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4-HYDROXY-2-QUINOLONES 173*. 1-R-3-(2-DIETHYLAMINO-ETHYL)-1H-QUINAZOLINE-2,4-DIONE HYDROCHLORIDES AS POTENTIAL LOCAL ANESTHETIC AGENTS

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Different variants of the preparation and procedures in the synthesis of a series of 1-R-3-(2-dialkyl-aminoethyl)-1H-quinazoline-2,4-dione hydrochlorides having a structural similarity to the 4-hydroxy-2-quinolinone anesthetic chinoxicaine are discussed. A comparative analysis of the biological properties of the synthesized compounds and the known local anesthetics chinoxicaine and lidocaine is reported.

Keywords: isatoic anhydride, local anesthetics, alkylation, 1H-quinazoline-2,4-diones, X-ray structural analysis.

Local anesthetic agents are a distinct group of drugs which, upon direct contact, can reversibly lower or fully shut down feelings of pain in a limited region of mucous membrane, skin, or other tissues. About 40 preparations of this type are currently used in anesthetic practice [2, 3]. Unfortunately none of these is without drawbacks, the most significant of which are high toxicity, inhibition of cardiac activity (up to cardiac arrest), and different kinds of allergic reaction. Hence the search for novel, efficient, and also safe local anesthetics is relevant at this time. The need to carry out an investigation of this type is also dictated by the fact that the last of these appeared in the pharmaceutical field all of 25 years ago (*ropivacaine* [4]) and is unfortunately still only an analog of the better known *lidocaine* and *bupivacaine* [2, 3].

The novel quinolone anesthetic *chinoxicaine* recently proposed [5] shows not only highly specific activity but also a series of other pharmacological properties useful for preparations of this type. However they

* For Communication 172 see [1].

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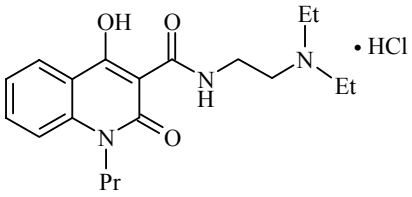
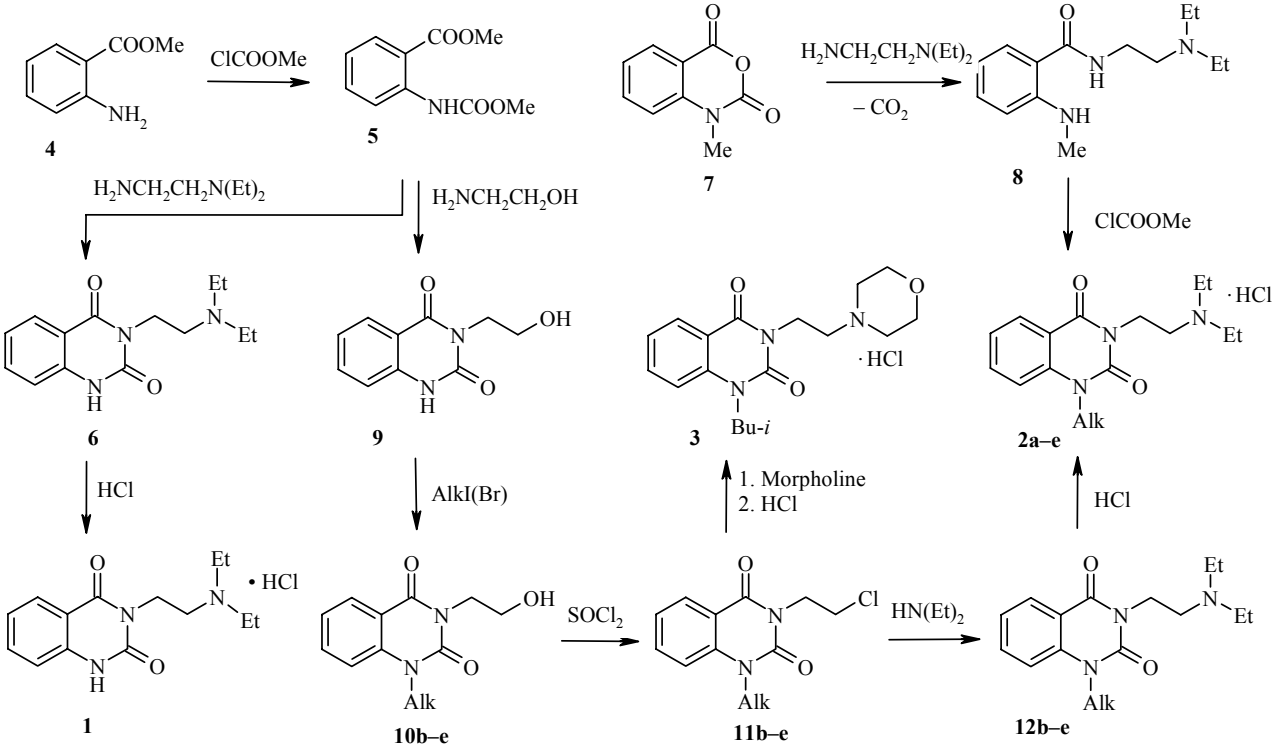
proved not without problems. If one of these (complicating the preparation of injectable drug forms through low solubility in water) can be resolved quite simply then the another arising from a burning sensation at the point of injection in patients has so far only been reduced and not eliminated [6].



Chinoxicaine

Most probably the main contribution to the observed *chinoxicaine* local anesthetic effect is the occurrence in its structure of a 4-OH group. With this in mind one of the variants we decided to study was the synthesis of compounds close in structure to *chinoxicaine* but, at the same time, without the acidic properties of the hydroxyl groups. The first examples of such compounds were the 1-R-3-(2-dialkylaminoethyl)-1H-quinazoline-2,4-dione hydrochlorides **1-3**. Different routes can be used in their synthesis. Hence the analog unsubstituted at position 1 can be obtained conveniently by the following scheme. Methyl anthranilate (**4**) → methyl 2-(methoxycarbonylamino)benzoate (**5**) → 3-(2-diethylaminoethyl)-1H-quinazoline-2,4-dione free base (**6**) → its hydrochloride (**1**).

N-Monoalkyl-substituted anthranilates are poorly acylated by alkyl chloroformates. Hence the synthesis of the 1-alkyl-3-(2-diethylaminoethyl)-1H-quinazoline-2,4-dione hydrochlorides **2a-e** began better from the corresponding isatoic anhydrides **7** which readily formed the anthranylamides **8** and, in turn, condensed to the target quinazolones. This method is quite simple in use, consists of only two stages, and does not demand



2, 10–12 **a** Alk = Me; **b** Alk = Et; **c** Alk = Pr; **d** Alk = Bu; **e** Alk = *i*-Bu

separation of intermediate products. However, its practical realization is markedly limited by the very limited range of N-alkyl-substituted isatoic anhydrides available. Independent synthesis of these acylating agents is far from always possible. For this reason attention to an alternative method is merited. Although multistage it is feasible in practice in any chemical laboratory. The starting material is methyl 2-(methoxycarbonyl-amino)benzoate (**5**) which is condensed with 2-aminoethanol to give 3-(2-hydroxyethyl)-1H-quinazoline-2,4-dione (**9**). The N-alkyl substituent is introduced in the next step which is carried out in DMSO/K_2CO_3 after which the 2-hydroxyethyl derivatives **10b-e** are treated with thionyl chloride to give the 1-alkyl-3-(2-chlorooethyl)-1H-quinazoline-2,4-diones **11b-e**. These are key compounds in the synthesis of the target 1-alkyl-substituted 3-(2-dialkylaminoethyl)-1H-quinazoline-2,4-dione hydrochlorides **2, 3**. For an unambiguous confirmation of their structure we have examined the 1-isobutyl derivative **11e** by X-ray structural analysis.

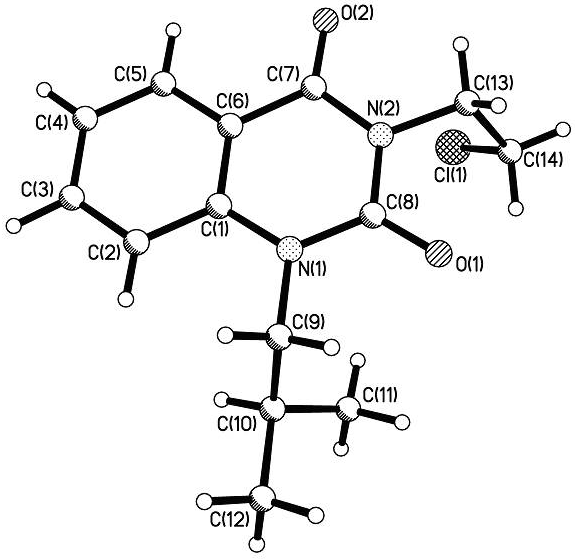


Fig. 1. Structure of the chloroethylquinazolone **11e** molecule with atomic numbering.

The quinazolone fragment and atoms O(1) and O(2) in this compound lie in a single plane to within 0.02 Å (see Fig. 1 and Tables 1 and 2). Strong repulsion between the substituent at atom N(1) and the neighboring carbonyl group and benzene ring atoms [shortened intramolecular contacts H(2)···C(9) 2.57 (sum of van der Waal radii 2.87), H(2)···H(9a) 2.19 (2.34), H(2)···C(10) 2.85 (2.87), H(2)···H(10) 2.28 (2.34),

TABLE 1. Bond Lengths (*l*) in the Chloroethylquinazolone **11e**

Bond	*l*, Å	Bond	*l*, Å
Cl(1)–C(14)	1.795(1)	N(1)–C(8)	1.381(1)
N(1)–C(1)	1.397(1)	N(1)–C(9)	1.475(1)
N(2)–C(7)	1.391(1)	N(2)–C(8)	1.402(1)
N(2)–C(13)	1.471(1)	O(1)–C(8)	1.221(1)
O(2)–C(7)	1.226(1)	C(1)–C(6)	1.398(1)
C(1)–C(2)	1.409(2)	C(2)–C(3)	1.385(2)
C(3)–C(4)	1.399(2)	C(4)–C(5)	1.386(2)
C(5)–C(6)	1.400(2)	C(6)–C(7)	1.468(1)
C(9)–C(10)	1.531(2)	C(10)–C(11)	1.526(2)
C(10)–C(12)	1.527(2)	C(13)–C(14)	1.516(2)

TABLE 2. Valence Angles (ω) in the Chloroethylquinazolone Structure **11e**

Angle	ω, deg	Angle	ω, deg
C(8)–N(1)–C(1)	122.2(1)	C(8)–N(1)–C(9)	117.2(1)
C(1)–N(1)–C(9)	120.6(1)	C(7)–N(2)–C(8)	125.2(1)
C(7)–N(2)–C(13)	118.4(1)	C(8)–N(2)–C(13)	116.4(1)
N(1)–C(1)–C(6)	119.6(1)	N(1)–C(1)–C(2)	121.7(1)
C(6)–C(1)–C(2)	118.7(1)	C(3)–C(2)–C(1)	119.8(1)
C(2)–C(3)–C(4)	121.5(1)	C(5)–C(4)–C(3)	118.8(1)
C(4)–C(5)–C(6)	120.4(1)	C(1)–C(6)–C(5)	120.8(1)
C(1)–C(6)–C(7)	120.6(1)	C(5)–C(6)–C(7)	118.6(1)
O(2)–C(7)–N(2)	121.6(1)	O(2)–C(7)–C(6)	123.5(1)
N(2)–C(7)–C(6)	115.0(1)	O(1)–C(8)–N(1)	122.8(1)
O(1)–C(8)–N(2)	120.0(1)	N(1)–C(8)–N(2)	117.3(1)
N(1)–C(9)–C(10)	114.1(1)	C(11)–C(10)–C(12)	110.8(1)
C(11)–C(10)–C(9)	112.2(1)	C(12)–C(10)–C(9)	108.0(1)
N(2)–C(13)–C(14)	112.4(1)	C(13)–C(14)–Cl(1)	111.1(1)

H(9a)···C(2) 2.66 (2.87), H(9b)···O(1) 2.31 (2.46), and H(10)···C(2) 2.84 Å (2.87 Å)] leads to some deviation of the substituent from the plane of the bicyclic fragment (torsional angle C(9)–N(1)–C(1)–C(2) -4.4(2)º) with retention of a trigonal-planar configuration of the nitrogen atom and to lengthening of the N(1)–C(8) 1.381(1) and N(1)–C(1) 1.397(1) Å bonds when compared with their mean values [8] of 1.353 and 1.371 Å respectively. The isopropyl fragment is positioned virtually perpendicularly to the quinazolone ring plane (torsional angle C(1)–N(1)–C(9)–C(10) 81.2(1)º) and is twisted such that the C–H bond occurs in a -*sc*-conformation relative to the N(1)–C(9) bond (torsional angle N(1)–C(9)–C(10)–H(10) -64.7º). The chloroethyl substituent is placed such that the bond C(14)–Cl(1) occurs in a +*sc*-conformation relative to the C(8)–N(2) bond (torsional angle C(8)–N(2)–C(13)–C(14) 73.2(1)º) and is twisted relative to the N(2)–C(13) bond (torsional angle N(2)–C(13)–C(14)–Cl(1) 58.7(1)º). An attractive interaction occurs between the $C(13)H_2$ methylene group atoms and the neighboring carbonyl groups H(13a)···O(2) 2.26 and H(13b)···O(1) 2.45 Å (sum of van der Waal radii 2.46 Å) which cannot be considered hydrogen bonding because of the too acute angles C–H···O (110 and 93º respectively).

In the crystal of the chloroethyl quinazolone **11e** there are weak intermolecular hydrogen bonds: C(2)–H(2)···Cl(1)' (*x*, *y*, 1+*z*) H···Cl 2.87 Å; C–H···Cl 145º, C(10)–H(10)···Cl(1)' (1-*x*, -*y*, 2-*z*) H···Cl 2.97 Å, C–H···Cl 128º, C(12)–H(12b)···Cl(1)' (1-*x*, -*y*, 2-*z*) H···Cl 2.96 Å, C–H···Cl 116º and a shortened intermolecular contact H(5)···H(13b)' (-*x*, -0.5+*y*, 1.5-*z*) 2.30 Å (2.34 Å).

As is known, 3-(2-chloroethyl)-1H-quinazoline-2,4-diones do not possess a high reactivity towards secondary amines. Hence the alkylation of piperidines in refluxing 4-methyl-2-pentanone or ethanol does not give the corresponding tertiary amines in greater than 30% yield [9]. In addition, attempts to prepare the 1-alkyl-3-(2-diethylaminoethyl)-1H-quinazoline-2,4-dione hydrochlorides **2a-e** by this method revealed to us a further weakness in that the tertiary amines **12** formed under these conditions are readily and strongly oxidized. The reaction mixture becomes dark-brown and this undoubtedly affects the quality of the final materials (the need for purification with regard to their potential use as injectable solutions being particularly high). Marked changes were introduced into the method in order to remove the indicated drawbacks. It was found that both the yield and purity of the target compounds can be significantly increased by treatment of the chloroethyl-quinazolones **11b-e** with a large excess of diethylamine in sealed, argon filled ampules. This method has also been used by us in the synthesis of the diethylaminoethyl derivatives **12b-e** isolated as the corresponding hydrochlorides **2** (Table 3). A similar method also gave the 1-isobutyl-3-(2-morpholin-4-ylethyl)-1H-quinazoline-2,4-dione hydrochloride (**3**) as an analog of the 2-morpholin-4-ylamides of 1-R-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acids which also show marked local anesthetic properties [10].

TABLE 3. Characteristics of the Quinazoline-2,4-diones **2, 3, 10,** and **11**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{15}H_{21}N_3O_2$•HCl	57.91 / 57.78	7.20 / 7.11	13.36 / 13.48	208-210	79
2b	$C_{16}H_{23}N_3O_2$•HCl	59.12 / 58.98	7.34 / 7.42	12.79 / 12.90	245-247	72
2c	$C_{17}H_{25}N_3O_2$•HCl	60.17 / 60.08	7.82 / 7.71	12.45 / 12.36	184-186	70
2d	$C_{18}H_{27}N_3O_2$•HCl	61.22 / 61.09	8.08 / 7.97	11.74 / 11.87	107-109	67
2e	$C_{18}H_{27}N_3O_2$•HCl	59.97 / 61.09	7.89 / 7.97	11.76 / 11.87	111-113	65
3	$C_{18}H_{25}N_3O_3$•HCl	58.66 / 58.77	7.22 / 7.12	11.55 / 11.42	115-117	71
10b	$C_{12}H_{14}N_2O_3$	61.65 / 61.53	6.13 / 6.02	12.04 / 11.96	121-123	88
10c	$C_{13}H_{16}N_2O_3$	62.79 / 62.89	6.62 / 6.50	11.21 / 11.28	94-96	83
10d	$C_{14}H_{18}N_2O_3$	64.20 / 64.11	7.03 / 6.92	10.56 / 10.68	97-99	77
10e	$C_{14}H_{18}N_2O_3$	64.22 / 64.11	6.99 / 6.92	10.77 / 10.68	91-93	81
11b	$C_{12}H_{13}ClN_2O_2$	56.95 / 57.04	5.06 / 5.19	11.02 / 11.09	102-104	94
11c	$C_{13}H_{15}ClN_2O_2$	58.47 / 58.54	5.55 / 5.67	10.41 / 10.50	73-75	95
11d	$C_{14}H_{17}ClN_2O_2$	60.02 / 59.89	6.24 / 6.10	10.10 / 9.98	56-58	92
11e	$C_{14}H_{17}ClN_2O_2$	59.98 / 59.89	6.15 / 6.10	10.07 / 9.98	87-89	97

The structure of all of the synthesized final 1-R-3-(2-dialkylaminoethyl)-1H-quinazoline-2,4-dione hydrochlorides **1-3** and the intermediate hydroxy- and chloroethylquinazolones **9-11** were confirmed by their ^{1}H NMR spectra (see Experimental and Table 4).

A study of the local irritant effects of the 1-R-3-(2-dialkylaminoethyl)-1H-quinazoline-2,4-dione hydrochlorides **1-3** was carried out on rabbits by the method reported by Lebo and Camage [11] which showed that 2% aqueous solutions of the compounds studied did not cause any kind of reactive changes on the skin surface of the experimental animal. It should be noted that the irritant effect is also not seen for chinoxicaine under analogous conditions. Hence for further studies it is essential to work with other more sensitive experimental models.

The ability of 2% solutions of the synthesized compounds to cause anesthesia penetration into the skin and subcutaneous tissues was studied on guinea pigs (the Buelbring-Yueid method [11]). This takes into account several indicators typifying the essential features of the pharmacological effect, i.e. the rate of onset of anesthesia, its depth (strength), and duration. The data in Table 5 shows that local anesthetic properties are present to some extent in all of the 1-R-3-(2-dialkylaminoethyl)-1H-quinazoline-2,4-dione hydrochlorides **1-3**.

In most cases the onset of anesthesia is quite rapid and several minutes after injection a phase of deep anesthesia starts. However, despite the high index value for the anesthesia penetration, sometimes reaching a maximum value, the overall duration of full anesthesia achieved by quinazolones **1-3** remains rather short and they marked fall short of *chinoxicaine* and *lidocaine* in this parameter.

None the less, in contrast to the compounds of greatest activity amongst the synthesized compounds (the hydrochlorides **1** and **2d,e**) there are discovered a series of novel properties amongst compounds with short but strong anesthetic effects which can be considered as useful. This is revealed in the lethargy and lassitude of the experimental animals up to full sleep sedation and also disturbance of motor activity or motor block upon

TABLE 4. ^{1}H NMR Spectra of the Quinazoline-2,4-diones **2, 3, 10**, and **11**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
2a	10.46 (1H, br. s, NH^+); 8.05 (1H, dd, *J* = 7.8 and *J* = 1.6, H-5); 7.80 (1H, td, *J* = 7.9 and *J* = 1.6, H-7); 7.47 (1H, d, *J* = 8.4, H-8); 7.31 (1H, t, *J* = 7.6, H-6); 4.28 (2H, t, *J* = 7.0, NCH_2); 3.51 (3H, s, CH_3); 3.22 (6H, m, $N(CH_2)_3$); 1.23 (6H, t, *J* = 7.5, $2CH_3$)
2b	10.68 (1H, br. s, NH^+); 8.05 (1H, dd, *J* = 7.8 and *J* = 1.4, H-5); 7.78 (1H, td, *J* = 7.9 and *J* = 1.6, H-7); 7.51 (1H, d, *J* = 8.4, H-8); 7.30 (1H, t, *J* = 7.5, H-6); 4.27 (2H, t, *J* = 7.1, $NC\underline{H}_2CH_2N$); 4.13 (2H, q, *J* = 7.2, $NC\underline{H}_2CH_3$); 3.21 (6H, m, $N(CH_2)_3$); 1.23 (9H, m, 1-$NCH_2C\underline{H}_3$ + $2CH_3$)
2c	10.07 (1H, br. s, NH^+); 8.06 (1H, dd, *J* = 7.9 and *J* = 1.4, H-5); 7.78 (1H, td, *J* = 7.9 and *J* = 1.6, H-7); 7.52 (1H, d, *J* = 8.6, H-8); 7.30 (1H, t, *J* = 7.5, H-6); 4.27 (2H, t, *J* = 6.9, $NC\underline{H}_2CH_2N$); 4.04 (2H, t, *J* = 7.6, $NC\underline{H}_2C_2H_5$); 3.22 (6H, m, $N(CH_2)_3$); 1.64 (2H, m, $NCH_2C\underline{H}_2CH_3$); 1.21 (6H, t, *J* = 7.1, $2CH_3$); 0.94 (3H, t, *J* = 7.5, $NCH_2CH_2C\underline{H}_3$)
2d	10.24 (1H, br. s, NH^+); 8.06 (1H, dd, *J* = 7.9 and *J* = 1.6, H-5); 7.78 (1H, td, *J* = 7.8 and *J* = 1.6, H-7); 7.50 (1H, d, *J* = 8.5, H-8); 7.30 (1H, t, *J* = 7.5, H-6); 4.27 (2H, t, *J* = 6.9, $NC\underline{H}_2CH_2N$); 4.08 (2H, t, *J* = 7.6, $NC\underline{H}_2C_3H_7$); 3.23 (6H, m, $N(CH_2)_3$); 1.60 (2H, q, *J* = 7.4, $C\underline{H}_2C_2H_5$); 1.39 (2H, m, $NCH_2CH_2C\underline{H}_2CH_3$); 1.22 (6H, t, *J* = 7.1, $2CH_3$); 0.91 (3H, t, *J* = 7.2, $NCH_2CH_2CH_2C\underline{H}_3$)
2e	10.36 (1H, br. s, NH^+); 8.06 (1H, dd, *J* = 7.8 and *J* = 1.7, H-5); 7.77 (1H, td, *J* = 7.8 and *J* = 1.6, H-7); 7.49 (1H, d, *J* = 8.3, H-8); 7.29 (1H, t, *J* = 7.5, H-6); 4.28 (2H, t, *J* = 6.9, $NC\underline{H}_2CH_2N$); 3.95 (2H, d, *J* = 7.3, $NC\underline{H}_2CH(CH_3)_2$); 3.21 (6H, m, $N(CH_2)_3$); 2.08 (1H, m, $C\underline{H}(CH_3)_2$); 1.21 (6H, t, *J* = 7.2, $2CH_3$); 0.92 (6H, d, *J* = 6.5, $NCH_2CH(C\underline{H}_3)_2$)
3	10.67 (1H, br. s, NH^+); 8.06 (1H, d, *J* = 7.8, H-5); 7.76 (1H, t, *J* = 7.8, H-7); 7.49 (1H, d, *J* = 8.5, H-8); 7.30 (1H, t, *J* = 7.4, H-6); 4.31 (2H, t, *J* = 6.8, $NC\underline{H}_2CH_2N$); 3.95 (2H, d, *J* = 7.4, $NC\underline{H}_2CH(CH_3)_2$); 3.77–3.04 (10H, m, $N(CH_2)_3$ + $O(CH_2)_2$); 2.09 (1H, m, $C\underline{H}(CH_3)_2$); 0.92 (6H, d, *J* = 6.5, $NCH_2CH(C\underline{H}_3)_2$)
10b	8.04 (1H, dd, *J* = 8.0 and *J* = 1.6, H-5); 7.75 (1H, td, *J* = 7.8 and *J* = 2.0, H-7); 7.47 (1H, d, *J* = 8.5, H-8); 7.26 (1H, t, *J* = 7.6, H-6); 4.76 (1H, t, *J* = 5.8, OH); 4.12 (2H, q, *J* = 7.1, $NC\underline{H}_2CH_3$); 4.02 (2H, t, *J* = 6.4, $NC\underline{H}_2CH_2OH$); 3.54 (2H, q, *J* = 6.4, $C\underline{H}_2OH$); 1.19 (3H, t, *J* = 7.1, CH_3)
10c	8.03 (1H, dd, *J* = 8.1 and *J* = 1.6, H-5); 7.74 (1H, td, *J* = 7.9 and *J* = 2.0, H-7); 7.45 (1H, d, *J* = 8.2, H-8); 7.26 (1H, t, *J* = 7.5, H-6); 4.76 (1H, t, *J* = 5.8, OH); 4.03 (4H, m, $NC\underline{H}_2C_2H_5$ + $NC\underline{H}_2CH_2OH$); 3.54 (2H, q, *J* = 6.5, $C\underline{H}_2OH$); 1.61 (2H, m, $C\underline{H}_2CH_3$); 0.92 (3H, t, *J* = 7.5, CH_3)
10d	8.04 (1H, d, *J* = 7.9, H-5); 7.74 (1H, t, *J* = 7.8, H-7); 7.45 (1H, d, *J* = 8.3, H-8); 7.26 (1H, t, *J* = 7.6, H-6); 4.75 (1H, t, *J* = 6.0, OH); 4.04 (4H, m, $NC\underline{H}_2C_3H_7$ + $NC\underline{H}_2CH_2OH$); 3.54 (2H, q, *J* = 6.2, $C\underline{H}_2OH$); 1.55 (2H, q, *J* = 7.2, $C\underline{H}_2C_2H_5$); 1.36 (2H, m, $C\underline{H}_2CH_3$); 0.90 (3H, t, *J* = 7.3, CH_3)
10e	8.04 (1H, dd, *J* = 7.9 and *J* = 1.6, H-5); 7.73 (1H, td, *J* = 7.8 and *J* = 1.8, H-7); 7.45 (1H, d, *J* = 8.5, H-8); 7.25 (1H, t, *J* = 7.6, H-6); 4.75 (1H, t, *J* = 5.9, OH); 4.03 (2H, t, *J* = 6.5, $NC\underline{H}_2CH_2OH$); 3.95 (2H, d, *J* = 7.7, $NC\underline{H}_2CH(CH_3)_2$); 3.53 (2H, q, *J* = 6.3, $C\underline{H}_2OH$); 2.06 (1H, m, $C\underline{H}(CH_3)_2$); 0.89 (6H, d, *J* = 6.8, $2CH_3$)
11b	8.06 (1H, dd, *J* = 7.8 and *J* = 1.6, H-5); 7.77 (1H, td, *J* = 7.9 and *J* = 1.6, H-7); 7.50 (1H, d, *J* = 8.4, H-8); 7.29 (1H, t, *J* = 7.6, H-6); 4.26 (2H, t, *J* = 6.8, $NC\underline{H}_2CH_2Cl$); 4.13 (2H, q, *J* = 7.0, $NC\underline{H}_2CH_3$); 3.79 (2H, t, *J* = 6.8, CH_2Cl); 1.19 (3H, t, *J* = 7.0, CH_3)
11c	8.05 (1H, dd, *J* = 7.9 and *J* = 1.6, H-5); 7.76 (1H, td, *J* = 7.9 and *J* = 1.6, H-7); 7.49 (1H, d, *J* = 8.5, H-8); 7.28 (1H, t, *J* = 7.6, H-6); 4.27 (2H, t, *J* = 6.7, $NC\underline{H}_2CH_2Cl$); 4.04 (2H, t, *J* = 7.6, $NC\underline{H}_2C_2H_5$); 3.79 (2H, t, *J* = 6.7, CH_2Cl); 1.62 (2H, m, $C\underline{H}_2CH_3$); 0.92 (3H, t, *J* = 7.4, CH_3)
11d	8.05 (1H, d, *J* = 7.9, H-5); 7.77 (1H, t, *J* = 7.8, H-7); 7.47 (1H, d, *J* = 8.5, H-8); 7.28 (1H, t, *J* = 7.5, H-6); 4.27 (2H, t, *J* = 6.8, $NC\underline{H}_2CH_2Cl$); 4.08 (2H, t, *J* = 7.4, $NC\underline{H}_2C_3H_7$); 3.79 (2H, t, *J* = 6.8, CH_2Cl); 1.58 (2H, q, *J* = 7.2, $C\underline{H}_2C_2H_5$); 1.35 (2H, m, $C\underline{H}_2CH_3$); 0.90 (3H, t, *J* = 7.3, CH_3)
11e	8.06 (1H, dd, *J* = 8.1 and *J* = 1.7, H-5); 7.76 (1H, td, *J* = 7.8 and *J* = 1.7, H-7); 7.48 (1H, d, *J* = 8.5, H-8); 7.29 (1H, t, *J* = 7.6, H-6); 4.28 (2H, t, *J* = 6.6, $NC\underline{H}_2CH_2Cl$); 3.96 (2H, d, *J* = 7.3, $NC\underline{H}_2CH(CH_3)_2$); 3.80 (2H, t, *J* = 6.6, CH_2Cl); 2.07 (1H, m, $C\underline{H}(CH_3)_2$); 0.89 (6H, d, *J* = 6.4, $2CH_3$)

TABLE 5. Biological Properties of the Quinazoline-2,4-diones Hydrochlorides **1-3**

Compound	Anesthesia penetration			Motor block, points	Sedative effect, points
	Onset of anesthesia, min	Index	Duration of full anesthesia, min		
1	1.1 ± 0.16	36.0	32.3 ± 1.38	4	1
2a	1.5 ± 0.19	35.8	30.1 ± 0.75	0	0
2b	4.4 ± 0.29	18.5	15.7 ± 1.05	0	1
2c	2.9 ± 0.32	35.7	29.8 ± 0.59	0	0
2d	2.8 ± 0.43	36.0	36.4 ± 2.53	5	1
2e	1.5 ± 0.25	34.2	29.2 ± 1.43	5	3
3	3.9 ± 0.35	22.2	18.9 ± 1.22	0	0
Chinoxicaine	1.5 ± 0.04	36.0	75.6 ± 4.54	0	0
Lidocaine	2.1 ± 0.19	36.0	52.8 ± 3.76	0	0

introduction of the test compound. In principle, a combination of the indicated hydrochlorides **2** and **3d,e** anesthetic, sedative, and immobilization resultant effects can be used to create medicines suitable for practice in fine surgical intervention, e.g. in veterinary practice.

EXPERIMENTAL

^{1}H NMR spectra for the synthesized compounds were recorded on a Varian Mercury VX-200 instrument (200 MHz) for solutions in DMSO-d_6 and with TMS as internal standard. Commercial methyl chloroformate and N-methylisatoic anhydride from Fluka and Aldrich respectively were used in the work.

3-(2-Diethylaminoethyl)-1H-quinazoline-2,4-dione Hydrochloride (1). 2-Propanol saturated with gaseous HCl was added with vigorous stirring to a cooled solution of 3-(2-diethylaminoethyl)-1H-quinazoline-2,4-dione **6** (2.61 g, 0.01 mol) in 2-propanol (15 ml) to pH ~ 5. A white precipitate of the hydrochloride **1** was produced. To lower deterioration, dry diethyl ether (20 ml) was added to the reaction mixture which was left for 3-4 h at -10ºC. The crystals of hydrochloride **1** were filtered off, washed with anhydrous ether, and dried. Yield 2.88 g (97%); mp 251-253ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.62 (1H, s, NH); 10.44 (1H, br. s, NH^+); 7.92 (1H, d, *J* = 7.9, H-5); 7.66 (1H, t, *J* = 7.7, H-7); 7.20 (2H, m, H-6,8); 4.21 (2H, t, *J* = 6.7, NCH_2); 3.19 (6H, m, $N(CH_2)_3$); 1.22 (6H, t, *J* = 7.0, $2CH_3$). Found, %: C 56.36; H 6.65; N 14.18. $C_{14}H_{19}N_3O_2 \cdot HCl$. Calculated, %: C 56.47; H 6.77; N 14.11.

3-(2-Diethylaminoethyl)-1-methyl-1H-quinazoline-2,4-dione Hydrochloride (2a). A mixture of the N-methylisatoic anhydride **7** (1.77 g, 0.01 mol) and 2-diethylaminoethylamine (1.42 ml, 0.01 mol) in dry *m*-xylene (15 ml) was refluxed for 1 h. Methyl chloroformate (2.31 ml, 0.03 mol) was added to the solution of the anthranylamide formed **8** in *m*-xylene and refluxed for a further 10 h. (Care, evolution of HCl!). The solvent was distilled off (in the end at reduced pressure). The residue was dissolved in water (20 ml), purified using carbon, and filtered. A 10% aqueous solution of NaOH was added to the filtrate to pH 8. The precipitate produced was extracted with methylene chloride (3×10 ml). The organic extracts were combined and the solvent was distilled off, simultaneously removing the water residue as an azeotrope. The 1-methyl-substituted diethylaminoethyl quinazolone produced was dissolved in 2-propanol (7 ml), converted to the hydrochloride **2a** by the method reported in the preceding experiment, and then crystallized from anhydrous ethanol.

3-(2-Diethylaminoethyl)-1-ethyl-1H-quinazoline-2,4-dione Hydrochloride (2b). A solution of the 1-ethyl-substituted chloroethylquinazolone **11b** (2.52 g, 0.01 mol) in diethylamine (20 ml) was placed in a

thick walled sealed ampule under an argon atmosphere and held for 24 h in a sand bath at a temperature of about 90ºC. Water (30 ml) and 10% aqueous NaOH solution (10 ml) were added to the reaction mixture after which diethylamine was fully distilled off. The residue was acidified with HCl to pH 4, purified with carbon, and filtered. The work up then followed that for the 1-methyl derivative **2a**. The product was crystallized from aqueous ethanol with the addition of anhydrous diethyl ether.

1-Alkyl-substituted 3-(2-Dialkylaminoethyl)-1H-quinazoline-2,4-dione Hydrochlorides (2c-e, 3) (Tables 3 and 4) were prepared similarly.

Methyl 2-(Methoxycarbonylamino)benzoate (5). Methyl chloroformate (15.38 ml, 0.2 mol) was added to a solution of methyl anthranilate **3** (12.93 ml, 0.1 mol) in dry toluene (70 ml) and refluxed for 8 h. (Work in a hood, reaction occurs with evolution of HCl!). Solvent was distilled off under reduced pressure and the residue was crystallized from hexane to give the urethane **5** (18.41 g, 88%) with mp 58-60ºC (hexane). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.24 (1H, s, NH); 8.15 (1H, d, *J* = 8.3, H-6); 7.89 (1H, dd, *J* = 7.9 and 1.6, H-3); 7.58 (1H, td, *J* = 8.0 and 1.6, H-4); 7.09 (1H, t, *J* = 7.6, H-5); 3.82 (3H, s, OCH_3). Found, %: C 57.32; H 5.18; N 6.63. $C_{10}H_{11}NO_4$. Calculated, %: C 57.41; H 5.30; N 6.70.

3-(2-Diethylaminoethyl)-1H-quinazoline-2,4-dione (6). A mixture of urethane **5** (2.09 g, 0.01 mol) and 2-diethylaminoethylamine (1.56 ml, 0.011 mol) was placed in a flask fitted a suitable fractionating column and held for 30 min in a metal bath at 140ºC, the temperature being gradually raised to 160ºC (Care, vigorous evolution of methyl alcohol!). The reaction mixture was cooled, diethyl ether (20 ml) added, and thoroughly triturated. The residue of quinazolone **6** was filtered off, washed with diethyl ether, and dried. Yield 2.12 g (81%); mp 124-126ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.36 (1H, s, NH); 7.90 (1H, d, *J* = 7.9, H-5); 7.62 (1H, t, *J* = 7.6, H-7); 7.16 (2H, m, H-6,8); 3.93 (2H, t, *J* = 6.6, NCH_2); 2.58 (6H, m, $N(CH_2)_3$); 0.91 (6H, t, *J* = 7.1, $2CH_3$). Found, %: C 64.43; H 7.45; N 16.19. $C_{14}H_{19}N_3O_2$. Calculated, %: C 64.35; H 7.33; N 16.08.

3-(2-Hydroxyethyl)-1H-quinazoline-2,4-dione (9). Condensation of urethane **5** with 2-aminoethanol was carried out as in the method for the preparation of quinazolone **6**. For separation of the product the reaction mixture was treated with water and acidified with HCl to pH 4. The precipitated hydroxyethylquinazolone **9** was filtered off, washed with water, and dried. Yield 86%; mp 239-241ºC (ethanol). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 11.34 (1H, s, NH); 7.89 (1H, d, *J* = 8.4, H-5); 7.61 (1H, td, *J* = 7.7 and *J* = 1.6, H-7); 7.15 (2H, m, H-6,8); 4.77 (1H, t, *J* = 5.5, OH); 3.97 (2H, t, *J* = 6.4, NCH_2); 3.54 (2H, q, *J* = 5.5, $NCH_2C\underline{H}_2$). Found, %: C 58.12; H 4.75; N 13.68. $C_{10}H_{10}N_2O_3$. Calculated, %: C 58.25; H 4.89; N 13.59.

1-Alkyl-substituted 3-(2-hydroxyethyl)-1H-quinazoline-2,4-diones 10b-e (General Method). Finely divided K_2CO_3 (2.76 g, 0.02 mol) and the corresponding alkyl iodide or alkyl bromide (0.012 mol) were added to a solution of the hydroxyethylquinazolone **9** (2.06 g, 0.01 mol) in DMSO (20 ml) and stirred at 90ºC for 4 h. The reaction product was cooled and diluted with cold water. The precipitate was filtered off, washed with cold water, dried, and crystallized from ethanol.

1-Alkyl-3-(2-chloroethyl)-1H-quinazoline-2,4-diones 11b-e (General Method). $SOCl_2$ (1.44 ml, 0.02 mol) was added to a solution of the 1-alkyl-substituted hydroxyethylquinazolone **10b-e** (0.01 mol) in dry methylene chloride (15 ml) and refluxed for 30 min. Solvent and excess $SOCl_2$ were distilled off at reduced pressure. The residue was treated with 5% aqueous Na_2CO_3 solution. The precipitated chloroethylquinazolones **11b-e** were filtered off, washed with water, dried, and crystallized from ethanol.

X-ray structural investigation. Crystals of the chloroethyl quinazolone **11e** are monoclinic (ethanol), at -173ºC: a = 9.948(1), b = 14.907(1), c = 9.438(1) Å, β = 100.70(1)º, V = 1375.3(1) Å^3, M_r = 280.75, Z = 4, space group $P2_1/c$, d_{calc} = 1.356 g/cm^3, μ(MoKα) = 0.277 mm^{-1}, F(000) = 592. The unit cell parameters and intensities of 21,839 reflections (3996 independent, R_{int} = 0.020) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning to $2\theta_{max}$ = 60ºC).

The structure was solved by a direct method using the SHELXTL program package [12]. The positions of the hydrogen atoms were revealed from electron density difference synthesis and refined isotropically. The

structure was refined by F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to wR_2 = 0.114 for 3914 reflections (R_1 = 0.037 for 3225 reflections with $F > 4\sigma(F)$, S = 1.124). Interatomic distances and valence angles are given in Tables 1 and 2.

The full crystallographic information has been placed in the Cambridge Structural Data Bank (reference CCDC 717537).

Study of local irritation activity by the Lebo and Camage method. Primary screening of the local irritation features was carried out on male rabbits of weight 2.0-2.5 kg. The rear dorsal surface along the spine was carefully freed from wool without damage to the skin. Solutions of the compounds studied were introduced intracutaneously in a volume of 0.1 ml. The site of introduction was marked with ink. The irritant effect was evaluated after 24 h from the size and nature of possible reactive changes (erythema, edema).

Study of local anesthetic effect by the Buelbring-Yueid method. Experiments were carried out on male guinea pigs of weight 200-250 g. Solutions of the compounds studied were introduced intracutaneously in a volume of 0.25 ml into a previously depilated area of skin on the back (as a square of sides ~ 4 cm). The biological effect was reckoned as an index of anesthesia penetration. This arbitrary indicator is defined as the overall number of needle touches not causing a response in the animal (skin twitching). These touches were carried out in a series of 6 for 3-4 seconds after every 5 minutes over a period of 30 min. The maximum value the index can reach is 36.

Esimation of motor block, arising in the experimental animals with introduction of the compounds studied was carried out on a 5 point scale. 0 points: tail root tone preserved, movements preserved in full. 1 point: weakening of the tail root tone. 2 points: weak tail root tone, sluggish movement, animal sitting more. 3 points: lowering of tail root tone and possible slight movement of animal during stimulation of skin section not occurring in the anesthetized zone, slight inhibition of the animal. 4 points: general atonia of tail root, appearance of some inhibition of movement in response to stimulation, overall inhibition of animal. 5 points: state of general atonia of tail root without movement upon pain or electrical stimulation of the skin outside the area of anesthesia, animal lying on side. The intensity of the motor block was evaluated at the peak of the local anesthesia.

Esimation of sedative effect in guinea pigs. 0 points: absent, animal moving independently in cage. 1 point: animal calm, sitting more, moving around cage only when disturbed by the experimenter. 2 points: animal slowed down, sitting in corner of cage, anxiety with experimenter significantly set aside and again sitting, often closing eyelids, sleep onset. 3 points: animal sleeping, lying on side, not responsive to stimulation by experimenter or to needle stick.

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