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4-HYDROXY-2-QUINOLONES. 179*. SYNTHESIS, STRUCTURE, AND ANTI-INFLAMMATORY ACTIVITY OF 4-HYDROXY-1-METHYL-2-OXO-1,2-DIHYDROQUINOLIN-3-YLACETIC ACID AND ITS DERIVATIVES

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The synthesis of 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic acid has been carried out and the structure and acid properties studied. Preparative methods for its esterification and amidation are proposed. The anti-inflammatory properties of the synthesized compounds have been evaluated.

Keywords: 4-hydroxy-2-oxo-1,2-dihydroquinolin-3-ylacetic acids, amidation, anti-inflammatory activity, X-ray analysis, esterification.

Pain and inflammation are the most widely distributed symptoms accompanying numerous pathological conditions. Nonsteroidal anti-inflammatory agents [2, 3] are currently widely used to remove these symptoms. For all their positive properties the majority of this group drugs is not without marked drawbacks which limit their practical use and reduce the efficiency of the pharmacotherapy of the inflammatory illness overall. Firstly high toxicity, sometimes limiting activity, can occur together with a series of additional effects including ulcerogenic activity, increased arterial pressure, blood disorders etc. Hence the problem of a search for novel anti-inflammatory agents meeting the ever growing demands of increased efficiency and safety remains current.

The rationale for carrying out this investigation was our previous discovery of the anti-inflammatory properties of 1H-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-ylacetic acids where, though its esters are not characterized by high activity [4], the 6-methylpyridin-2-ylamide has demonstrated an antiexudative effect greater than that of Voltaren with a markedly lower toxicity [5]. With the aim of developing a structure – biological activity relationship in this series we have prepared the N-methyl analogs of the previously reported compounds. For this purpose, methyl N-methylanthranilate (**1**) was acylated with β-methoxycarbonylpropionyl chloride and the anilide **2** formed was treated with sodium methylate in methanol. As is known [6] such a

* For Communication 178, see [1].

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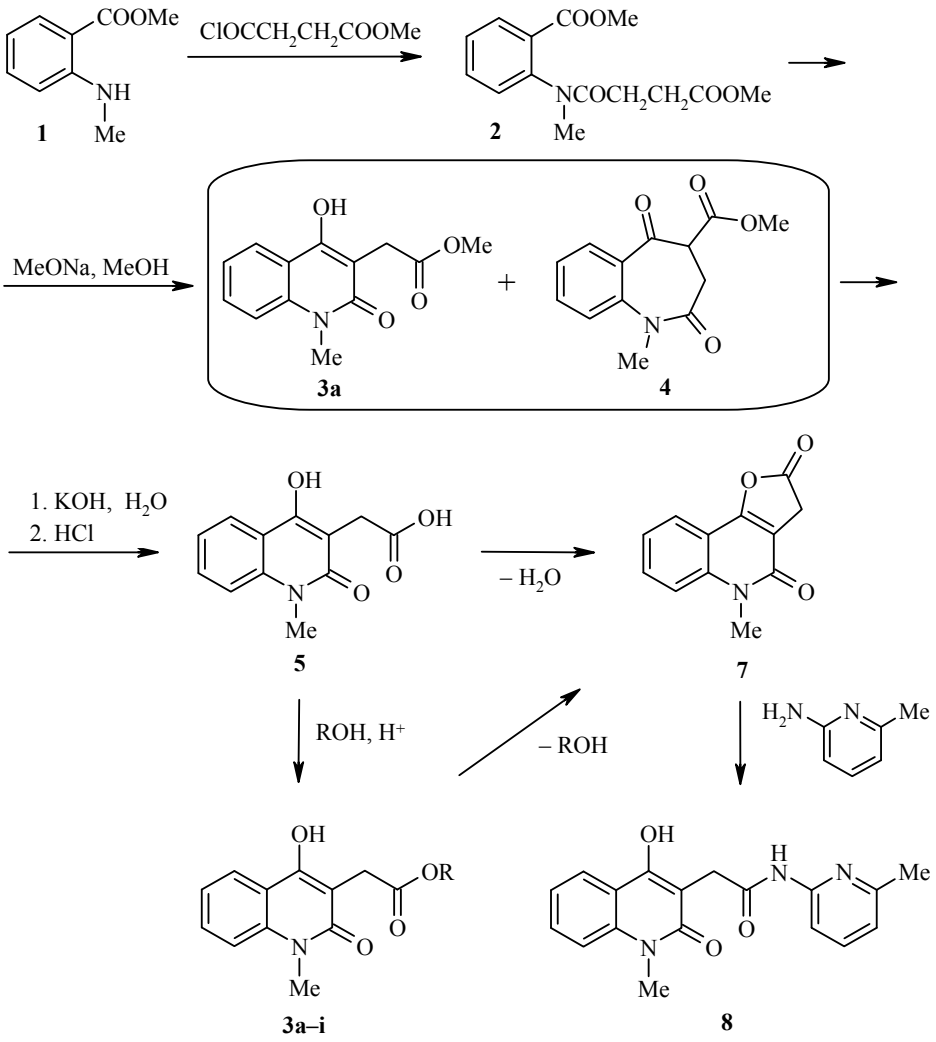
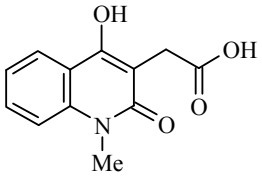
reaction normally occurs to give a mixture of two heterocycles *viz*. a quinoline **3** and a benzazepine **4** even though carrying out an ester condensation in the higher boiling toluene does not exclude formation of a further small amount of a biquinoline [7]. None the less, if the synthesis is carried out with the aim of preparing quinoline derivatives a separation of the reaction mixture is not needed, or even logical, since the base hydrolysis of the esters of quinoline and benzazepine carboxylic acids **3a** and **4** in fact gives the same final product [6, 8], in this case the 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic acid (**5**).



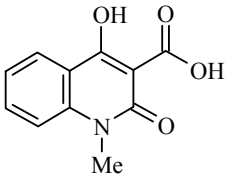
3 a R = Me, **b** R = Et, **c** R = $CH_2CH{=}CH_2$, **d** R = Pr, **e** R = *i*-Pr, **f** R =Bu, **g** R = *i*-Bu, **h** R = C_5H_{11}, **i** R = *i*-C_5H_{11}

When comparing the acidic properties of 1H-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carboxylic acid and its nearest homolog (the corresponding quinolin-3-ylacetic acid) it was noticed that separation of the carboxyl group and quinolone ring by a methylene bridge did not, as against all expectations, lower but rather increased it by more than an order for the COOH acidity and by almost two orders for the 4-OH group. It was proposed that the reason for this unusual effect lies in the impossibility of the reaction centers of the quinolineacetic acid forming strong intramolecular hydrogen bonds, thanks to which its acidic properties are markedly increased [9]. A similar relationship is seen in the N-methyl-substituted derivative pair **5** and **6**.

X-ray crystallographic studies carried out by us have shown that 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic acid (**5**, see Fig. 1 and Tables 1 and 2) and its ethyl ester **3b** [10] in fact form completely different systems of hydrogen bonds (basically intermolecular) to those of the carboxy- [11] and alkoxycarbonylquinolines [12].



5



6

pKa^{COOH} = 6.13 ± 0.04
p$Ka^{4\text{-}OH}$ = 11.70 ± 0.10

pKa^{COOH} = 7.49 ± 0.01
p$Ka^{4\text{-}OH}$ = 13.35 ± 0.08

Hence, in particular, it was found that two molecules (**A** and **B**) occur in the symmetrically independent part of the unit cell of acid **5** and they are differentiated by several geometric parameters. In both molecules the bicyclic fragment is planar to within 0.02 Å. The planar carboxyl group on atom C(10) is placed virtually perpendicularly to the bicycle plane (torsional angle C(9)–C(8)–C(10)–C(11) 77.3(1)º in molecule **A** and -92.1(1)º in **B**) and is slightly noncoplanar to C(8)–C(10) bond (torsional angle C(8)–C(10)–C(11)–O(3) 8.5(2)º in **A** and 10.8(2)º in **B**).

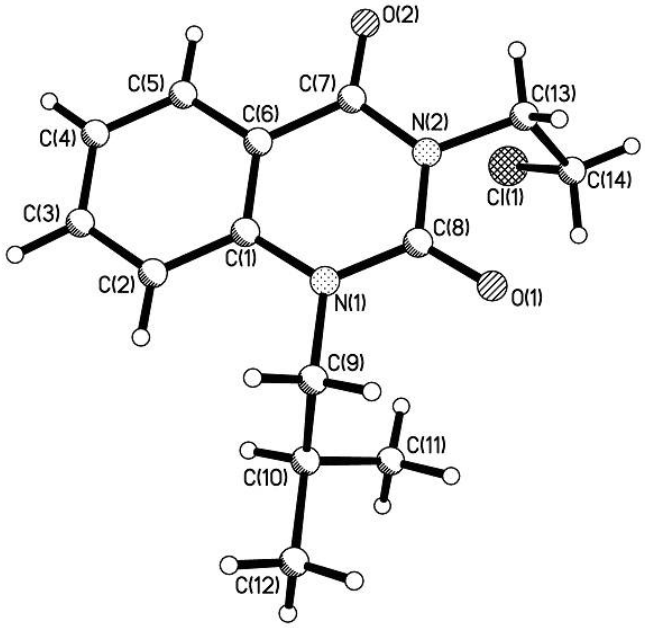


Fig. 1. Structure of the molecules **A** and **B** of the quinolineacetic acid **5** with atomic numbering.

The hydrogen atom of the hydroxyl group in molecule **A** is turned towards the substituent at atom C(8) and this leads to formation of overall shortened intramolecular contacts H(10B)···H(20A) 2.13 Å (sum of van der Waal radii 2.34 Å [13]) and H(5A)···O(2A) 2.39 Å (2.46 Å). The marked repulsion between the sterically close substituents causes an increase in the valence angles C(7)–C(8)–C(10) and O(2)–C(7)–C(8) to 124.4(1)º and 125.3(1)º and also a decrease in the angles C(9)–C(8)–C(10) and O(2)–C(7)–C(6) to 115.8(1)º and 113.6(1)º respectively.

In the **B** molecule the hydrogen atom of the 4-OH group is orientated towards the benzene ring and this results in the appearance of the shortened intramolecular contacts H(5B)···H(20B) 2.06 (2.34) and H(10D)···O(2B) 2.41 (2.46 Å). Moreover, the change in exocyclic valence angles at atom C(7) when compared with molecule **A** occurs in the opposite direction. The O(2)–C(7)–C(8) angle is decreased to 116.0(1)º and O(2)–C(7)–C(6) is increased to 123.1(1)° even though the angles at atom C(8) remain close to 120º.

TABLE 1. Bond Lengths (*l*) in the Structure of the Quinolineacetic Acid **5**

Bond	*l*, Å	Bond	*l*, Å
N(1A)–C(9A)	1.384(2)	N(1A)–C(1A)	1.400(2)
N(1A)–C(12A)	1.466(2)	O(1A)–C(9A)	1.254(1)
O(2A)–C(7A)	1.347(1)	O(3A)–C(11A)	1.222(2)
O(4A)–C(11A)	1.316(2)	C(1A)–C(6A)	1.408(2)
C(1A)–C(2A)	1.412(2)	C(2A)–C(3A)	1.380(2)
C(3A)–C(4A)	1.384(2)	C(4A)–C(5A)	1.375(2)
C(5A)–C(6A)	1.409(2)	C(6A)–C(7A)	1.445(2)
C(7A)–C(8A)	1.360(2)	C(8A)–C(9A)	1.445(2)
C(8A)–C(10A)	1.503(2)	C(10A)–C(11A)	1.497(2)
N(1B)–C(9B)	1.377(2)	N(1B)–C(1B)	1.395(2)
N(1B)–C(12B)	1.473(2)	O(1B)–C(9B)	1.252(1)
O(2B)–C(7B)	1.343(1)	O(3B)–C(11B)	1.223(2)
O(4B)–C(11B)	1.318(2)	C(1B)–C(2B)	1.409(2)
C(1B)–C(6B)	1.415(2)	C(2B)–C(3B)	1.377(2)
C(3B)–C(4B)	1.387(2)	C(4B)–C(5B)	1.382(2)
C(5B)–C(6B)	1.404(2)	C(6B)–C(7B)	1.445(2)
C(7B)–C(8B)	1.360(2)	C(8B)–C(9B)	1.437(2)
C(8B)–C(10B)	1.503(2)	C(10B)–C(11B)	1.505(2)

TABLE 2. Valence Angles (ω) in the Structure of the Quinolineacetic Acid **5**

Angle	ω, deg	Angle	ω, deg
C(9A)–N(1A)–C(1A)	122.35(9)	C(9B)–N(1B)–C(1B)	122.29(10)
C(9A)–N(1A)–C(12A)	118.06(11)	C(9B)–N(1B)–C(12B)	118.08(11)
C(1A)–N(1A)–C(12A)	119.60(11)	C(1B)–N(1B)–C(12B)	119.62(11)
N(1A)–C(1A)–C(6A)	118.99(10)	N(1B)–C(1B)–C(2B)	120.89(11)
N(1A)–C(1A)–C(2A)	122.41(11)	N(1B)–C(1B)–C(6B)	119.85(10)
C(6A)–C(1A)–C(2A)	118.59(12)	C(2B)–C(1B)–C(6B)	119.27(11)
C(3A)–C(2A)–C(1A)	120.50(13)	C(3B)–C(2B)–C(1B)	119.91(13)
C(2A)–C(3A)–C(4A)	121.06(13)	C(2B)–C(3B)–C(4B)	121.19(14)
C(5A)–C(4A)–C(3A)	119.30(14)	C(5B)–C(4B)–C(3B)	119.85(13)
C(4A)–C(5A)–C(6A)	121.41(14)	C(4B)–C(5B)–C(6B)	120.60(13)
C(1A)–C(6A)–C(5A)	119.12(12)	C(5B)–C(6B)–C(1B)	119.15(12)
C(1A)–C(6A)–C(7A)	118.92(10)	C(5B)–C(6B)–C(7B)	123.05(11)
C(5A)–C(6A)–C(7A)	121.96(11)	C(1B)–C(6B)–C(7B)	117.80(10)
O(2A)–C(7A)–C(8A)	125.34(11)	O(2B)–C(7B)–C(8B)	116.02(11)
O(2A)–C(7A)–C(6A)	113.60(10)	O(2B)–C(7B)–C(6B)	123.06(10)
C(8A)–C(7A)–C(6A)	121.05(10)	C(8B)–C(7B)–C(6B)	120.92(10)
C(7A)–C(8A)–C(9A)	119.83(11)	C(7B)–C(8B)–C(9B)	120.73(11)
C(7A)–C(8A)–C(10A)	124.37(10)	C(7B)–C(8B)–C(10B)	120.21(11)
C(9A)–C(8A)–C(10A)	115.76(10)	C(9B)–C(8B)–C(10B)	119.05(10)
O(1A)–C(9A)–N(1A)	121.18(10)	O(1B)–C(9B)–N(1B)	119.05(10)
O(1A)–C(9A)–C(8A)	120.22(11)	O(1B)–C(9B)–C(8B)	122.67(11)
N(1A)–C(9A)–C(8A)	118.59(10)	N(1B)–C(9B)–C(8B)	118.27(10)
C(11A)–C(10A)–C(8A)	113.11(10)	C(8B)–C(10B)–C(11B)	113.69(11)
O(3A)–C(11A)–O(4A)	122.76(12)	O(3B)–C(11B)–O(4B)	122.84(12)
O(3A)–C(11A)–C(10A)	123.69(11)	O(3B)–C(11B)–C(10B)	123.51(11)
O(4A)–C(11A)–C(10A)	113.55(11)	O(4B)–C(11B)–C(10B)	113.64(12)

The C(8)–C(7) 1.360(2) in **A** and **B** and the O(1)–C(9) bonds (1.254(1) in **A** and 1.252(1) Å in **B**) are lengthened when compared with their mean values [14] of 1.326 and 1.210 Å respectively and the C(8)–C(9) bond 1.445(2) in **A** and 1.437(2) Å in **B** is shortened (mean value 1.455 Å) and this enables the formation of the intermolecular hydrogen bonds O(2A)–H(2OA)···O(1B)' (*x*-1, *y*, *z*-1) H···O 1.75 Å, O–H···O 162º and O(2B)–H(2OB)···O(1A)' H···O 1.80 Å, O–H···O 156º. It should be noted that the length of the bonds O(2)–C(7) 1.347(1) Å in **A** and 1.343(1) Å in **B** are comparable with their mean value of 1.333 Å. A similar effect is observed in previously studied, closely structured compounds [10, 15].

A rather strong repulsion is seen between the atoms of the N-methyl substituent and the neighboring carbonyl group and hydrogen atom in the *peri* position of the benzene ring [shortened intramolecular contacts H(2)···C(12) 2.56 in **A** and 2.50 in **B** (2.87); H(2)···H(12C) 2.11 in **A** and 2.31 in **B** (2.34); H(12C)···C(2) 2.59 in **A** and 2.78 in **B** (2.87); H(12B)···O(1) 2.29 in **A** and 2.19 Å in **B** (2.46 Å)].

The crystal of the acid molecule **5** forms dimers *via* the intermolecular hydrogen bonds O(4A)–H(4OA)···O(3A)' (1-*x*, 1-*y*, 1-*z*) H···O 1.75 Å, O–H···O 177º and O(4B)–H(4OB)···O(3B)' (2-*x*, -*y*, 2-*z*) H···O 1.77Å, O–H···O 175ºC. The formation of the dimers evidently results in some lengthening of the O(3)–C(11) bond to 1.222(2) in **A** and to 1.223(2) Å in **B** when compared with their mean value of 1.210 Å. In turn, the dimers form infinite chains along the crystallographic [1 0 1] axis *via* the intermolecular hydrogen bonds mentioned above O(2A)–H(2OA)···O(1B)' and O(2B)–H(2OB)···O(1A)'. The crystal shows the intermolecular hydrogen bond C(10A)–H(10B)···O(1B)' (*x*-1, *y*, *z*-1) H···O 2.33 Å, C–H···O 153º as well as the shortened intermolecular contacts H(12D)···C(5B)' (2-*x*, 1-*y*, 2-*z*) 2.83 (2.87) and H(12D)···C(6B)' (2-*x*, 1-*y*, 2-*z*) 2.74 Å (2.87 Å).

The esters of 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic acids **3a-i** (Tables 3 and 4) offered interest for pharmacological study and were prepared in high yields from quinolineacetic acids **5** by the conventional acid catalyzed esterification developed for the 1H-derivatives [4].

It was assumed that the well recommended method of preparation of 1H-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-ylacetic acid N-R-amides would also prove useful for the synthesis of the N-alkyl-substituted analogs. Since neither 1H-quinolineacetic acid nor its esters are amidated directly, for increasing acylating ability

TABLE 3. Characteristics of the 4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic Acids **3a-i***

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %	Anti-inflammatory activity, reduction of edema, %
		C	H	N			
3a	$C_{13}H_{13}NO_4$	63.23 / 63.15	5.41 / 5.30	5.57 / 5.66	179-181	96	12.7
3b	$C_{14}H_{15}NO_4$	64.47 / 64.36	5.88 / 5.79	5.43 / 5.36	184-186	93	45.5
3c	$C_{15}H_{15}NO_4$	66.05 / 65.93	5.64 / 5.53	5.21 / 5.13	131-133	94	52.5
3d	$C_{15}H_{17}NO_4$	65.36 / 65.44	6.13 / 6.22	4.97 / 5.09	138-140	91	20.4
3e	$C_{15}H_{17}NO_4$	65.56 / 65.44	6.17 / 6.22	5.00 / 5.09	177-179	80	3.1
3f	$C_{16}H_{19}NO_4$	66.32 / 66.42	6.71 / 6.62	4.95 / 4.84	164-166	89	46.2
3g	$C_{16}H_{19}NO_4$	66.30 / 66.42	6.54 / 6.62	4.77 / 4.84	109-111	90	27.3
3h	$C_{17}H_{21}NO_4$	67.44 / 67.31	7.10 / 6.98	4.54 / 4.62	95-97	88	44.5
3i	$C_{17}H_{21}NO_4$	67.42 / 67.31	7.09 / 6.98	4.51 / 4.62	106-108	85	9.6

* Anti-inflammatory activity (reduction of edema, %) of the comparison preparation Voltaren was (49.8).

TABLE 4. ^{1}H NMR Spectra of 4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic Acids (**3a-i**)

Compound	OH (1H, s)	Chemical shifts, δ, ppm (*J*, Hz)						
		Quinolone ring				CH_2COOR (2H, s)	N–CH_3 (3H, s)	R
		H-5 (1H, dd)	H-7 (1H, td)	H-8 (1H, d)	H-6 (1H, td)			
3a	10.23	8.00 (*J* = 8.2 and *J* = 1.5)	7.59 (*J* = 7.7 and *J* = 1.6)	7.45 (*J* = 8.6)	7.24 (*J* = 7.6 and *J* = 1.3)	3.65	3.59	3.57 (3H, s, CH_3)
3b	10.31	8.00 (*J* = 8.1 and *J* = 1.5)	7.59 (*J* = 7.7 and *J* = 1.5)	7.47 (*J* = 8.5)	7.26 (*J* = 7.5 and *J* = 1.3)	3.66	3.57	4.03 (2H, q, *J* = 7.1, OCH_2); 1.15 (3H, t, *J* = 7.1, CH_3)
3c	10.34	8.01 (*J* = 8.1 and *J* = 1.4)	7.60 (*J* = 7.8 and *J* = 1.5)	7.46 (*J* = 8.4)	7.25 (*J* = 7.6 and *J* = 1.4)	3.67	3.58	5.89 (1H, m, C<u>H</u>=CH_2); 5.28 (1H, d, *J* = 17.5, NCH_2CH=C<u>H</u>-*trans*); 5.17 (1H, d, *J* = 10.4, CH_2CH=C<u>H</u>-*cis*); 4.54 (2H, d, *J* = 5.3, NCH_2)
3d	10.09	8.01 (*J* = 8.0 and *J* = 1.5)	7.60 (*J* = 7.7 and *J* = 1.6)	7.46 (*J* = 8.6)	7.24 (*J* = 7.5 and *J* = 1.3)	3.63	3.57	3.97 (2H, t, *J* = 6.7, OCH_2); 1.56 (2H, m, $OCH_2C\underline{H}_2$); 0.86 (3H, t, *J* = 7.5, CH_3)
3e	10.21	8.00 (*J* = 8.1 and *J* = 1.4)	7.59 (*J* = 7.8 and *J* = 1.6)	7.46 (*J* = 8.5)	7.24 (*J* = 7.5 and *J* = 1.2)	3.59	3.57	4.88 (1H, m, CH); 1.18 (6H, d, *J* = 6.2, $2CH_3$)
3f	10.29	8.01 (*J* = 8.0 and *J* = 1.4)	7.59 (*J* = 7.8 and *J* = 1.6)	7.45 (*J* = 8.4)	7.24 (*J* = 7.6 and *J* = 1.3)	3.63	3.57	4.04 (2H, t, *J* = 6.8, OCH_2); 1.54 (2H, quint., *J* = 7.0, $C\underline{H}_2CH_2CH_3$); 1.31 (2H, m, $C\underline{H}_2CH_3$); 0.86 (3H, t, *J* = 7.3, CH_3)
3g	10.28	8.01 (*J* = 8.0 and *J* = 1.6)	7.60 (*J* = 7.8 and *J* = 1.4)	7.46 (*J* = 8.5)	7.24 (*J* = 7.6 and *J* = 1.2)	3.65	3.57	3.81 (2H, d, *J* = 6.1, OCH_2); 1.84 (1H, m, CH); 0.85 (6H, d, *J* = 6.8, $2CH_3$)
3h	10.26	8.00 (*J* = 8.1 and *J* = 1.5)	7.59 (*J* = 7.7 and *J* = 1.6)	7.45 (*J* = 8.6)	7.24 (*J* = 7.5 and *J* = 1.3)	3.63	3.57	4.00 (2H, t, *J* = 6.6, OCH_2); 1.55 (2H, quint., *J* = 6.8, $OCH_2C\underline{H}_2$); 1.26 (4H, m, $(C\underline{H}_2)_2CH_3$); 0.82 (3H, t, *J* = 6.8, CH_3)
3i	10.22	8.00 (*J* = 8.0 and *J* = 1.5)	7.59 (*J* = 7.7 and *J* = 1.4)	7.45 (*J* = 8.5)	7.24 (*J* = 7.5 and *J* = 1.3)	3.64	3.57	4.01 (2H, t, *J* = 6.4, OCH_2); 1.46 (1H, m, CH); 1.25 (2H, q, *J* = 6.5, $OCH_2C\underline{H}_2$); 0.88 (6H, d, *J* = 6.7, $2CH_3$)

there was proposed a preliminary conversion by different methods to the highly electrophilic 1H-3,5-dihydrofuro[3,2-*c*]quinoline- 2,4-dione [16]. However, attempts to apply these known methods to quinolineacetic acid **5** were not successful. In the workup with condensation agents (thionyl chloride, N,N'-dicyclohexylcarbodiimide, or N,N'-carbonyl- diimidazole) it was found that the anhydride **7** was formed together with a wider chemical transformation. The result was an intensely red colored (probably through formation of cyanine dyes) and hard to identify mixture of different products.

The preparative importance of thermolysis of lower alkyl esters in the synthesis of 1H-derivatives has not proved of value. The N-methyl-substituted anhydride **7** could not be obtained by this method in a satisfactory degree of purity. In this case a derivatographic study was made to help understand the reason.

As is evident from the derivatogram presented, dry heating of ethyl 1H-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl acetate shows two successive processes clearly separated by a temperature interval of about 40ºC (Fig. 2, *a*). The first of these occurs between 195 and 227ºC and is accompanied by the loss of about 19% of the mass corresponding to elimination of ethanol, i.e. the closure of the hydrofuran ring. The second begins at a much higher temperature (270ºC) and, judged by the loss of around 12% of the mass, results from decarbonylation of the initially formed 1H-3,4-dihydrofuro[3,2-*c*]quinoline-2,4-dione.

The thermal behavior of ethyl 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl acetate (**3b**) proved quite different. Here no kind of difference between heterocyclization and decarbonylation is seen and a single process occurs (Fig. 2, *b*). As a result, in place of the anhydride **7**, a mixture of colored side products is formed.

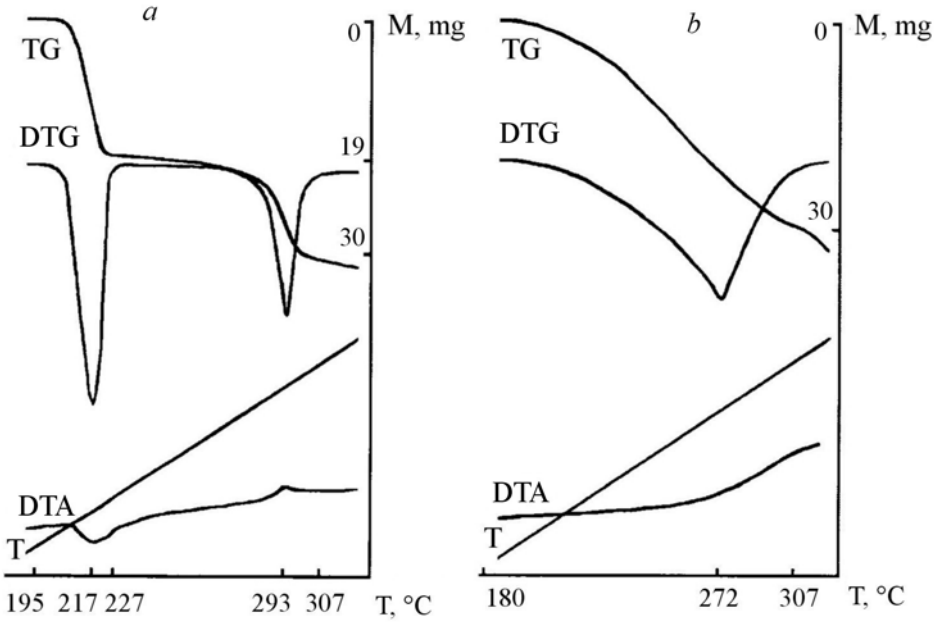


Fig. 2. Derivatograms of ethyl 1H-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-ylacetic acid (*a*) and its N-methyl-substituted analog **3b** (*b*): T – thermal analysis curve, DTA – differential thermal analysis curve, TG – thermogravimetric curve, DTG – differential thermogravimetric curve, Weighted portions = 100 mg.

None the less, a small modification of a known method led to a synthesis of 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic acid 6-methylpyridin-2-ylamide (**8**) in high yield and purity. The two separate reactions of conversion of ether to anhydride and the amidation were combined in a single stage, i.e. by a simple thermolysis of a mixture of equimolar amounts of the ester **3b** and the 2-amino-6-methylpyridine at 190-200ºC for 20 min. Of course, the intermediate formation of the anhydride **7** under these conditions is not in doubt. However, the hetarylamine in the reaction mixture reacts immediately with it giving the chemically rather inert final amide **8** hence avoiding the unwanted side processes.

In a search for anti-inflammatory agents one of the defining criteria of effectiveness is antiexudative activity. In this connection, we began testing of biological activity with a study of their effect on the exudative aspect of acute aseptic inflammation. This was carried out on the carrageenan edema model in mice [17]. The preparation chosen for comparison was the classical nonsteroidal anti-inflammatory Voltaren (Diclofenac sodium) [2] at a dose of 8 mg/kg (ED_{50}). The results obtained as a whole show a positive effect for introduction of an N-methyl group. Hence the starting quinolineacetic acid **5** in a dose equimolar to Voltaren can lower the edema by 23.1%, markedly exceeding this indicator in the non-alkylated analog [4]. Even more successful is the effect of this modification on the anti-exudate properties of the esters (Table 3), amongst which were found substances in virtually no way inferior to Voltaren (esters **3b**,**f**,**h**) and even exceeding it somewhat (allyl ester **3c**). An interesting dependence is seen in this same series where the transition from a normal alkyl chain to an isostructure is accompanied by an almost total loss of anti-inflammatory activity.

It should be noted, however, that N-methylation of the quinolone ring is far from always reflected in a positive change in the biological activities. In particular the 6-methylpyridin-2-ylamide **8** inhibits the carrageenan edema by only 40.3%. This can be regarded as a marked fall in activity since the indicator in the 1-H derivative is 53.0% [5].

EXPERIMENTAL

^{1}H NMR spectra for the compounds synthesized were obtained on a Varian Mercury-VX-200 instrument (200 MHz) in DMSO-d_6 using TMS as internal standard. Investigations of acid-base equilibria were made by method [18] using 80% aqueous dioxane as solvent. For preparation of mixed solvent freshly prepared bidistillates freed from CO_2 were used and also dioxane for UV spectroscopy from the Labscan company. The titrant was a 0.01 M aqueous solution of KOH freed from CO_2. The concentration of the titrant solutions was 0.0005 mol·l^{-1} at the half neutralization point. Potentiometric titration was carried out on a stationary SevenEasy S-20-K Mettler Toledo pH meter and using an InLab 413 combination electrode at 25ºC. The titration for each compound was carried out three times. The accuracy of the results obtained was evaluated by a mathematical statistics method [19]. The derivatographic studies of the ethyl 1H-4-hydroxy-2-oxo-1,2-di-hydroquinolin-3-yl acetate and its N-methyl-substituted analog **3b** were carried out on a thermochemical Derivatograf Q-1500 D equipment package in a platinum crucible with a lid and at a heating rate of 5ºC/min. Commercial methyl N-methylanthranilate (**1**) from the Fluka company was used in this work.

4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic Acid (5). β-Methoxycarbonylpropionyl chloride (16.56 g, 0.11 mol) was added dropwise with cooling and stirring to a mixture of methyl N-methyl-anthranilate (**1**) (16.52 g, 0.1 mol), and triethylamine (14 ml, 0.1 mol) in dichloromethane (150 ml) and allowed to stand at room temperature for 7-8 h. The reaction mixture was treated with cold water (2×200 ml). An organic layer separated following thorough stirring. The solvent was distilled off (at the end under reduced pressure) simultaneously removing water as an azeotrope. The residue (anilide **2**) was treated with a solution of sodium methylate prepared from metallic sodium (4.6 g, 0.2 mol) and absolute methanol (100 ml) and refluxed for 4 h. The product was cooled. A solution of KOH (11.22 g, 0.2 mol) in water (200 ml) was added to the mixture of the methyl esters of the quinoline and benzazepine carboxylic acids **3a** and **4** after which it was refluxed for 5 h with simultaneous distillation of the main part of the methanol. The reaction mixture was cooled and acidified to about pH 4 using dilute (1:1) HCl. The precipitated acid **5** was filtered off, washed with cold water, and dried. Yield 14.22 g (61%). Recrystallization from ethanol gave mp 248-250ºC (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): the protons of the COOH group were not seen due to rapid deuterium exchange; 10.67 (1H, br. s, 4-OH); 8.00 (1H, dd, *J* = 8.0 and *J* = 1.5, H-5); 7.58 (1H, td, *J* = 7.7 and *J* = 1.5, H-7); 7.44 (1H, d, *J* = 8.6, H-8); 7.23 (1H, td, *J* = 7.6 and *J* = 1.3, H-6); 3.59 (2H, s, C$\underline{H_2}$COOH); 3.57 (3H, s, NCH_3). Found, %: C 61.93; H 4.84; N 6.11. $C_{12}H_{11}NO_4$. $C_{12}H_{11}NO_4$. Calculated, %: C 61.80; H 4.75; N 6.01.

X-ray Structural Investigation. Crystals of the quinolineacetic acid **5** are triclinic (ethanol), at 20ºC: $a = 7.493(2)$, $b = 12.196(3)$, $c = 12.356(2)$ Å, $\alpha = 96.49(2)^\circ$, $\beta = 103.58(2)^\circ$, $\gamma = 92.60(2)^\circ$, $V = 1087.5(4)$ Å^3, $M_r = 233.22$, $Z = 4$, space group $P\bar{1}$, $d_{calc} = 1.424$ g/cm^3, $\mu(MoK\alpha) = 0.108$ mm^{-1}, $F(000) = 488$. The unit cell parameters and intensities of 23,952 reflections (4981 independent, $R_{int} = 0.026$) were measured on an Xcalibur-3 diffractometer (MoKα radiation, CCD detector, graphite monochromator, ω-scanning, $2\theta_{max} = 55^\circ$).

The structure was solved by the direct method using the *SHELXTL* program package [20]. The positions of the hydrogen atoms were revealed in difference electron density synthesis and refined isotropically. The structure was refined in a F^2 full-matrix least-squares analysis in the anisotropic approximation for non-hydrogen atoms to $wR_2 = 0.099$ for 4949 reflections ($R_1 = 0.035$ for 3327 reflections with $F > 4\sigma(F)$, $S = 0.974$). The full crystallographic information has been placed in the Cambridge Structural Database as deposit CCDC 756716. Interatomic distances and valence angles are presented in Tables 1 and 2 respectively.

Esters of 4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic Acids 3a-i (General Method). Conc. H_2SO_4 (2-3 drops) was added to a solution of the quinolineacetic acid **5** (2.33 g, 0.01 mol) in the corresponding alcohol (20 ml) and refluxed for 5 h. The product was cooled and poured into cold water (in the preparation of esters **3f-i** the excess of alcohol unmixed with water was initially removed under reduced pressure). The precipitated ester **3** (Tables 3 and 4) was filtered off, washed with cold water, and dried.

4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-ylacetic Acid 6-Methylpyridin-2-ylamide (8). A mixture prepared from the ethyl ester **3b** (2.61 g, 0.01 mol) and 2-amino-6-methylpyridine (1.08 g, 0.01 mol) was held in a Woods metal bath at 200ºC for 20 min. After some time the final product began to crystallize from the reaction mixture. At the end of the amidation it was cooled and thoroughly triturated with ethanol (20 ml) to give the amide **8** precipitate which was filtered off, washed with cold ethanol, and dried. Yield 2.81 g (87%); mp 272-274ºC (DMF). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 10.59 (1H, br. s, 4-OH); 10.43 (1H, s, NH), 8.00 (1H, d, $J = 8.1$, H-5); 7.81 (1H, d, $J = 8.2$, H-3'); 7.60 (2H, m, H-7 and H-4'); 7.48 (1H, d, $J = 8.5$, H-8); 7.26 (1H, t, $J = 7.3$, H-6); 6.92 (1H, d, $J = 7.3$, H-5'); 3.76 (2H, s, C$\underline{H}_2$CO); 3.57 (3H, s, NCH_3); 2.39 (3H, s, 6'-CH_3). Found, %: C 66.72; H 5.21; N 12.87. $C_{18}H_{17}N_3O_3$. Calculated, %: C 66.86; H 5.30; N 13.00.

Study of the Anti-inflammatory Activity on the Carrageenan Edema Model in Mice. Experiments were carried out on white, nonpedigree mice of weight 18-22 g. The studied compounds were introduced orally as fine aqueous suspensions stabilized by Tween-80 in doses equimolar to voltaren and in volumes not more than 0.3 ml per 10 g animal weight. Each compound was studied on 6 animals having the same body weight (within ± 0.5 g limits). The same volume of water was introduced into the control group. One hour after introduction of the test compounds into the aseptic inflammation was modeled in animals by a subcutaneous injection of a freshly prepared 1% solution of carrageenan (0.05 ml) into the right hind paw. After 3 h the animal was killed by dislocation of the cervical vertebrae and the hind legs were amputated at the level of the hip joint. The absolute value of the edema in each experiment was calculated by the difference in mass between the edematous and the healthy paws. The specific activity for the test compound was calculated from their ability to decrease the spread of the edema when compared with the control and expressed as a percentage. Statistical treatment of the experimental data was evaluated using the method of variational statistics [21]. The accuracy of the results obtained was determine using Student *t*-test criteria [22].

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