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4-HYDROXY-2-QUINOLONES. 35. SYNTHESIS AND STUDY OF ANTITHYROID PROPERTIES OF 1H-2-OXO-3-(COUMARIN-3-YL)-4-HYDROXYQUINOLINES

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The methyl ester of 1H-2-oxo-4-hydroxyquinoline-3-acetic acid is condensed in pyridine with salicylaldehydes to 1H-2-oxo-3-(coumarin-3-yl)-4-hydroxyquinolines. We present the results of a study of the effect of the synthesized compounds on thyroid function.

Determination of the biological activity of a specific compound in modern practice [2] is generally followed up by a series of papers on synthesis of numerous analogs of the parent structure. This report is part of specifically such an investigation, the goal of which is continuation of the search for potential antithyroid drugs in the series of structural analogs of 1H-2-oxo-3-(2-benzimidazolyl)-4-hydroxyquinoline [3,4] by replacing the benzimidazole ring by other heterocycles, in this case coumarins.

The conventional route to obtaining coumarins (well known under the name of Knoevenagel condensation) is the reaction of methylene-active compounds with salicylaldehydes in the presence of relatively weak bases, most often piperidine, followed by spontaneous closure of the benzopyran ring [5]. The fact that such reactions proceed so easily is why synthesis of the target 1H-2-oxo-3-(coumarin-3-yl)-4-hydroxyquinolines (I) is done by condensation of salicylaldehydes (II) with the methyl ester of 1H-2-oxo-4-hydroxyquinonlin-3-acetic acid (III) as the methylene-active component. Considering the pronounced acidic properties of the 4-hydroxy groups in 2-oxo-4-hydroxyquinolines [6], we slightly modified the traditional route for synthesis of coumarins, proposing the use of catalytic amounts of piperidine [7]. However, carrying out the reaction in piperidine as the basic catalyst and simultaneously the solvent unexpectedly led to the piperidylamide of 1H-2-oxo-4-hydroxyquinoline-3-acetic acid (IV). Direct amidation of ester III by a secondary amine is unlikely. So the result obtained obviously can be explained by cyclization of ester III under conditions of synthesis to the anhydride V, which in turn easily acylates piperidine with formation of the amide IV obtained. From this it follows that a positive result may be expected only in the case when we replace piperidine with a base, eliminating the possibility of amidation. In fact, in pyridine, ester III is condensed with salicylaldehydes to 1H-2-oxo-3-(coumarin-3-yl)-4-hydroxyquinolines I without any complications (Table 1), although we do not exclude the possibility that even in this case the reaction proceeds through a stage of formation of compound V.

The effect of the synthesized compounds on thyroid function was studied by determining the thyroid hormones triiodothyronine (T_3) and thyroxine (T_4) in blood serum of experimental animals. Antithyroid drugs, as we know, depending on their mechanism of action may activate or inhibit thyroid function, as a result of which sometimes it is rather complicated to evaluate and compare its condition according to individual indices. So for a more accurate evaluation of thyroid function, we also used the functional activity coefficients (the activation coefficient $K_a = h/d \cdot 10^{-2}$ and the inhibition coefficient $K_i = d/h$), combining such indices as the follicle diameter (d) and the height (h) of follicle cells. The indicated coefficients are most effective and representative in evaluating thyroid function. Comparing them with control values lets us judge the degree of antithyroid action. Analysis of the experimental data obtained, presented in Table 2, shows that of all the coumarin quinolines, only the halogen-substituted derivatives Ig,e reduce the triiodothyronine content to the mercazolyl level. However, according to other indices, they are significantly inferior to the reference drug. The methyl ester of 1H-2-oxo-4-hydroxyquinoline-3-acetic

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TABLE 1. Characteristics of Coumarin Quinolines Ia-f

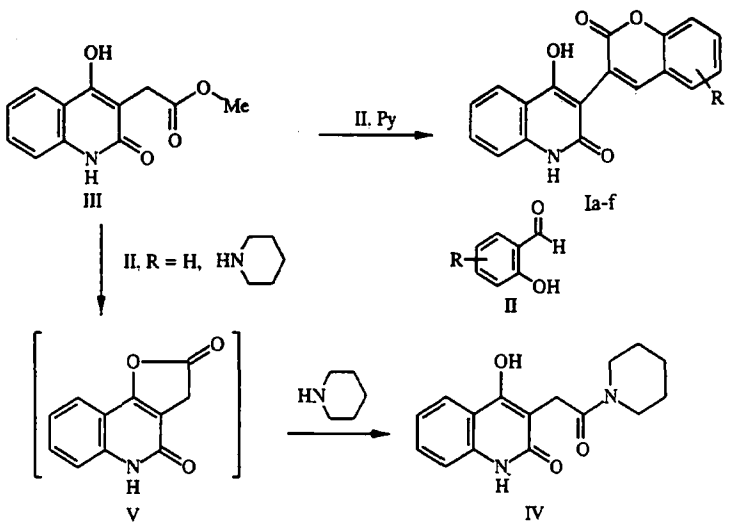
Compound	Empirical formula	Found % / Calculated %				T_{mp}, °C* (DMF)	PMR spectrum, δ, ppm				Yield, %
		C	H	N	Cl/Br		NH (1H, s)	OH (1H, s.)	H_{arom} (m)	R	
Ia	$C_{18}H_{11}NO_4$	70,76 / 70,82	3,60 / 3,63	4,64 / 4,59	—	352 - 354	11,33	10,53	8,01 - 7,07 (9H)	—	92
Ib	$C_{19}H_{13}NO_5$	68,14 / 68,06	3,90 / 3,91	4,16 / 4,18	—	337 - 339	11,33	10,49	8,00 - 7,09 (8H)	3,83 (3H, s., OCH_3)	94
Ic	$C_{22}H_{20}N_2O_4$	70,13 / 70,20	5,28 / 5,36	7,51 / 7,44	—	296 - 298	11,18	10,27	7,96 - 6,54 (8H)	3,47 (4H, q, CH_2); 1,17 (6H, t, CH_3)	81
Id	$C_{18}H_{10}ClNO_4$	63,60 / 63,64	2,96 / 2,97	4,14 / 4,12	10,41 / 10,44	348 - 350	11,53	10,74	7,99 - 7,10 (8H)	—	87
Ie	$C_{18}H_{10}BrNO_4$	56,33 / 56,27	2,60 / 2,62	3,64 / 3,65	20,87 / 20,80	357 - 359	11,54	10,75	8,03 - 7,11 (8H)	—	90
If	$C_{22}H_{13}NO_4$	74,43 / 74,36	3,74 / 3,69	3,92 / 3,94	—	369 - 371	11,35	10,48	8,79 - 7,12 (11H)	—	76

*All the compounds melt with decomposition.

TABLE 2. Effect of Synthesized Compounds on Thyroid Function

Compound	Concentration of thyroid hormones, nmoles/liter		Diameter of follicles, mm	Height of follicular epithelium, mm	K_T	K_a	Relative mass of thyroid gland ($M \times 10^{-5}$)
	T_3	T_4					
Ia	3,31 ± 0,27	239,00 ± 25,61	4,50 ± 0,21	0,67 ± 0,03	6,71 ± 0,24	14,80 ± 0,23	9,70 ± 0,71
Ib	2,32 ± 0,45	206,40 ± 25,89	4,41 ± 0,22	0,74 ± 0,04	5,94 ± 0,27	16,81 ± 0,29	12,50 ± 1,55
Ic	1,46 ± 0,35	117,08 ± 28,84	4,37 ± 0,18	0,78 ± 0,02	5,60 ± 0,11	17,80 ± 0,16	9,32 ± 1,18
Id	0,92 ± 0,23	120,52 ± 14,11	4,70 ± 0,31	0,86 ± 0,03	5,42 ± 0,40	18,29 ± 0,48	13,30 ± 0,08
Ie	1,03 ± 0,21	124,61 ± 13,14	4,66 ± 0,33	0,81 ± 0,02	5,75 ± 0,36	17,38 ± 0,39	12,94 ± 1,19
If	3,51 ± 0,11	143,96 ± 4,94	4,00 ± 0,18	0,55 ± 0,02	7,27 ± 0,14	13,70 ± 0,17	10,70 ± 1,09
III	2,19 ± 0,36	133,42 ± 22,23	4,72 ± 0,29	0,82 ± 0,04	5,73 ± 0,21	17,40 ± 0,27	14,70 ± 2,99
IV	0,39 ± 0,08	34,97 ± 6,99	4,48 ± 0,59	0,96 ± 0,04	4,66 ± 0,58	21,40 ± 0,67	12,20 ± 2,03
Mercazolyl	0,92 ± 0,20	75,00 ± 4,84	4,64 ± 0,23	1,47 ± 0,09	3,15 ± 0,16	31,70 ± 0,71	16,66 ± 1,13
Control	2,04 ± 0,34	126,80 ± 19,34	4,80 ± 0,31	0,70 ± 0,02	6,85 ± 0,18	14,50 ± 0,19	8,90 ± 0,84

acid III has practically no effect on thyroid function, while its piperidylamide IV considerably surpasses mercazolyl in activity with respect to the level of reduction of thyroid hormones. It is also noteworthy that the goitrogenic effect (the increase in the relative mass of the thyroid gland compared with control data) for this compound is less pronounced than for mercazolyl.



I, II a R = H, b R = 6-OMe, c R = 7-N(Et)$_2$, d R = 6-Cl, e R = 6-Br, f R = 5,6-benzo

EXPERIMENTAL

The PMR spectra of the synthesized compounds were recorded on a Bruker WP-100 SY in DMSO-D_6, internal standard TMS.

The methyl ester of 1H-2-oxo-4-hydroxyquinoline-3-acetic acid (III) was synthesized according to the procedure in [8]. The pharmacological studies were done using the familiar procedure in [3,9].

General Procedure for Obtaining 1H-2-oxo-3-(coumarin-3-yl)-4-hydroxyquinolines (Ia-f). A mixture of 2.33 g (0.01 moles) ester III and 0.01 moles of the corresponding salicylaldehyde II in 15 ml pyridine was boiled for 5 h. Then it was cooled down and diluted with water and acidified with a 1:1 HCl solution down to pH ~4 (in the case of coumarin-quinoline Ic, the reaction mixture was neutralized with acetic acid). The precipitate was filtered off, washed with water, and dried.

Piperidylamide of 1H-2-oxo-4-hydroxyquinoline-3-acetic Acid (IV). 1.22 g (0.01 moles) salicylaldehyde was added to a solution of 2.33 g (0.01 moles) ester III in 15 ml piperidine and boiled for 5 h. This was cooled down, diluted with water, and acidified with HCl down to pH ~4. The precipitate of amide IV was filtered off, washed with water, and dried. Yield 2.23 g (78%). T_{mp} 220-222°C (ethanol). PMR spectrum: 12.70 (1H, s, OH); 11.42 (1H, s, NH); 7.83 (1H, d, J = 7.5 Hz, 5-H); 7.49 (1H, t, J = 7.0 Hz, 7-H); 7.27 (1H, d, J = 7.0 Hz, 8-H); 7.14 (1H, t, J = 7.5 Hz, 6-H); 3.68 (2H, s, CH_2CO); 3.44 (4H, t, $N(CH_2)_2$); 1.54 ppm (6H, s, $NCH_2(\underline{CH_2})_3$). Found, %: C 67.27; H 6.22; N 9.71. $C_{16}H_{18}N_2O_3$. Calculated, %: C 67.12; H 6.34; N 9.78.

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