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4-HYDROXY-2-QUINOLONES. 40.* SYNTHESIS AND BIOLOGICAL PROPERTIES OF ANILIDES OF 1H-2-OXO-4-HYDROXYQUINOLINE-3-CARBOXYLIC ACID

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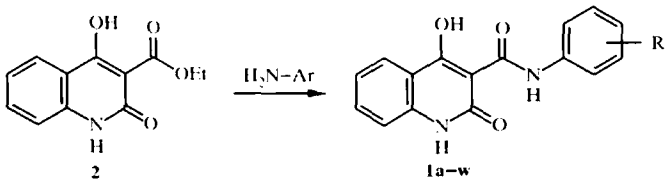
An improved method for the synthesis of anilides of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid was proposed. Results of the study of antithyroid and anti-tuberculosis activity of the compounds synthesized are presented.

Keywords: anilide, carbostyryl, 4-hydroxy-2-quinolone, antithyroid activity, antituberculotic action.

In the study of the influence of 3-(benzimidazol-2-yl)- and 3-(4-oxo-3H-quinazolin-2-yl)-1-R-2-oxo-4-hydroxyquinolines, [2, 3] and [4] respectively, on the function of the thyroid gland, it was established that high antithyroid activity is shown in a series of cases by synthetic precursors of the indicated 3-heteryl-substituted 2-oxo-4-hydroxyquinolines, i.e. 2-amino- and 2-carbamylanilides correspondingly. Marked antithyroid action is also shown by alkyl- and arylalkylamides of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid [5]. A logical continuation of the search for potential antithyroid agents in the series of compounds studied is the synthesis and investigation of biological properties of anilides of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid (**1**).

Regrettably, none of the approaches previously proposed by us [6] for the synthesis of alkylamides of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid is suitable for the synthesis of the anilides (**1**). At the same time, the thermolysis of the mixture of the ester (**2**) and the corresponding amine, utilized in the synthesis of heterylamides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids [7, 8], enables the requisite anilides (**1**) (Table 1)



1 a R = H, **b** R = 2-Me, **c** R = 3-Me, **d** R = 4-Me, **e** R = 2,4-Me_2, **f** R = 2-OMe, **g** R = 3-OMe, **h** R = 4-OMe, **i** R = 2-OH, **j** R = 2-F, **k** R = 3-F, **l** R = 4-F, **m** R = 2-CF_3, **n** R = 3-CF_3, **o** R = 2-Cl, **p** R = 3-Cl, **q** R = 4-Cl, **r** R = 2,4-Cl_2, **s** R = 2-OMe-5-Cl, **t** R = 2-Br, **u** R = 4-Br, **v** R = 3-I, **w** R = 4-I

* For the Communication 39, see [1].

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TABLE 1. Anilides of 1H-2-Oxo-4-hydroxyquinoline-3-carboxylic Acid (**1a-w**)

Compound	Empirical formula	Found, % / Calculated, %			mp, °C (DMF)	^{1}H NMR spectrum, δ, ppm					Yield, %
		C	H	N		OH (1H, s)	NH in 1H (1H, s)	CONH (1H, s)	H_{arom}, m	R	
1	2	3	4	5	6	7	8	9	10	11	12
1a	$C_{16}H_{12}N_2O_3$	68.45 / 68.57	4.39 / 4.32	9.91 / 9.99	298-303	16.34	12.57	11.87	8.20-6.90 (9H)	---	98
1b	$C_{17}H_{14}N_2O_3$	69.44 / 69.38	4.84 / 4.79	9.50 / 9.52	307-309	16.53	12.45	11.84	8.30-7.20 (8H)	2.36 (3H, s, Me)	94
1c	$C_{17}H_{14}N_2O_3$	69.31 / 69.38	4.70 / 4.79	9.47 / 9.52	282-283	16.44	12.57	11.97	8.10-6.70 (8H)	3.33 (3H, s, Me)	90
1d	$C_{17}H_{14}N_2O_3$	69.32 / 69.38	4.86 / 4.79	9.59 / 9.52	312-314	16.25	12.45	11.73	8.25-6.70 (8H)	2.29 (3H, s, Me)	95
1e	$C_{18}H_{16}N_2O_3$	70.17 / 70.12	5.29 / 5.23	9.16 / 9.09	305-307	16.66	12.42	12.03	8.10-7.00 (7H)	2.31 (3H, s, Me); 2.26 (3H, s, Me)	95
1f	$C_{17}H_{14}N_2O_4$	65.75 / 65.80	4.67 / 4.55	9.10 / 9.03	285-287	16.58	12.76	11.94	8.40-6.80 (8H)	3.90 (3H, s, OMe)	94
1g	$C_{17}H_{14}N_2O_4$	65.88 / 65.80	4.63 / 4.55	9.08 / 9.03	238-240	16.34	12.61	11.95	8.20-6.65 (8H)	3.79 (3H, s, OMe)	93
1h	$C_{17}H_{14}N_2O_4$	65.86 / 65.80	4.46 / 4.55	9.06 / 9.03	309-311	16.30	12.42	11.93	8.00-6.80 (8H)	3.75 (3H, s, OMe)	96
1i	$C_{16}H_{12}N_2O_4$	64.77 / 64.86	4.14 / 4.08	9.52 / 9.45	291-293	16.78	12.61	11.90	8.35-6.70 (8H)	10.16 (1H, s, OH)	90
1j	$C_{16}H_{11}FN_2O_3$	64.36 / 64.43	3.79 / 3.72	9.46 / 9.39	214-216	16.27	12.33	11.94	8.23-6.77 (8H)	-	88

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10	11	12
1k	$C_{16}H_{11}FN_2O_3$	64.48 64.43	3.80 3.72	9.44 9.39	218-220	16.34	12.84	11.89	8.20-6.64 (8H)	—	91
1l	$C_{16}H_{11}FN_2O_3$	64.54 64.43	3.65 3.72	9.31 9.39	230-232	16.09	12.90	11.87	8.19-6.70 (8H)	—	95
1m	$C_{17}H_{11}F_3N_2O_3$	58.66 58.63	3.25 3.18	8.08 8.04	199-201	16.77	12.65	11.92	8.33-6.78 (8H)	—	83
1n	$C_{17}H_{11}F_3N_2O_3$	58.61 58.63	3.28 3.18	8.07 8.04	220-222	16.68	12.71	11.95	8.30-6.76 (8H)	—	86
1o	$C_{16}H_{11}ClN_2O_3$	61.12 61.06	3.47 3.52	8.92 8.90	328-330	16.08	12.92	11.85	8.40-6.50 (8H)	—	97
1p	$C_{16}H_{11}ClN_2O_3$	61.15 61.06	3.59 3.52	8.85 8.90	216-218	16.15	12.68	11.90	8.24-7.07 (8H)	—	95
1q	$C_{16}H_{11}ClN_2O_3$	61.10 61.06	3.58 3.52	8.97 8.90	334-335	16.24	12.66	11.88	8.20-7.10 (8H)	—	97
1r	$C_{16}H_{10}Cl_2N_2O_3$	55.08 55.04	2.94 2.89	8.07 8.02	337-339	15.34	12.97	11.80	8.45-6.75 (7H)	—	93
1s	$C_{17}H_{13}ClN_2O_4$	59.16 59.23	3.87 3.80	8.19 8.13	210-211	16.08	12.68	11.80	8.23-7.13 (7H)	3.91 (3H, s, Me)	98
1t	$C_{16}H_{11}BrN_2O_3$	53.58 53.50	3.13 3.09	7.77 7.80	312-313	16.14	12.78	11.74	8.40-6.30 (8H)	—	94
1u	$C_{16}H_{11}BrN_2O_3$	53.59 53.50	3.14 3.09	7.86 7.80	321-323	16.02	12.67	11.89	8.10-7.15 (8H)	—	91
1v	$C_{16}H_{11}IN_2O_3$	47.25 47.31	2.78 2.73	6.99 6.90	320-322	16.08	12.66	11.91	8.20-7.15 (8H)	—	90
1w	$C_{16}H_{11}IN_2O_3$	47.38 47.31	2.66 2.73	6.97 6.90	325-327	16.20	12.67	11.96	8.15-7.20 (8H)	—	89

to be synthesized readily with high yields. The best results are obtained by performing such a reaction in the presence of a small amount of DMF. On the one hand, this modification guarantees the best mixing of the reagents and, on the other hand, it prevents local overheating of the reaction mixture. Consequently, the purity of the final product increases.

Analysis of the investigation into the influence of the anilides (**1**) on the function of the thyroid gland, which was performed by known methods [9, 10], showed that only the 2-chloroanilide of 1H-2-oxo-4-hydroxyquinoline-3-carboxylic acid (**1o**) out of the whole group of substances synthesized merits attention. In its antithyroid activity, (**1o**) has virtually no inferiority to Mercazole, whereby the mechanism of action of these substances – the stimulation of the thyroid gland – is also analogous from the data of histological investigations. The antituberculosis activity of the anilides (**1**) was studied in vitro by a known method [11, 12]. It was thereby established that only the anilides (**1j,p,u,v**) at the concentration of 12 μg/ml produce noticeable (9-54%) inhibition of the growth of Mycobacterium tuberculosis H37Rv ATCC 27294.

EXPERIMENTAL

The PMR spectra of the compounds synthesized were recorded on the Bruker WP-100 SY instrument in DMSO-d_6. The internal standard was TMS.

General Method for the Synthesis of Anilides of 1H-2-Oxo-4-hydroxyquinoline-3-carboxylic Acid (1). The mixture of ethyl 1H-2-oxo-4-hydroxyquinoline-3-carboxylate (**2**) (2.33 g, 0.01 mol), the corresponding aniline (0.01 mol), and DMF (2 ml) is carefully stirred and held on a metal bath at 180-190°C for 10 min. The mixture is cooled prior to the addition of ethyl alcohol (20 ml) and stirred. The residue is filtered off and washed on the funnel with alcohol. The residue is crystallized from DMF (Table 1).

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