Chemistry of Heterocyclic Compounds, Vol. 30, No. 7, 1994

4-HYDROXY-2-QUINOLONES. 22.* SYNTHESIS AND BIOLOGICAL PROPERTIES OF 1-ALKYL(ARYL)-2-OXO-3-CARBETHOXY-4-HYDROXYQUINOLINES AND THEIR DERIVATIVES

I. V. Ukrainets, O. V. Gorokhova, S. G. Taran, P. A. Bezuglyi, A. V. Turov, N. A. Marusenko, and O. A. Evtifeeva

The presently known method for obtaining ethyl esters of 1-alkyl(or aryl)-2-oxo-4-hydroxyquinoline-3-carboxylic acids and their derivatives has been improved. Results are presented from an investigation of the anticoagulant, analgesic, and antiinflammatory activities of the synthesized compounds.

In our earlier comprehensive study of the biological properties of 2,4-dioxo-3H-quinoline-3-carboxylic acid and the corresponding ethyl ester, we showed that it would be advantageous to search in this series for compounds with high analgesic, anticoagulant, and antiinflammatory activities [2].

In extending the scope of that work, the present study has been devoted to the synthesis and study of biological properties of 1-alkyl(or aryl)-substituted 2-oxo-3-carbethoxy-4-hydroxyquinolines Ia-u, and also certain derivatives of these compounds.

The objects of investigation were synthesized by a known scheme [3], i.e., by acylation of the ethyl esters of N-alkyl(aryl)anthranilic acids by ethoxymalonyl chloride, with subsequent treatment of the anilide products II with an aqueous solution of potassium hydroxide (for the compounds with R = Alk) or with an alcoholic solution of sodium ethylate (for the compounds with R = Ar). In the latter case, the cyclization could not be performed in an aqueous medium, owing to the ease of hydrolysis of the amide bond of the esters of N-arylanthranilides of malonic acid II (R = Ar or substituted Ar).

From the experience we accumulated in the synthesis of 2-oxo-4-hydroxyquinoline systems, we noted that the alkyl-substituted esters Ia-ℓ are best isolated and purified in the form of the corresponding potassium salts III. There are several reasons for this modification, one of which is the high lipophilicities and low melting points of the esters Ia-l, making them difficult to isolate in crystalline form without prepurification. Moreover, when using the potassium salts, a simple operation permits easy removal of the 1H-derivative I (R = H) that is present as an impurity, derived from the ester of anthranilic acid and often present in its N-alkylated derivatives. Hydrolysis of the esters I proceeds under severe conditions — extended boiling in an aqueous potassium hydroxide solution — and yields the corresponding acids IV; in the case R = (C_8-C_{10}), the acid can be isolated in the form of the potassium salts V, which are quite insoluble in cold water. In terms of the preparative chemistry, acid hydrolysis is simpler, and it requires considerably less reaction time.

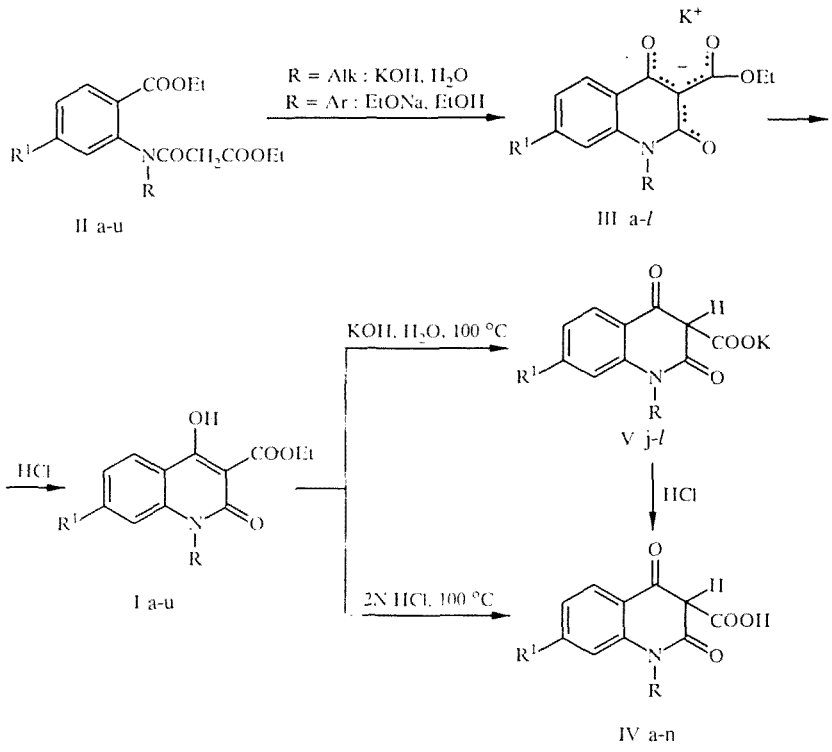
The analgesic activities of the acids IV and their ethyl esters I were investigated in the model of acetic acid "spasms" [4]. The test substance was introduced in a dose of 25 mg/kg in the form of a finely dispersed aqueous suspension stabilized with Tween 80, administered orally 1 h before applying the painful stimulus. The comparison preparation, Voltaren, was used in a dose corresponding to ED_{50} [5]. Among all the substances that were investigated, it was found that the strongest analgesic effect was given by 1-butyl-2,4-dioxo-3H-quinoline-3-carboxylic acid (IVe) and its ethyl ester (Ie), which reduced the number

*For Communication 21, see [1].

Ukraine Pharmaceutical Academy, Khar'kov 310002. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 958-966, July, 1994. Original article submitted June 24, 1994.

0009-3122/94/3007-0829$12.50

of acetic acid-induced spasms by 60-79% in comparison with the control. In general, the ethyl esters I proved to be more active than the corresponding acids IV (see Table 5).



I—V R^1 = H: a R = CH_3; b R = C_2H_5; c R = $CH_2CH{=}CH_2$; d R = C_3H_7; e R = C_4H_9; f R = C_5H_{11}; g R = =*i*-C_5H_{11}; h R = C_6H_{13}; i R = C_7H_{15}; j R = C_8H_{17}; k R = C_9H_{19}; l R = $C_{10}H_{21}$; m R = CH_2Ph; n R = Ph; o R = *p*-MeC_6H_4; p R = *p*-$OMeC_6H_4$; q R = *m*-$OMeC_6H_4$; r R = 2,3-$(Me)_2C_6H_3$. R^1 = Cl: s R = *p*-MeC_6H_4; t R = *p*-$OMeC_6H_4$; u R = 3,4-$(Me)_2C_6H_3$

The effects of the synthesized compounds on the blood coagulation system was investigated by means of a procedure that we had described previously [6]. As shown by the results of our studies, in most cases the potassium salts of the 1-R-2-oxo-3-carbethoxy-4-hydroxyquinolines III do not have any significant effect on the blood coagulation system. An anticoagulant effect was noted only for the salt IIIh. Of all of the ethyl esters I, only the N-methyl, N-butyl, and N-pentyl derivatives (Ia, Ie, and If, respectively) gave a slight increase of the time to the initial reaction of blood clotting (by 41-25% in comparison with the controls). The other indexes of the thromboelastograms (TEGs) did not exhibit any reliable differences from the control results. Higher activities were observed for the potassium salts of 1-R-2,4-dioxo-3H-quinoline-3-carboxylic acids Vj,*l*, which increased the indexes R and K by 59-80% and 17-30%, respectively. However, the change of the index of clot formation time (K) was not statistically reliable for these substances. In view of the special importance of changes in the index R of the coagulation system, we can consider that the substances of this group do have hypocoagulant activity, even though their effects are not as great as those of preparations with the coumarin or indandione structure (Fepromaron, Fenilin, and others) [7]. Of all the compounds that we examined, a total hypocoagulant effect was noted only for 1-pentyl-2,4-dioxo-3H-quinoline-3-carboxylic acid (IVf), the introduction of which gave a statistically reliable change of all of the TEG indexes: R 76%, K 46%, and Ma (maximum amplitude) 33% relative to the control.

The antiinflammatory (antiexudative) effect of the ethyl esters of 1-aryl-2-oxo-4-hydroxyquinoline-3-carboxylic acids In-u was determined oncometrically in a model of acute carragenin inflammation (edema) [8]. A comparison of the results obtained in these experiments shows that the greatest retardation of the exudative reaction (a 30% retardation) is produced by the methoxy-substituted esters Ip,q. Under analogous conditions, Voltaren manifests antiinflammatory activity at the level of 48%.

Thus, the results obtained in these studies provide firm grounds for believing that subsequent chemical modification of the substances noted in this article will open up possibilities of creating both analgesics and indirect anticoagulants on the basis of 4-hydroxy-2-quinolones.

TABLE 1. Characteristics of Potassium Salts of 1-Alkyl-2-oxo-3-carbethoxy-4-hydroxyquinolines

Compound	Empirical formula	mp, °C*	PMR spectrum, δ, ppm							Yield, %*2
			H_{arom}				OCH_2 + NCH_2 (4H, m)	$OCH_2\underline{CH_2}$ (3H, t)	R	
			5-H (1H, dd)	7-H (1H, td)	8-H (1H, d)	6-H (1H, td)				
III a	$C_{13}H_{12}KNO_4$	320...322	7,94	7,37	7,13	6,98	4,20 (2H, q, OCH_2)	1,21	3,41 (3H, s, CH_3)	71
III b	$C_{14}H_{14}KNO_4$	324...326	7,96	7,35	7,12	6,95	4,04	1,22	1,17 (3H, t, CH_3)	85
III c	$C_{15}H_{14}KNO_4$	304...306	7,98	7,37	7,16	6,99	4,18 (2H, q, OCH_2)	1,24	5,79 (1H, m, CH); 4,98 (2H, d, NCH_2); 4,70 (2H, d, $=CH_2$)	72
III d	$C_{15}H_{16}KNO_4$	330...332	7,97	7,38	7,15	6,94	4,04	1,21	1,52 (2H, m, $NCH_2C\underline{H_2}$); 0,94 (3H, t, CH_3)	69
III e	$C_{16}H_{18}KNO_4$	321...323	7,98	7,36	7,15	6,95	4,03	1,22	1,36 (4H, m, $NCH_2(C\underline{H_2})_2$); 0,91 (3H, t, CH_3)	74
III f	$C_{17}H_{20}KNO_4$	310...312	7,95	7,36	7,13	6,93	4,02	1,19	1,37 (6H, m, $NCH_2(C\underline{H_2})_3$); 0,88 (3H, t, CH_3)	72
III g	$C_{17}H_{20}KNO_4$	313...314	7,95	7,37	7,11	6,93	4,03	1,19	1,68 (1H, m, CH); 1,41 (2H, q, $NCH_2C\underline{H_2}$); 0,96 (6H, d, CH_3 ×2)	77
III h	$C_{18}H_{22}KNO_4$	309...310	7,95	7,36	7,13	6,93	4,03	1,19	1,32 (8H, m, $NCH_2(C\underline{H_2})_4$; 0,87 (3H, t, CH_3)	80
III i	$C_{19}H_{24}KNO_4$	298...299	7,93	7,35	7,12	6,91	3,99	1,18	1,27 (10H, m, $NCH_2(C\underline{H_2})_5$; 0,85 (3H, t, CH_3)	79
III j	$C_{20}H_{26}KNO_4$	302...304	7,96	7,37	7,14	6,94	4,00	1,20	1,27 (12H, m, $NCH_2(C\underline{H_2})_6$; 0,87 (3H, t, CH_3)	86
III k	$C_{21}H_{28}KNO_4$	312...314	7,95	7,36	7,13	6,92	3,99	1,19	1,25 (14H, m, $NCH_2(C\underline{H_2})_7$; 0,86 (3H, t, CH_3)	85
III l	$C_{22}H_{30}KNO_4$	308...310	7,98	7,38	7,14	6,94	4,00	1,20	1,26 (16H, m, $NCH_2(C\underline{H_2})8$; 0,87 (3H, t, CH_3)	79

*Yields of salts IIIa-*l* may vary greatly depending on the purity of the original esters of N-alkylanthranilic acids.

TABLE 2. Characteristics of Ethyl Esters of 1-R-2-Oxo-4-hydroxyquinoline-3-carboxylic Acids Ia-u

Compound	Empirical formula	mp, °C*	PMR spectrum, δ, ppm								Yield, %*2
			OH (1H, s)	H_{arom}				OCH_2 (2H, q)	OCH_2CH_3 (3H, t)	R	
				5-H (1H, dd)	7-H (1H, td)	6-H (1H, td)	8-H (1H, d)				
1	2	3	4	5	6	7	8	9	10	11	12
Ia	$C_{13}H_{13}NO_4$	105...106	13,06	8,03	7,73	7,28	7,48	4,34	1,30	3,52 (3H, s, CH_3)	96
Ib	$C_{14}H_{15}NO_4$	66...68	13,05	8,08	7,78	7,30	7,56	4,37	1,25	4,22 (2H, q, NCH_2); 1,19 (3H, t, CH_3)	98
Ic	$C_{15}H_{15}NO_4$	82...84	13,20	8,03	7,69	7,27	7,39	4,31	1,30	5,87 (1H, m, CH); 5,09 (2H, d, NCH_2); 4,79 (2H, d, $=CH_2$)	94
Id	$C_{15}H_{17}NO_4$	86...88	13,11	8,05	7,76	7,29	7,56	4,35	1,31	4,14 (2H, t, NCH_2); 1,60 (2H, m, $NCH_2\underline{CH_2}$); 0,95 (3H, t, CH_3)	92
Ie	$C_{16}H_{19}NO_4$	48...50	13,09	8,06	7,69	7,27	7,49	4,33	1,32	4,14 (2H, t, NCH_2); 1,47 (4H, m, $NCH_2(\underline{CH_2})_2$); 0,93 (3H, t, CH_3)	94
If	$C_{17}H_{21}NO_4$	55...56	13,01	8,03	7,69	7,22	7,44	4,28	1,28	4,10 (2H, t, NCH_2); 1,50 (6H, m, $NCH_2(\underline{CH_2})_3$); 0,85 (3H, t, CH_3)	99
Ig	$C_{17}H_{21}NO_4$	66...68	13,20	8,04	7,73	7,27	7,45	4,30	1,29	4,15 (2H, t, NCH_2); 1,70 (1H, m, CH); 1,50 (2H, q, $NCH_2C\underline{H_2}$); 0,96 (6H, d, $CH_3 \times 2$)	98
Ih	$C_{18}H_{23}NO_4$	59...60	13,08	8,05	7,69	7,23	7,45	4,28	см. R	3,97 (2H, t, NCH_2); 1,29 (11H, m, $NCH_2(\underline{CH_2})_4 + COOCH_2C\underline{H_3}$); 0,86 (3H, t, CH_3	90
Ii	$C_{19}H_{25}NO_4$	54...55	13,02	8,06	7,75	7,29	7,53	4,32	см. R	3,98 (2H, t, NCH_2); 1,30 (13H, m, $NCH_2(\underline{CH_2})_5 + COOCH_2C\underline{H_3}$); 0,86 (3H, t, CH_3)	94
Ij	$C_{20}H_{27}NO_4$	67...68	13,13	8,03	7,57	7,13	7,37	4,20	см. R	4,06 (2H, t, NCH_2); 1,25 (15H, m, $NCH_2(\underline{CH_2})_6 + COOCH_2C\underline{H_3}$); 0,83 (3H, t, CH_3)	97

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
Ik	$C_{21}H_{29}NO_4$	60...62	13,04	8,07	7,72	7,30	7,53	4,28	mx. R	4,14 (2H, t, NCH_2); 1,32 (17H, m, $NCH_2(CH_2)_7$ + $COOCH_2CH_3$); 0,85 (3H, t, CH_3)	97
Il	$C_{22}H_{31}NO_4$	63...65	13,12	8,05	7,70	7,25	7,48	4,28	mx. R	4,13 (2H, t, NCH_2); 1,30 (19H, m, $NCH_2(CH_2)_8$ + $COOCH_2CH_3$); 0,85 (3H, t, CH_3)	96
Im	$C_{19}H_{17}NO_4$	112...114	13,17	8,09	7,61	7,45...7,10 (7H, m, 6-H, 8-H, Ph)		4,36	1,34	mx. 6-H & 8-H; 5,48 (2H, s, CH_2–Ph)	69
In	$C_{18}H_{15}NO_4$	178...179	13,38	8,10		7,78...7,12 (7H, m, 7-H, 6-H, Ph)	6,47	4,32	1,27	mx. 7-H & 6-H	74
Io	$C_{19}H_{17}NO_4$	171...172	13,28	8,09	7,55	7,43	6,50	4,33	1,27	7,41 (2H, d, 2'-H, 6'-H); 7,15 (2H, d, 3'-H, 5'-H); 2,42 (3H, s, CH_3)	61
Ip	$C_{19}H_{17}NO_5$	154...156	13,37	8,08	7,55	7,26	6,55	4,33	1,29	7,18 (4H, d, H_{arom}); 3,86 (3H, s, OCH_3)	60
Iq	$C_{19}H_{17}NO_5$	156 157	13,37	8,10	7,58	7,19	6,54	4,33	1,29	7,52 (1H, t, 5'-H); 7,33 (1H, d, 4'-H); 6,92 (1H, s, 2'-H); 6,83 (1H, d, 6'-H); 3,78 (3H, s, OCH_3)	64
Ir	$C_{20}H_{19}NO_4$	120...122	13,35	8,11	7,57	7,43...6,95 (4H, m, 6-H, 4'-H, 5'-H, 6'-H)	6,40	4,34	1,29	mx. 6-H; 2,34 (3H, s, 3'-CH_3); 1,80 (3H, s, 2'-CH_3)	67
Is	$C_{19}H_{16}ClNO_4$	150...152	13,36	8,08	–	7,50...7,11 (5H, m, 6-H, 2'-H, 3'-H, 5'-H, 6'-H)	6,41 s	4,32	1,28	mx. 6-H; 2,43 (3H, s, CH_3)	58
It	$C_{19}H_{16}ClNO_5$	218...220	13,34	8,08	–	7,39...7,01 (5H, m, 6-H, 2'-H, 3'-H, 5'-H, 6'-H)	6,46 s	4,30	1,27	mx. 6-H; 3,86 (3H, s, OCH_3)	64
Iu	$C_{20}H_{18}ClNO_4$	205...207	13,32	8,09	–	7,50...6,95 (4H, m, 6-H, 2'-H, 5'-H, 6'-H)	6,45 s	4,31	1,27	mx. 6-H; 2,34 (3H, s, 4'-CH_3); 2,29 (3H, s, 3'-CH_3)	57

*Compounds Ia-*l* were crystallized from diethyl ether, other compounds from alcohol.

*2Yields of esters Ia-*l* have been recalculated to the corresponding potassium salts III, yields of esters Im-u to the original esters of N-R-anthranilic acids.

TABLE 3. Characteristics of 1-R-2,4-Dioxo-3H-quinoline-3-carboxylic Acids IVa,b,d-*l*,n

Compound	Empirical formula	mp, °C (from alcohol)	PMR spectra, δ, ppm							Yield, %
			COOH (1H, s)	H_{arom}				3-H (1H, s)	R	
				5-H (1H, dd)	7-H (1H, td)	6-H (1H, td)	8-H (1H, d)			
IVa	$C_{11}H_9NO_4$	268...269	11,33	7,90	7,64	7,23	7,46	5,88	3,53 (3H, s, CH_3)	89
IVb	$C_{12}H_{11}NO_4$	266...267	11,34	7,90	7,63	7,22	7,50	5,88	4,21 (2H, q, CH_2); 1,17 (3H, t, CH_3)	90
IVd	$C_{13}H_{13}NO_4$	223...225	11,31	7,90	7,64	7,23	7,48	5,87	4,12 (2H, t, NCH_2); 1,59 (2H, m, CH_2CH_3); 0,92 (3H, t, CH_3)	92
IVe	$C_{14}H_{15}NO_4$	213...215	11,31	7,90	7,64	7,23	7,48	5,87	4,17 (2H, t, NCH_2); 1,32 (4H, m, $(CH_2)_2CH_3$); 0,93 (3H, t, CH_3)	89
IVf	$C_{15}H_{17}NO_4$	201...203	11,35	7,90	7,64	7,22	7,47	5,87	4,14 (2H, t, NCH_2), 1,45 (6H, m, $(CH_2)_3CH_3$); 0,87 (3H, t, CH_3)	90
IVg	$C_{15}H_{17}NO_4$	188...190	11,33	7,84	7,63	7,21	7,42	5,86	4,17 (2H, t, NCH_2); 1,68 (1H, m, $CH(CH_3)_2$); 1,48 (2H, q, CH_2CH); 0,94 (6H, d, $CH_3 \times 2$)	92
IVh	$C_{16}H_{19}NO_4$	186...187	11,31	7,90	7,63	7,22	7,46	5,86	4,14 (2H, t, NCH_2); 1,40 (8H, m, $(CH_2)_4CH_3$); 0,86 (3H, t, CH_3)	93
IVi	$C_{17}H_{21}NO_4$	155...157	11,30	7,89	7,62	7,21	7,45	5,85	4,14 (2H, t, NCH_2); 1,45 (10H, m, $(CH_2)_5CH_3$); 0,85 (3H, t, CH_3)	94
IVj	$C_{18}H_{23}NO_4$	154...155	11,30	7,89	7,63	7,21	7,44	5,85	4,13 (2H, t, NCH_2); 1,43 (12H, m, $(CH_2)_6CH_3$); 0,84 (3H, t, CH_3)	96
IVk	$C_{19}H_{25}NO_4$	146...148	11,33	7,89	7,63	7,22	7,47	5,86	4,15 (2H, t, NCH_2); 1,42 (14H, m, $(CH_2)_7CH_3$); 0,85 (3H, t, CH_3)	94
IV*l*	$C_{20}H_{27}NO_4$	138...140	11,35	7,89	7,63	7,21	7,45	5,87	4,13 (2H, t, NCH_2); 1,45 (16H, m, $(CH_2)_8CH_3$); 0,85 (3H, t, CH_3)	95
IVn	$C_{16}H_{11}NO_4$	297...299	11,64	7,93	7,73...7,11 (7H, m, 7-H, 6-H, Ph			6,49	5,92	mx. 7-H & 6-H	97

TABLE 4. Characteristics of Potassium Salts of 1-R-2,4-Dioxo-3H-quinoline-3-carboxylic Acids Vj-*l*

Compound	Empirical formula	mp, °C (from alcohol)	PMR spectra, δ, ppm						Yield, %
			H_{arom}				3-H (1H, s)	R	
			5-H (1H, dd)	7-H (1H, td)	8-H (1H, d)	6-H (1H, td)			
Vj	$C_{18}H_{22}KNO_4 \cdot 3H_2O$	79...80	7,93	7,30	7,11	6,88	4,87	4,00 (2H, t, NCH_2); 1,27 (12H, m, $(CH_2)_6CH_3$); 0,85 (3H, t, CH_3)	82
Vk	$C_{19}H_{24}KNO_4 \cdot 3H_2O$	84...85	7,93	7,34	7,12	6,89	4,87	4,00 (2H, t, NCH_2); 1,25 (14H, m, $(CH_2)_7CH_3$); 0,87 (3H, t, CH_3)	83
V*l*	$C_{20}H_{26}KNO_4 \cdot 3H_2O$	81...83	7,94	7,35	7,12	6,89	4,87	4,00 (2H, t, NCH_2); 1,25 (16H, m, $(CH_2)_8CH_3$); 0,86 (3H, t, CH_3)	74

*Water of crystallization was determined by drying [11].

TABLE 5. Pharmacological Properties of Synthesized Compounds

Compound	Anticoagulant activity, effect on TEG index, %			Analgesic activity, % reduction of number of spasms relative to control
	R	K	Ma	
IIIe	-9	-6	-3	—
IIIf	-17	-9	-5	—
IIIg	+12	+22	+7	—
IIIh	+38	+40	-7	—
IIIi	-43	-34	+30	—
IIIk	+9	-27	+22	—
Ia	+41	+9	-6	75
Ib	-14	+18	+5	51
Id	-3	+1	-6	34
Ie	+25	+10	-11	79
If	+32	-3	-13	41
Ig	+4	+3	-7	18
Ih	+6	+8	-2	41
Ii	+6	+8	+10	36
Ij	+20	+16	-2	31
Ik	+5	+21	-7	57
I*l*	+7	+14	-8	46
IVa	-42	+2	+13	48
IVb	+4	+19	-8	40
IVd	-25	-7	+19	27
IVe	+21	+9	-6	60
IVf	+76	+46	-33	36
IVg	-6	+9	-18	46
IVh	-12	+1	+3	20
IVi	+7	+8	-16	2
IVj	+53	+2	-11	19
IVk	+15	+9	-3	4
IV*l*	0	+13	+4	5
IVn	-6	+12	-12	—
Vj	+59	+30	-13	—
V*l*	+80	+17	-22	—
Fepromaron	+197	+102	-16	—
Voltaren	—	—	—	49

*Plus-sign denotes an increase of the index, minus-sign a decrease.

EXPERIMENTAL

PMR spectra of the compounds were recorded in a Bruker WP-100 SY instrument in DMSO-d_6, internal standard TMS.

Elemental analyses for C, H, N, and K were consistent with the calculated values. The ethyl esters of 1-aryl-2-oxo-4-hydroxyquinoline-3-carboxylic acids In-u were obtained by a procedure given in [3]. All of the results of the biological tests were processed statistically by the variation method with Student's test taken into account [9, 10]; these results are summarized in Table 5 (level of probability ≤ 0.05).

General Procedure for Obtaining Potassium Salts of 2-Oxo-3-carbethoxy-4-hydroxyquinolines IIIa-*l*. To a solution of 0.1 mole of the ethyl ester of an N-alkylanthranilic acid and 14 ml (0.1 mole) of triethylamine in 100 ml of methylene chloride, 16.6 g (0.11 mole) of ethoxymalonyl chloride was added while stirring and cooling the solution. The mixture was left for 7-8 h at room temperature, after which the precipitate (triethylamine hydrochloride) was filtered off and washed on the funnel with methylene chloride. A 100-ml portion of water was added to the filtrate, and the mixture was stirred. After settling for 1 h, the organic layer was separated and the solvent was driven off (under vacuum in the last stage). To the residue (an anilide II), a solution of 16.8 g (0.3 mole) of KOH in 50 ml of water was added. After mixing for 5 h, the potassium salt III that precipitated was filtered off, washed with cold water, and immediately crystallized from 80° ethanol.

General Procedure for Obtaining Ethyl Esters of 1-Alkyl-2-oxo-4-hydroxyquinoline-3-carboxylic Acids Ia-*l*. A suspension of 0.01 mole of the appropriate potassium salt III in 20 ml of water was acidified with HCl to pH 4. The mixture was stirred for 1 h. The precipitate of I was filtered off, washed with water, and dried.

Potassium Salt of 1-Octyl-2,4-dioxo-3H-quinoline-3-carboxylic acid (Vj, $C_{18}H_{22}KNO_4 \cdot 3H_2O$). A mixture of 3.45 g (0.01 mole) of the ester Ij and 20 ml of a 20% aqueous KOH solution was refluxed for 20 h. After cooling, the precipitated salt Vj was filtered off, washed with cold water, and dried.

The salts Vk,*l* were obtained analogously.

1-R-2,4-Dioxo-3H-quinoline-3-carboxylic acids IVa-n were obtained by acidifying aqueous solutions of the corresponding potassium salts V that had been synthesized by the procedure described in the preceding experiment, or by acid hydrolysis of the esters I (boiling for 5 h in a 2 N HCl solution).

REFERENCES

1. I. V. Ukrainets, S. G. Taran, O. V. Gorokhova, P. A. Bezuglyi, N. A. Marusenko, and V. I. Treskach, Farm. Zh. (1994, in press).
2. P. A. Bezuglyi, I. V. Ukrainets, V. I. Treskach, A. V. Turov, S. V. Gladchenko, Yu. F. Krylov, N. P. Moryakov, and T. M. Aleksandrova, Khim.-farm. Zh., **26**, 33 (1992).
3. I. V. Ukrainets, P. A. Bezuglyi, V. I. Treskach, A. V. Turov, and S. V. Slobodzyan, Khim. Geterotsikl. Soedin., No. 5, 636 (1992).
4. G. Ya. Shvarts and R. D. Syubaev, Farmakol. Toksikol., **45**, 46 (1982).
5. Ya. A. Sigidin, G. Ya. Shvarts, A. P. Arzamastsev, and S. S. Liberman, Drug Therapy of the Inflammation Process [in Russian], Meditsina, Moscow (1988).
6. P. A. Bezuglyi, V. I. Treskach, I. V. Ukrainets, Yu. F. Krylov, M. Yu. Ladinskaya, N. P. Moryakov, and Z. G. Lobanova, Khim.-Farm. Zh., **24**, 31 (1990).
7. M. D. Mashkovskii, Pharmaceuticals [in Russian], Meditsina, Moscow (1988), Part 2, p. 76.
8. C. A. Winter, E. A. Risley, and G. W. Nuss, Proc. Soc. Exp. Biol. Med. (NY), **111**, 544 (1962).
9. O. P. Mintser, B. N. Ugarov, and V. V. Vlasov, Methods for Processing Medical Information [in Russian], Vishcha Shkola, Kiev (1982).
10. R. B. Strelkov, Methods for Calculating Standard Error and Confidence Intervals of Arithmetical Mean Values by the Use of Tables [in Russian], Alashara, Sukhumi (1966).
11. State Pharmacopoeia of the USSR, No. 1, General Methods of Analysis, Ministry of Health of the USSR [in Russian], 11th ed., Meditsina, Moscow (1987), p. 176.