydrochloride **2**. The yield is 2.73 g (78%); mp 170-172 (anhydrous ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.30 (1H, br. s, NH^+); 9.93 (1H, t, *J* = 5.8, CONH); 8.85 (1H, s, H-4); 8.03 (1H, dd, *J* = 7.9 and *J* = 1.3, H-5); 7.78 (1H, td, *J* = 7.7 and *J* = 1.3, H-7); 7.70 (1H, d, *J* = 8.0 H-8); 7.44 (1H, td, *J* = 7.1 and *J* = 1.3, H-6); 4.38 (2H, q, *J* = 7.1, 1-NCH_2; 3.71 (2H, q, *J* = 6.0, CONHC$\underline{H}_2$); 3.16 (6H, m, $N(CH_2)_3$); 1.23 (9H, m, 3 CH_3). Found, %: C 61.35; H 7.32; N 12.07. $C_{18}H_{25}N_3O_2$·HCl. Calculated, %: C 61.44; H 7.45; N 11.94.

Compounds **5b-d** were prepared by the analogous method.

2-Oxo-1-propyl-1,2-dihydroquinoline-3-carboxylic Acid 2-(Diethylamino)ethylamide Hydrochloride (5b). Yield 80%; mp 151-153ºC (anhydrous ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.41 (1H, br. s, NH^+); 9.94 (1H, t, *J* = 5.9, CONH); 8.84 (1H, s, H-4); 8.02 (1H, d, *J* = 8.0, H-5); 7.76 (1H, t, *J* = 7.8, H-7); 7.69 (1H, d, *J* = 8.2, H-8); 7.36 (1H, t, *J* = 7.2, H-6); 4.29 (2H, t, *J* = 7.6, 1-NCH_2); 3.72 (2H, q, *J* = 6.2, CONHC$\underline{H}_2$); 3.16 (6H, m, $N(CH_2)_3$); 1.66 (2H, m, $NCH_2C\underline{H}_2CH_3$); 1.22 (6H, t, *J* = 7.2, $N(CH_2C\underline{H}_3)_2$); 0.96 (3H, t, *J* = 7.4, $NCH_2CH_2C\underline{H}_3$). Found, %: C 62.46; H 7.82; N 11.60. $C_{19}H_{27}N_3O_2$·HCl. Calculated, %: C 62.37; H 7.71; N 11.48.

1-Butyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 2-(Diethylamino)ethylamide Hydrochloride (5c). Yield 75%; mp 117-119ºC (acetone). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.37 (1H, br. s, NH^+); 9.94 (1H, t, *J* = 5.9, CONH); 8.85 (1H, s, H-4); 8.02 (1H, d, *J* = 7.9, H-5); 7.77 (1H, t, *J* = 7.8, H-7); 7.67 (1H, d, *J* = 8.4, H-8); 7.36 (1H, t, *J* = 7.1, H-6); 4.33 (2H, t, *J* = 7.3, 1-NC$\underline{H}_2$); 3.72 (2H, q, *J* = 6.3, CONHC$\underline{H}_2$); 3.19

(6H, m, $N(CH_2)_3$); 1.61 (2H, m, $NCH_2C\underline{H}_2CH_2CH_3$); 1.40 (2H, m, $NCH_2CH_2C\underline{H}_2CH_3$); 1.22 (6H, t, J = 7.1, $N(CH_2C\underline{H}_3)_2$); 0.93 (3H, t, J = 7.2, $NCH_2CH_2CH_2C\underline{H}_3$). Found, %: C 63.36; H 8.09; N 11.18. $C_{20}H_{29}N_3O_2 \cdot HCl$. Calculated, %: C 63.23; H 7.96; N 11.06.

1-Isobutyl-2-oxo-1,2-dihydroquinoline-3-carboxylic Acid 2-(Diethylamino)ethylamide Hydrochloride (5d). Yield 83%; mp 129-131ºC (acetone). ^{1}H NMR spectrum, δ, ppm (J, Hz): 10.29 (1H, br. s, NH^+); 9.91 (1H, t, J = 5.7, CONH); 8.84 (1H, s, H-4); 7.95 (1H, d, J = 8.0, H-5); 7.71 (1H, t, J = 7.7, H-7); 7.43 (1H, d, J = 8.2, H-8); 7.28 (1H, t, J = 7.2, H-6); 4.23 (2H, d, J = 7.0, 1-NCH_2); 3.71 (2H, q, J = 6.3, $CONHC\underline{H}_2$); 3.19 (6H, m, $N(CH_2)_3$); 2.16 (1H, m, $C\underline{H}(CH_3)_2$); 1.21 (6H, t, J = 7.1, $N(CH_2C\underline{H}_3)_2$); 0.90 (6H, d, J = 6.8, $CH(C\underline{H}_3)_2$). Found, %: C 63.32; H 8.04; N 10.95. $C_{20}H_{29}N_3O_2 \cdot HCl$. Calculated, %: C 63.23; H 7.96; N 11.06.

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