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4-HYDROXY-2-QUINOLONES.
46.* ESTERS OF 1H-2-OXO-
4-HYDROXY-3-QUINOLINEACETIC ACID

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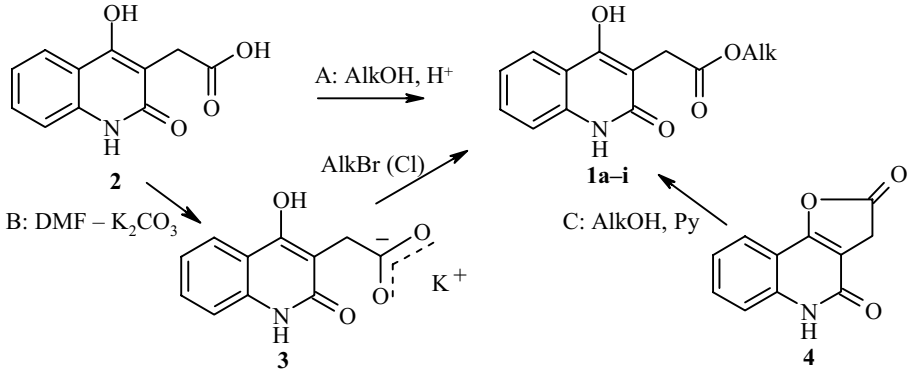
Different methods of synthesizing esters of 1H-2-oxo-4-hydroxy-3-quinolineacetic acid were studied. Results are given for tests of the anti-inflammatory activity of these products.

Keywords: esters, 3-quinolineacetic acid, anti-inflammatory activity.

Arylacetic and heterylacetic acids and their derivatives have an important place in the arsenal of modern nonsteroid anti-inflammatory agents which are widely used in medicine in the treatment of rheumatism, arthritis, osteoarthrosis, gout, and other inflammatory diseases [2-6]. A pronounced antiexudative effect was also found for 1-R-2,4-dioxo-3-quinolinecarboxylic acids and their ethyl esters. The activity of the esters was found to be higher than for the acids [7, 8].

We have studied the synthesis of esters of 1H-2-oxo-4-hydroxy-3-quinolineacetic acid (**1**) and the anti-inflammatory activity of these compounds.

Lower alkyl esters **1a-c** are readily formed in the usual acid-catalyzed esterification of quinolineacetic acid **2** (method A). This method is also applicable for higher alcohols but it is complicated by the necessity of removing the excess alcohol. Thus, the alkylation of acid **2** by the corresponding alkyl chlorides or bromides in DMF in the presence of K_2CO_3 (method B) is more convenient in such cases. The reaction of alcohols with 2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline-2,4-dione (**4**) carried out in anhydrous pyridine (method C) is an alternative to method B, which permits the synthesis of esters **1** in higher yields.



1 a Alk = CH_3, **b** Alk = C_2H_5; **c** Alk = C_3H_7, **d** Alk = *i*-C_3H_7, **e** Alk = C_4H_9, **f** Alk = *i*-C_4H_9, **g** Alk = C_5H_{11}, **h** Alk = $C_{10}H_{21}$, **i** Alk = C_6H_{11}-*cyclo*

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TABLE 1. Physical Characteristics of Esters of 1H-2-Oxo-4-hydroxy-3-quinolineacetic Acid (**1a-i**)

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (ethanol)	Yield, % (method)
		C	H	N		
1a	$C_{12}H_{11}NO_4$	61.91 61.80	4.66 4.75	6.09 6.01	203-204	92 (A)
1b	$C_{13}H_{13}NO_4$	63.08 63.15	5.37 5.30	5.60 5.66	222-224	95 (A)
1c	$C_{14}H_{15}NO_4$	64.44 64.36	5.72 5.79	5.40 5.36	192-194	86 (A)
1d	$C_{14}H_{15}NO_4$	64.32 64.36	5.85 5.79	5.31 5.36	220-222	83 (C)
1e	$C_{15}H_{17}NO_4$	65.40 65.44	6.31 6.22	5.02 5.09	175-177	56 (A) 87 (C)
1f	$C_{15}H_{17}NO_4$	65.52 65.44	6.17 6.22	5.11 5.09	178-180	70 (B)
1g	$C_{16}H_{19}NO_4$	66.41 66.42	6.59 6.62	4.87 4.84	169-171	53 (C) 82 (B)
1h	$C_{21}H_{29}NO_4$	70.26 70.17	8.08 8.13	3.94 3.90	102-104	74 (B)
1i	$C_{17}H_{19}NO_4$	67.70 67.76	6.42 6.36	4.61 4.65	194-196	77 (C)

TABLE 2. ^{1}H NMR Spectra of Esters of 1H-2-Oxo-4-hydroxy-3-quinolineacetic Acid (**1a-i**), ppm

Compound	OH (1H, s)	NH (1H, s)	5-H (1H, d)	7-H (1H, t)	8-H (1H, d)	6-H (1H, t)	CH_2CO (2H, s)	Alk
1a	10.51	11.42	7.91	7.49	7.28	7.16	3.59 (5H, s, CH_2 + OMe)	see CH_2CO
1b	10.50	11.39	7.90	7.50	7.28	7.17	3.58	4.05 (2H, q, OCH_2); 1.18 (3H, t, Me);
1c	10.50	11.40	7.91	7.49	7.29	7.18	3.59	3.97 (2H, t, OCH_2); 1.57 (2H, m, $C\underline{H}_2$Me); 0.86 (3H, t, Me)
1d	10.50	11.39	7.88	7.48	7.28	7.16	3.53	4.87 (1H, m, OCH); 1.17 (6H, d, Me × 2)
1e	10.52	11.41	7.90	7.50	7.29	7.18	3.59	4.01 (2H, t, OCH_2); 1.70-1.17 (4H, m, $(C\underline{H}_2)_2$Me); 0.86 (3H, t, Me)
1f	10.49	11.39	7.89	7.48	7.28	7.17	3.60	3.79 (2H, d, OCH_2); 1.85 (1H, m, $C\underline{H}Me_2$); 0.84 (6H, d, Me × 2)
1g	10.49	11.40	7.89	7.48	7.29	7.16	3.58	4.00 (2H, t, OCH_2); 1.54 (2H, q, $OCH_2C\underline{H}_2$); 1.26 (4H, m, $(C\underline{H}_2)_2$Me); 0.82 (3H, t, Me)
1h	10.54	11.68	7.87	7.50	7.29	7.18	3.54	4.01 (2H, t, OCH_2); 1.78 (2H, q, $OCH_2C\underline{H}_2$); 1.21 (14H, m, $(C\underline{H}_2)_7$Me); 0.84 (6H, d, Me)
1i	10.45	11.37	7.89	7.49	7.28	7.16	3.55	4.62 (1H, q, OCH); 1.81-1.12 (10H, m, $(CH_2)_5$)

The study of the anti-inflammatory (antiexudative) activity of 1H-2-oxo-4-hydroxy-3-quinolineacetic acid (**2**) and its esters **1a-i** was carried out using the model of acute carragheen inflammation edema of the paw of white male rats according to Winter et al. [9] upon oral intake in comparison with voltaren.

The experimental results indicate that, on the whole, the antiinflammatory activity is not characteristic for esters **1**. Acid **2** was also found to be inactive. Only decyl ester **1h** and cyclohexyl ester **1i** showed slight inhibition of the exudative reaction, which was much weaker than for the reference substance.

EXPERIMENTAL

The ^{1}H NMR spectra of the products were taken on a Bruker WP-100SY spectrometer for solutions in DMSO-d_6 with TMS as the internal standard. A sample of 2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline-2,4-dione **4** was prepared according to our previous procedure [1].

Butyl Ester of 1H-2-Oxo-4-hydroxy-3-quinolineacetic Acid (1e). A. Two or three drops of concentrated sulfuric acid were added to a mixture of quinolineacetic acid **2** (2.19 g, 0.01 mol) in butanol (40 ml) and heated at reflux for 10 h. Excess butanol was distilled off at reduced pressure (in the case of esters **1a-c**, the reaction mixture was poured into water). The residue was treated with hexane. The precipitate of ester **1e** was filtered off, washed with hexane and, then, water, and dried.

C. Butanol (0.92 ml, 0.01 mol) was added to a suspension of 2,3,4,5-tetrahydrofuro[3,2-*c*]quinoline-2,4-dione **4** (2.01 g, 0.01 mol) in anhydrous pyridine (20 ml) and heated at reflux for 20 h. The mixture was cooled, diluted with water, and brought to pH 3 by adding hydrochloric acid. The precipitate of ester **1e** was filtered off, washed with water, and dried.

The melting point of a mixed sample of ester **1e** obtained by methods A and C was undepressed.

Decyl Ester of 1H-2-Oxo-4-hydroxy-3-quinolineacetic acid (1h). B. K_2CO_3 (1.38 g, 0.01 mol) and 1-chlorodecane (2.03 ml, 0.01 mol) were added to a solution of acid **2** (2.19 g, 0.01 mol) in DMF (30 ml) and stirred for 10 h at 80-90°C. The reaction mixture was cooled, diluted with water, and brought to pH 3 by adding hydrochloric acid. The precipitate of ester **1h** was filtered off, washed with water, and dried.

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