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Full Length Research Paper

Synthesis, structure and analgesic activity of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid hydroxy-alkylamides and their derivatives

Igor V. Ukrainets[1]*, Olga V. Gorokhova[1], Xeniya V. Andreeva[1] and Galina Sim[2]

[1]Department of Pharmaceutical Chemistry, National University of Pharmacy, Kharkiv 61002, Ukraine.
[2]Department of Pharmaceutical Chemistry, Far Eastern State Medical University, Khabarovsk 680000, Russia.

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The simple methods for obtaining have been suggested and the synthesis of new hydroxyalkylamides of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid and their derivatives has been carried out by alcoholic hydroxyl. The peculiarities of the spatial structure of the given group of substances have been considered by an example of 3-isopropoxypropylamide. The research results of the analgesic activity of all the compounds synthesized are given; they confirm the expediency of searching new painkillers among quinoline-3-carboxamides. According to the results of pharmacological tests for in-depth study recommended (3-chloropropyl)-amide of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid.

Key words: 3-aminopropanenitrile, 4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbox-amides, triethyl methanetricarboxylate, analgesia, pain syndrome.

INTRODUCTION

As a matter of fact, pain is a normal reaction of a living organism on potent stimuli of the chemical, physical or mechanical nature. Being a complex psychophysiological phenomenon, pain is manifested not only as a sense of discomfort, but emotional (sometimes very powerful) experience as well (Divakaran, 2011; van der Veek et al., 2012). On the one hand, signaling about occurrence of exogenous or endogenous destructive effects on any given organ (Foster et al., 2012; Henderson and Lachiewicz, 2012; Yuxiang et al., 2012; Balagué et al., 2012; Foster, 2011; Goebel et al., 2009; Alexander, 2011), it has a protective function and it is simply necessary for the organism's survival. On the other hand, strong and continuous pain can rapidly exhaust its adaptation resources and cause serious disorders of vitally important functions. Based on these facts the International Association for the Study of Pain considers pain as a global factor, which causes problems of both medical and social economic character in modern society (Bond, 2011; Goldberg and McGee, 2011; Sarzi-Puttini et al., 2012; McGee et al., 2011).

Pains of different origin and pain syndromes occur so often that it is difficult to find a person among the world population who does not know this feeling. Hence, it is not surprising that analgesics belong to the most increasingly in demand and often used medicines. The drug assortment of this pharmacological group available in modern medicine is extremely wide (Kleemann et al., 2008). Nevertheless, even under such conditions it is not always successful to provide the appropriate pain control. The cause can be side effects and, as a result, numerous contraindications and limitations in administration (Aronson, 2009). That is why the search of new highly effective and safe painkillers is rather relevant.

Over a period of about 20 years our laboratory has carried out the comprehensive study of synthetic methods, physicochemical and biological properties of a wide range of derivatives of 4-hydroxy-2-quinolones and it has shown the prospects for creating medicines with

*Corresponding author. E-mail addresses: uiv-2@mail.ru. Tel: +38-057-7098643.

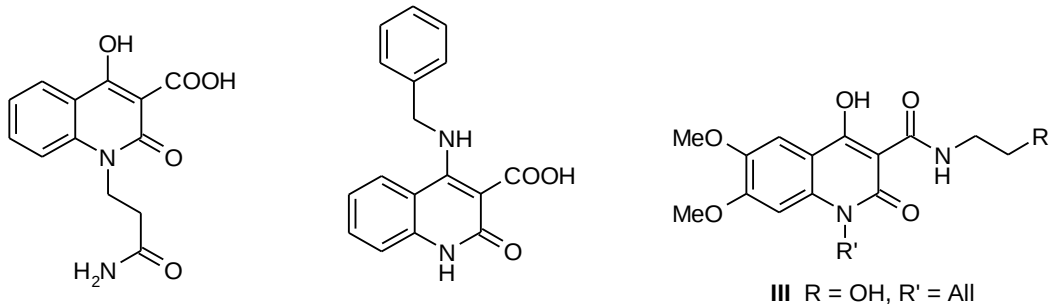

Figure 1. Quinolin-2-ones revealing high analgesic activity.

different pharmacological action, including potential analgesics, based on this heterocyclic molecular system. For example, it has been found that 1-(2-carbamoylethyl)-4-hydroxy- (I) and 4-benzylamino- (II) 2-oxo-1,2-dihydroquinoline-3-carboxylic acids (Ukrainets et al., 2010a) possess a high activity exceeding the analgesic properties of the known analgesics (Diclofenac, Ketorolac and even Tramadol) with much low toxicity. (2-Hydroxyethyl)amide of 1-allyl-4-hydroxy-6,7-dimethoxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (III) (Ukrainets et al., 2010b) and propylamide IV (Ukrainets et al. 2012) that is structurally similar to it have shown the excellent results in the experiments *in vivo* (Figure 1).

Continuing research in the direction selected the present paper is devoted to hydroxyl-alkylamides of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid and their functional derivatives according to the alcoholic hydroxyl. The interest specifically to quinoline-3-carboxamides is stipulated not only by the structural similarity with the highly active compounds studied previously. A weighty argument in favour of our choice is the absence of the marked acid properties (Ukrainets, 1988) in the compounds, which are responsible for the ulcerogenic effect (Aronson, 2009) that is characteristic for the most analgesics. A huge synthetic potential of the basic molecule is also of great importance, it allows to alter easily and without restriction the structural leaders found and, thus, to achieve improvement of their properties in the desired direction.

MATERIALS AND METHODS

Chemistry

^{1}H NMR spectra for amides 4-6 were recorded on a Varian Mercury VX-200 (200 MHz) spectrometer. The solvent was DMSO-d_6 and TMS as an internal standard for all cases. The chemical shifts values were recorded on δ scale and the coupling constants (*J*) in hertz. The following abbreviations were used in reporting spectra: s = singlet, d = doublet, t = triplet, quin = quintet, m = multiplet. Melting points were determined by using the open capillary method and are uncorrected. Elemental analysis was done on EuroVector EA-3000 analyzer. The synthesis of ethyl 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (3) was carried out by the method in the study (Ukrainets et al., 2010c).

(2-Hydroxyethyl)-amide of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (4a). To a solution of 2.86 g (0.01 mole) of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (3) in 15 ml of ethanol was added 0.67 g (0.011 mole) of 2-aminoetyl alcohol and the mixture was boiled under reflux for 2 h. The reaction mixture was cooled, treated with 50 ml of water, and acidified with concentrated HC1 to pH 3. The resulting precipitate was filtered off, washed with water, and dried to give 2.92 g (97%) of (2-hydroxyethyl)-amide 4a. Mp. 177-179 °C (ethanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 17.52 (1H, s, 4-OH), 10.32 (1H, t, *J* = 4.8, NH), 8.09 (1H, d, *J* = 8.1, H-5), 7.81–7.74 (2H, м, H-7,8), 7.37 (1H, td, *J* = 6.5 and 2.7, H-6), 4.95 (1H, br. s, OH), 4.53 (2H, t, *J* = 6.8, 1-NC$\underline{H}_2$), 3.55 (2H, br. s, C$\underline{H}_2$-OH), 3.42 (2H, q, *J* = 5.4, NHC$\underline{H}_2$), 2.92 (2H, t, *J* = 6.8, 1-NCH$_2$C$\underline{H}_2$); Elemental analysis: calcd. for $C_{15}H_{15}N_3O_4$: C, 59.80; H, 5.02; N, 13.95%; found: C, 59.88; H, 4.95; N, 14.06%.

(3-Hydroxypropyl)-amide of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (4b). To a solution of 2.86 g (0.01 mole) of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (3) in 15 ml of ethanol was added 0.83 g (0.011 mole) of 3-aminopropyl alcohol and the mixture was boiled under reflux for 2 h. The reaction mixture was cooled, treated with 50 ml of water, and acidified with concentrated HC1 to pH 3. The resulting precipitate was filtered off, washed with water, and dried to give 2.90 g (92%) of (3-hydroxypropyl)-amide 4b. Mp. 136 to 138°C (ethanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 17.51 (1H, s, 4-OH), 10.24 (1H, t, *J* = 4.9, NH), 8.06 (1H, d, *J* = 8.0, H-5), 7.80–7.72 (2H, м, H-7,8), 7.34 (1H, td, *J* = 6.4 and 2.8, H-6), 4.62 (1H, t, *J* = 4.6, OH), 4.50 (2H, t, *J* = 6.9, 1-NC$\underline{H}_2$), 3.53-3.37 (4H, m, NHC$\underline{H}_2$CH$_2$C$\underline{H}_2$OH), 2.91 (2H, t, *J* = 6.9, 1-NCH$_2$C$\underline{H}_2$), 1.69 (2H, quin., *J* = 6.3, NHCH$_2$C$\underline{H}_2$CH$_2$OH);

Elemental analysis: calcd. for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33%; found: C, 61.05; H, 5.49; N, 13.24%.

(2-Chloroxyethyl)-amide of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (5a). A mixture of 3.01 g (0.01 mole) of (2-hydroxyethyl)-amide 4a and 1.8 g (0.015 mole) of $SOCl_2$ in 30 ml of CH_2Cl_2 was boiled under reflux for 20 min. 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 3.15 g (99%) of (2-chloroxyethyl)-amide 5a was filtered off. Mp. 150-152 °C (ethanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 17.20 (1H, s, 4-OH), 10.41 (1H, t, *J* = 5.3, NH), 8.09 (1H, d, *J* = 8.1, H-5), 7.85–7.74 (2H, м, H-7,8), 7.38 (1H, td, *J* = 6.8 and 2.9, H-6), 4.54 (2H, t, *J* = 6.8, 1-NCH_2), 3.79 (2H, t, *J* = 4.6, CH_2-Cl), 3.72 (2H, q, *J* = 5.6, NHC$\underline{H}_2$), 2.93 (2H, t, *J* = 6.8, 1-NCH_2C$\underline{H}_2$); Elemental analysis: calcd. for $C_{15}H_{14}ClN_3O_3$: C, 56.35; H, 4.41; N, 13.14%; found: C, 56.27; H, 4.30; N, 13.06%.

(3-Chloropropyl)-amide of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (5b). A mixture of 3.15 g (0.01 mole) of (3-hydroxypropyl)-amide 5a and 1.8 g (0.015 mole) of $SOCl_2$ in 30 ml of CH_2Cl_2 was boiled under reflux for 20 min. 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 3.26 g (98%) of (3-chloropropyl)-amide 5b was filtered off. Mp. 124 to 126°C (ethanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 17.42 (1H, s, 4-OH), 10.25 (1H, t, *J* = 5.8, NH), 8.09 (1H, d, *J* = 8.0, H-5), 7.84–7.75 (2H, м, H-7,8), 7.37 (1H, td, *J* = 6.7 and 2.6, H-6), 4.53 (2H, t, *J* = 6.8, 1-NCH_2), 3.69 (2H, t, *J* = 6.3, CH_2-Cl), 3.50 (2H, q, *J* = 6.8, NHC$\underline{H}_2$), 2.93 (2H, t, *J* = 6.8, 1-NCH_2C$\underline{H}_2$), 2.02 (2H, quin., *J* = 6.8, NHCH_2C$\underline{H}_2$CH_2Cl); Elemental analysis: calcd. for $C_{16}H_{16}ClN_3O_3$: C, 57.58; H, 4.83; N, 12.59%; found: C, 57.51; H, 4.74; N, 12.66%.

(3-Methoxypropyl)-amide of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (6a). To a solution of 2.86 g (0.01 mole) of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (3) in 15 ml of ethanol was added 0.98 g (0.011 mole) of 3-methoxypropylamine and the mixture was boiled under reflux for 2 h. The reaction mixture was cooled, treated with 50 ml of water, and acidified with concentrated HC1 to pH 3. The resulting precipitate was filtered off, washed with water, and dried to give 2.96 g (90%) of (3-methoxypropyl)-amide 6a. Mp. 125 to 127°C (ethanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 17.58 (1H, s, 4-OH), 10.24 (1H, t, *J* = 5.6, NH), 8.09 (1H, d, *J* = 8.1, H-5), 7.84–7.73 (2H, м, H-7,8), 7.37 (1H, td, *J* = 6.7 and 2.8, H-6), 4.53 (2H, t, *J* = 6.9, 1-NCH_2), 3.48-3.35 (4H, m, NHC$\underline{H}_2$CH_2C$\underline{H}_2$OCH_3), 3.24 (3H, s, OCH_3), 2.92 (2H, t, *J* = 6.9, 1-NCH_2C$\underline{H}_2$),1.79 (2H, quin., *J* = 6.4, NHCH_2C$\underline{H}_2$CH_2OCH_3); Elemental analysis: calcd. for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76%; found: C, 62.12; H, 5.90; N, 12.83%.

(3-Isopropoxypropyl)-amide of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (6b). To a solution of 2.86 g (0.01 mole) of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (3) in 15 ml of ethanol was added 1.29 g (0.011 mole) of 3-methoxypropylamine and the mixture was boiled under reflux for 2 h. The reaction mixture was cooled, treated with 50 ml of water, and acidified with concentrated HC1 to pH 3. The resulting precipitate was filtered off, washed with water, and dried to give 3.25 g (91%) of (3-isopropoxypropyl)-amide 6b. Mp. 119-121°C (ethanol); ^{1}H NMR (200 MHz, DMSO-d_6): δ 17.60 (1H, s, 4-OH), 10.23 (1H, t, *J* = 5.6, NH), 8.08 (1H, d, *J* = 8.0, H-5), 7.83–7.73 (2H, м, H-7,8), 7.36 (1H, td, *J* = 6.6 and 2.7, H-6), 4.52 (2H, t, *J* = 6.8, 1-NCH_2), 3.54 (1H, m, C$\underline{H}$(CH_3)$_2$), 3.46-3.37 (4H, m, NHC$\underline{H}_2$CH_2C$\underline{H}_2$OPr-*i*), 2.92 (2H, t, *J* = 6.8, 1-NCH_2C$\underline{H}_2$), 1.75 (2H, quin., *J* = 6.3, NHCH_2C$\underline{H}_2$CH_2OPr-*i*), 1.08 (6H, d, *J* = 6.5, OCH(C$\underline{H}_3$)$_2$); Elemental analysis: calcd. for $C_{19}H_{23}N_3O_4$: C, 63.85; H, 6.49; N, 11.76%; found: C, 63.94; H, 6.58; N, 11.64%.

X-ray structural analysis

Crystal data for (3-isopropoxypropyl)-amide of 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid (6b): colorless, monoclinic (ethanol). At 20°C *a* = 23.699(9), *b* = 11.317(2), *c* = 15.546(5) Å, β = 119.68(5)°, *V* = 3623(2) Å^3, M_r = 357.40, *Z* = 8, space group C2/c, d_{calc} = 1.311 g/cm^3, μ(MoK_α) = 0.093 mm^{-1}, F(000) = 1520. The unit cell parameters and intensities of 20633 reflections (5273 independent, R_{int} = 0.030) were measured on an Xcalibur-3 diffractometer (MoK_α radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 60°). The structure was solved by the direct method using the *SHELXTL* program package (Sheldrick 2008). The positions of the hydrogen atoms were revealed by electron density difference synthesis and refined using the "riding" model with $U_{iso} = n\ U_{eq}$ (*n* = 1.5 for a methyl and hydroxyl group and *n* = 1.2 for remaining hydrogen atoms). The structure was refined using F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.187 for 5207 reflections (R_1 = 0.060 for 2216 reflections with $F > 4\sigma$ (*F*), *S* = 0.830). The full crystallographic information for the (3-isopropoxypropyl)-amide 6b has been placed in the Cambridge Crystallographic Data Centre as deposit CCDC 881943. Interatomic distances and valence angles are given in Tables 1 and 2, respectively.

Biological investigation

The analgesic activity for the compounds synthesized was measured by the “acetic acid induced writhing” test (Singh et al., 1983). While carrying out the biological

Table 1. Bond Lengths (*l*) in the (3-Isopropoxypropyl)-amide 6b structure.

Bond	*l*, Å	Bond	*l*, Å
N(1)-C(1)	1.381(2)	N(1)-C(9)	1.399(2)
N(1)-C(17)	1.482(2)	N(2)-C(10)	1.313(2)
N(2)-C(11)	1.440(2)	N(3)-C(19)	1.115(3)
O(1)-C(9)	1.221(2)	O(2)-C(7)	1.316(2)
O(3)-C(10)	1.256(2)	O(4)-C(13)	1.388(3)
O(4)-C(14)	1.406(2)	C(1)-C(6)	1.398(2)
C(1)-C(2)	1.402(3)	C(2)-C(3)	1.360(3)
C(3)-C(4)	1.364(3)	C(4)-C(5)	1.366(3)
C(5)-C(6)	1.391(3)	C(6)-C(7)	1.432(3)
C(7)-C(8)	1.368(2)	C(8)-C(9)	1.438(2)
C(8)-C(10)	1.470(3)	C(11)-C(12)	1.536(1)
C(12)-C(13)	1.536(1)	C(14)-C(16)	1.536(1)
C(14)-C(15)	1.538(1)	C(17)-C(18)	1.538(1)
C(18)-C(19)	1.479(3)		

Table 2. Valence angles (ω) in the (3-Isopropoxypropyl)-amide 6b structure.

Valence Angle	ω, deg.	Valence Angle	ω, deg.
C(1)-N(1)-C(9)	122.6(1)	C(1)-N(1)-C(17)	121.8(2)
C(9)-N(1)-C(17)	115.6(2)	C(10)-N(2)-C(11)	123.0(2)
C(13)-O(4)-C(14)	112.1(1)	N(1)-C(1)-C(6)	119.9(2)
N(1)-C(1)-C(2)	121.7(2)	C(6)-C(1)-C(2)	118.4(2)
C(3)-C(2)-C(1)	119.8(2)	C(2)-C(3)-C(4)	122.2(2)
C(3)-C(4)-C(5)	119.0(2)	C(4)-C(5)-C(6)	121.0(2)
C(5)-C(6)-C(1)	119.6(2)	C(5)-C(6)-C(7)	121.9(2)
C(1)-C(6)-C(7)	118.5(2)	O(2)-C(7)-C(8)	122.7(2)
O(2)-C(7)-C(6)	116.2(2)	C(8)-C(7)-C(6)	121.2(2)
C(7)-C(8)-C(9)	120.3(2)	C(7)-C(8)-C(10)	118.6(1)
C(9)-C(8)-C(10)	121.1(2)	O(1)-C(9)-N(1)	118.3(2)
O(1)-C(9)-C(8)	124.4(2)	N(1)-C(9)-C(8)	117.3(2)
O(3)-C(10)-N(2)	121.3(2)	O(3)-C(10)-C(8)	118.8(2)
N(2)-C(10)-C(8)	119.8(2)	N(2)-C(11)-C(12)	112.2(2)
C(13)-C(12)-C(11)	112.1(2)	O(4)-C(13)-C(12)	108.7(2)
O(4)-C(14)-C(16)	107.5(2)	O(4)-C(14)-C(15)	112.4(2)
C(16)-C(14)-C(15)	108.5(2)	N(1)-C(17)-C(18)	106.9(2)
C(19)-C(18)-C(17)	107.6(2)	N(3)-C(19)-C(18)	175.3(3)

experiments the animals were treated in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes. Investigations were carried out on white mice - 6 animals for each test substance. Amides 4-6 and the reference drug Diclofenac were administered *per os* in the form of a thin aqueous suspension stabilized be Tween-80 in the dose of 5 mg/kg. This dose corresponds to ED_{50} of Diclofenac exactly for the model of “acetic acid induced writhing” (Sigidin et al. 1988). The control group received only water with Tween-80.

RESULTS AND DISCUSSION

The initial ethyl 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (3) was obtained by condensation of 3-anilinopropanenitrile 1 with triethyl methane-tricarboxylate 2 according to the known method (Ukrainets et al., 2010c) (Figure 2).

The subsequent amidation of ester 3 by hydroxyalkylamines occurs in boiling ethanol without any complications and gives the corresponding hydroxyalkylamides 4a,b with high yields (Figure 3).

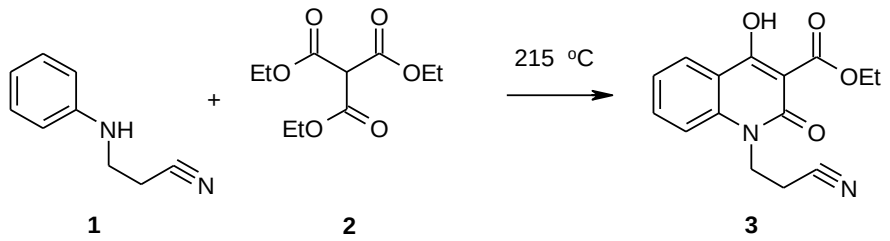

Figure 2. Synthesis of ethyl 1-(2-cyanoethyl)-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylate (3).

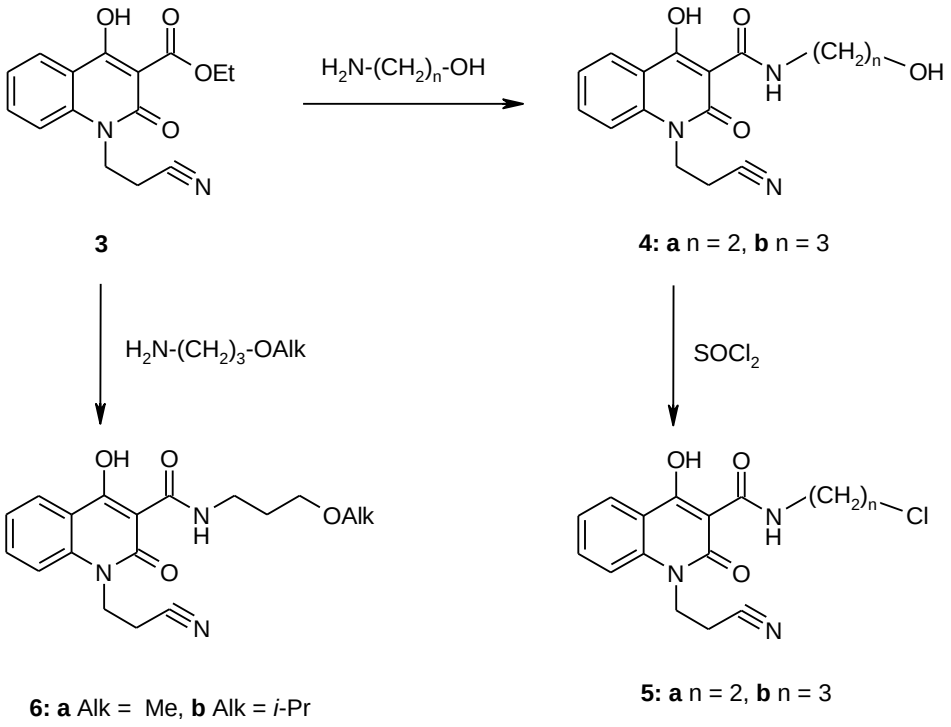

Figure 3. Synthesis of N-R-amides 4-6.

Substitution of alcoholic hydroxyls in hydroxyalkylamides 4a,b to chlorine is more suitable to carry out with the help of the thionyl chloride excess – the reaction completes in 15 to 20 min with formation of chloroalkylamides 5a,b practically with the quantitative yields.

The synthesis of alkoxyalkylamides 6a, b is theoretically possible by various pathways. However, in practice the most evident of them do not provide positive results. Thus, in particular, when interacting chloroalkylamides of type 5a,b with sodium alkoxides in anhydrous alcohols there is no change of halogen to the alkoxy group, but the intramolecular alkylation of 4-OH-group (Ukrainets et al., 1993) resulting in formation of oxazepino- or oxazocinoquinolinones occurs.

The similar process differing only by the fact that it is not accompanied by heterocyclization is observed in common alkylation of 4-hydroxy-2-quinolones by alkylhalides in the presence of inorganic bases – primarily 4-OH- group (Ukrainets et al., 1996) is also subjected to electrophilic attack. Thus, it is expedient to obtain alkoxypropylamides 6a,b using manufactured alkoxypropylamines.

All the products were characterized by ^{1}H NMR data. The spatial structure of (3-isopropoxypropyl)-amide 6b was also studied with the help of X-ray crystallographic analysis (Figure 4). It has been found that the quinolone bicycle, the carbonyl and hydroxyl groups, as well as the carbamide fragment of this compound lie in a single plane with the accuracy of 0.01 Å. The intramolecular hydrogen bonds $O_{(2)}$-$H_{(2O)}\cdots O_{(3)}$ (H···O 1.72 Å, O-H···O 146°) and $N_{(2)}$-$H_{(2N)}\cdots O_{(1)}$ (H···O 1.97 Å, N-H···O 136°) contribute to it. The formation of hydrogen bonds leads

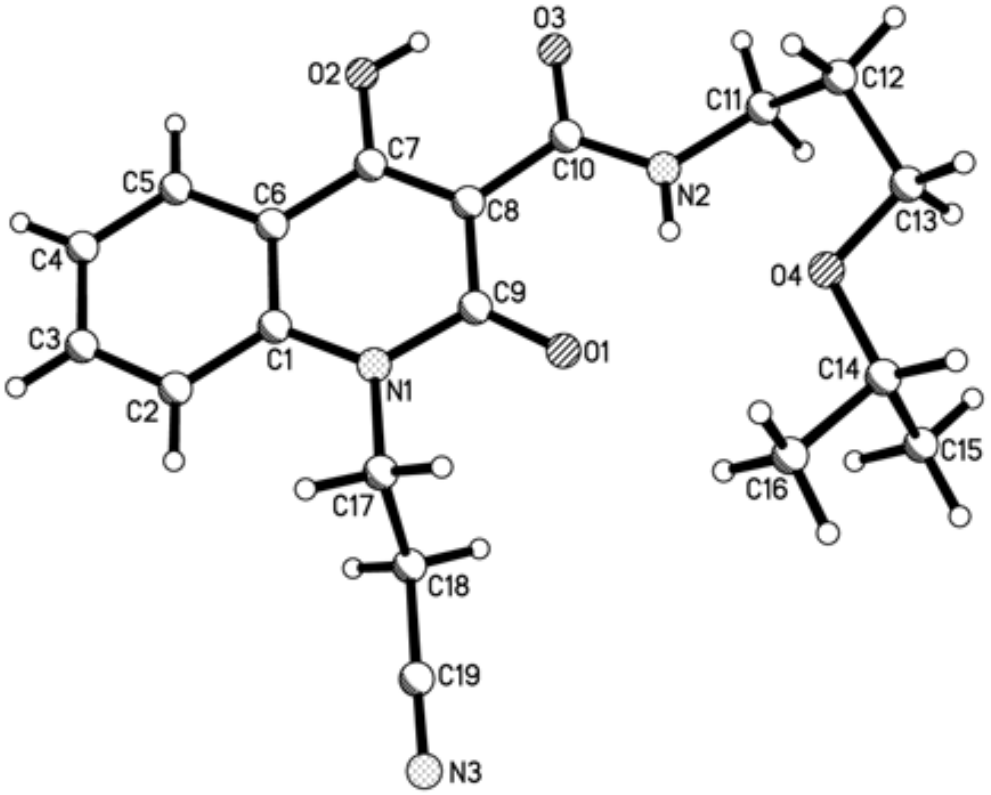

Figure 4. The structure of the (3-isopropoxypropyl)-amide 6b with atomic numbering.

also to elongation of $O_{(1)}$-$C_{(9)}$ bonds to 1.221(2) Å and $O_{(3)}$-$C_{(10)}$ bonds to 1.256(2) Å comparing to their mean value (Burgi and Dunitz, 1994) 1.210 Å and shortening of $O_{(2)}$-$C_{(7)}$ bonds to 1.316(2) Å and $C_{(8)}$-$C_{(9)}$ bonds to 1.438(2) Å (mean values are 1.362 and 1.455 Å, respectively).

The bond of $C_{(7)}$-$C_{(8)}$ is elongated to 1.368(2) Å (the mean value is 1.326 Å), and it is characteristic for quinolones. It should be noted that the NH group of the amide fragment forms the bifurcation hydrogen bond, in which the oxygen atom of the isopropoxy group: $N_{(2)}$-$H_{(2N)}\cdots O_{(4)}$ (H···O 2.28 Å, N-H···O 122°) participates. The formation of this hydrogen bond result in that the substituent at the nitrogen atom of the amide fragment is in the antiperiplanar position in relation to $C_{(8)}$-$C_{(10)}$ bond [the torsional angle of $C_{(8)}$-$C_{(10)}$-$N_{(2)}$-$C_{(11)}$ is 179.8(2)°] and has conformation of *ac* – *+sc* – *-sc* [the torsional angle for $C_{(10)}$-$N_{(2)}$-$C_{(11)}$-$C_{(12)}$ is 125.2(2)°, for $N_{(2)}$-$C_{(11)}$-$C_{(12)}$-$C_{(13)}$ is 75.0(2)° and for $C_{(11)}$-$C_{(12)}$-$C_{(13)}$-$O_{(4)}$ is -61.5(3)°]. The isopropyl group is in *ap*-conformation in relation to $C_{(12)}$-$C_{(13)}$ bond and spread in such way that $C_{(14)}$-$H_{(14)}$ bond is synclinal to $C_{(13)}$-$O_{(4)}$ bond [torsional angles are $C_{(14)}$-$O_{(4)}$-$C_{(13)}$-$C_{(12)}$ 179.4(2)°, $C_{(13)}$-$O_{(4)}$-$C_{(14)}$-$H_{(14)}$ 43.7°]. Such conformation of the substituent results in appearance of the shortened intramolecular contacts: $H_{(11b)}\cdots O_{(3)}$ 2.34 Å [sum of van der Waal radii (Zefirov 1997) 2.46 Å], $H_{(13a)}\cdots H_{(14)}$ 2.25 Å (2.34 Å), $H_{(13b)}\cdots C_{(15)}$ 2.72 Å (2.87 Å), $H_{(13b)}\cdots H_{(15a)}$ 2.20 Å (2.34 Å) and $H_{(15a)}\cdots C_{(13)}$ 2.79 Å (2.87 Å). The cyanomethylene fragment of the substituent at $N_{(1)}$ atom is located practically perpendicular to the plane of the quinolone nucleus, and the cyanogroup is in *ap*-conformation in relation to $C_{(17)}$-$C_{(18)}$ bond [torsional angles are $C_{(1)}$-$N_{(1)}$-$C_{(17)}$-$C_{(18)}$ 94.5(2)º, $N_{(1)}$-$C_{(17)}$-$C_{(18)}$-$C_{(19)}$ -179.7(2)°]. An appreciable repulsion between atoms of $N_{(1)}$-substituent and the quinolone fragment [shortened intramolecular contacts $H_{(2)}\cdots C_{(17)}$ 2.58 Å (the sum of van der Waal radii 2.87 Å), $H_{(2)}\cdots H_{(17b)}$ 2.06 Å (2.34 Å), $H_{(17b)}\cdots C_{(2)}$ 2.57 Å (2.87 Å) and $H_{(17a)}\cdots O_{(1)}$ 2.33 Å (2.46 Å)] leads to elongation of $N_{(1)}$-$C_{(9)}$ bonds to 1.399(2) Á and $N_{(1)}$-$C_{(17)}$ to 1.482(2) Á comparing to their mean values 1.353 and 1.469 Å, respectively. The test results of all the compounds synthesized by us having had analgesic activity are given in Table 3.

The analysis of the research data obtained shows that all the substances investigated actually reveal the marked and statistically significant ($p \leq 0.05$) analgesic properties. Among the group (3-chloropropyl)-amide 5b, which analgesic effect is significantly higher the effect of the reference drug, is of special interest. From the combination of chemical and biological characteristics of this compound merits further study as a potential analgesic. Therefore, our research testifies the

Table 3. The analgesic activity for compounds 4-6 and diclofenac.

Compound	The average number of writhing	%
4a	30.8 ± 1.3	51
4b	33.4 ± 1.2	47
5a	47.9 ± 1.4	24
5b	23.3 ± 0.9	63
6a	31.5 ± 1.0	50
6b	34.6 ± 1.2	45
Diclofenac	30.2 ± 1.3	52
Control	63.0 ± 1.1	–

perspectivity of searching new painkillers among quinoline-3-carboxamides.

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