4-HYDROXY-2-QUINOLONES

7.* SYNTHESIS AND BIOLOGICAL PROPERTIES OF 1-R-3-(2-BENZIMIDAZOLYL)-4-HYDROXY-2-QUINOLONES

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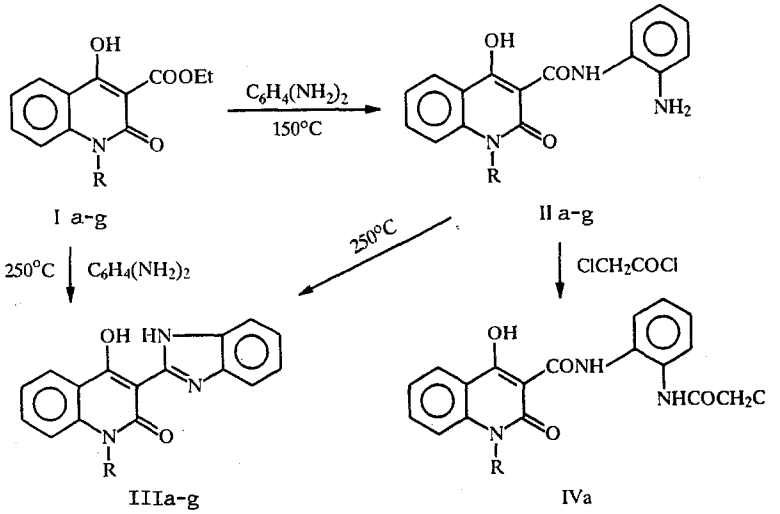
Condensation of 1-R-3-carbethoxy-4-hydroxy-2-quinolones with o-phenylene diamine gives the corresponding 1-R-3-(2-benzimidazolyl)-4-hydroxy-2-quinolones. Data on a study of the antithyroid activity of the synthesized compounds is presented.

It is common knowledge that among diseases connected with dysfunction of organs of the endocrine system second place according to rate of occurrence is occupied by pathology of the thyroid gland. At the present time, according to VOZ data, there are worldwide more than 200 million afflicted with endemic goiter. The complicated, insufficiently effective conservative and surgical methods for medical treatment of diseased thyroid gland points to the necessity for a further search for more effective pharmacological materials for the correction of pathology of this type.

"Designed screening" conducted by us for 2-oxo-4-hydroxyquinoline-3-carboxamides by the use of the complex ORACLE program, developed jointly with the BIKhS Scientific Research Institute and the Institute of Organic Synthesis of the Latvian Academy of Sciences [2], showed the advisability of an experimental study of the antithyroid activity of compounds of this type (confidence coefficient = 0.26). On the other hand, fairly high antithyroid action has been recorded for benzimidazoles [3]. We were therefore interested in combining in one molecule these two heterocyclic systems with the aim of creating potential drug materials, useful for treatment of diseased thyroid glands associated with thyrotoxicosis.

The present study is devoted to the development of means for preparing and studying the biological activity of 1-R-3-(2-benzimidazolyl)-4-hydroxy-2-quinolones, which were synthesized by fusing the corresponding esters I with an equimolar quantity of *o*-phenylene diamine. It was thus shown that, depending upon the conditions of synthesis, the intermediate aminoanilide II maybe isolated, the free amino group of which can be easily identified by ^{1}H NMR spectral data (Table 1) or by the formation of the N-acyl derivative, for example IV, or finally the benzimidazoles III (Table 2).



IIIa-g IVa

I-IVa R = Me, b R = Et, c R = C_3H_7, d R = C_4H_9, e R = C_5H_{11}, f R = C_6H_{13}, g R = C_9H_{19}

*For Communication 6, see [1].

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TABLE 1. Characteristics of 2-Aminoanilides of 1-R-4-Hydroxyl-2-quinone-3-carboxylic Acids IIa-g

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm⁻¹, C=O	^{1}H NMR spectrum, δ, ppm*			Yield, %
				H_{arom} (8H, m)	NH_2 (2H, s)	R	
IIa	$C_{17}H_{15}N_3O_3$	230...232	1647, 1636	8,15...6,63	4,96	3,70 (3H, s, CH_3)	94
IIb	$C_{18}H_{17}N_3O_3$	130...132	1643, 1630	8,13...6,66	4,98	4,36 (2H, q, CH_2); 1,25 (3H, t, CH_3)	93
IIc	$C_{19}H_{19}N_3O_3$	187...189	1642, 1635	8,14...6,65	4,92	4,27 (2H, t, NCH_2); 1,69 (2H, m, CH_2CH_3); 1,00 (3H, t, CH_3)	90
IId	$C_{20}H_{21}N_3O_3$	175...176	1645, 1631	8,16...6,65	4,95	4,30 (2H, t, NCH_2); 1,56 (4H, m, $(CH_2)_2CH_3$); 0,96 (3H, t, CH_3)	88
IIe	$C_{21}H_{23}N_3O_3$	166...168	1646, 1635	8,15...6,64	4,98	4,30 (2H, t, NCH2); 1,65 (2H, m, NCH_2CH_2); 1,41 (4H, s, $(CH_2)_2CH_3$); 0,90 (3H, t, CH_3)	89
IIf	$C_{22}H_{25}N_3O_3$	133...135	1653, 1633	8,14...6,66	4,94	4,30 (2H, t, NCH_2); 1,66 (2H, m, NCH_2CH_2); 1,34 (6H, s, $(CH_2)_3CH_3$); 0,88 (3H, t, CH_3)	92
IIg	$C_{25}H_{31}N_3O_3$	102...103	1654, 1636	8,17...6,65	4,94	4,30 (2H, t, NCH_2); 1,64 (2H, m, NCH_2CH_2); 1,25 (12H, s, $(CH_2)_6CH_3$); 0.86 (3H, t, CH_3)	85

*Signals for the protons of the 4-OH groups are singlets at 17.92-16.87 ppm; protons for the NH-groups in the anilide residues are singlets at 12.01-11.98 ppm.

Study of the antithyroid properties of the synthesized compounds was carried out by the method of [4], compared to the clinically useful preparation Mercazolyl [5] (methimazole) by determining the level of triiodothyronine and thyroxine in the blood serum with the help of standard radioimmunological series. Analysis of the results obtained showed that the series of compounds, especially IIId and IIIe, individually showed essentially no less activity than Mercazolyl (in lowering of the level of triiodotyronine). In addition, a morphological study of the thyroid tissues of the experimental animals, conducted according the method of [6], established that, in contrast to Mercazolyl, benzimidazoles IIId and IIIe did not show goiterogenic action and possess significant immunomodulant effects.

EXPERIMENTAL

The IR spectra of the synthesized compounds were obtained with a Specord M-80 in KBr tablets at a sample concentration of 1%. The ^{1}H NMR spectra were recorded on a Bruker WP-100 SY (100 MHz) instrument in DMSO-d_6, with TMS as internal standard.

Elemental analysis data for C, H, and N for compounds II-IV agreed with the calculated values.

1-R-3-Carbethoxy-4-hydroxy-2-quinolones (Ia-g) were prepared by the method of [7].

General Method for the Synthesis of 2-Aminoanilides of 1-R-4-Hydroxy-2-quinolone-3-carboxylic Acids (IIa-g). A mixture of equimolar quantities of the corresponding ethyl ester I and *o*-phenylene diamine was kept at 150°C in a metal bath for 30 min, cooled and crystallized from DMF.

General Method for the Synthesis of 1-R-3-(2-Benzimidazolyl)-4-hydroxy-2-quinolones (IIIa-g). The corresponding anilide II or a mixture of equimolar quantities of ester I and *o*-phenylene diamine was kept at 250°C in a metal bath for 30 min, cooled and crystallized from DMF.

2-Chloroacetylaminoanilide of 1-Methyl-4-hydroxy-2-quinolone-3-carboxylic Acids (IVa, $C_{19}H_{16}ClN_3O_4$). To 3.09 g (0.01 mole) of anilide IIa in 15 ml of dioxane was added 1.54 ml (0.011 mole) of triethylamine, and 1.42 g (0.011 mole) of chloroacetyl chloride and the mixture was kept for 5 h. The reaction mixture was diluted with water, the precipitate was filtered off, washed with water, and dried to give mp 222-224°C (dioxane). ^{1}H NMR spectrum: 16.52 (1H, s, OH); 12.66 (1H, s, NH); 10.13 (1H, s, NH); 8.28-7.20 (8H, m, H_{arom}); 4.42 (2H, s, CH_2); 3.70 (3H, s, CH_3). Yield 3.42 g (89%).

TABLE 2. Characteristics of the 1-R-3-(2-Benzimidazolyl)-4-hydroxy-2-quinolones IIIa-g

Compound	Empirical formula	mp, °C	IR, spectrum, ν, cm^{-1}, C=N	^{1}H NMR spectrum, δ, ppm* R	Yield, %
IIIa	$C_{17}H_{13}N_3O_2$	323...325	1631, 1590	3,62 (3H, s, CH_3)	95
IIIb	$C_{18}H_{15}N_3O_2$	262...264	1634, 1589	4,32 (2H, q, NCH_2); 1,27 (3H, t, CH_3)	91
III c	$C_{19}H_{17}N_3O_2$	220...222	1628, 1591	4,22 (2H, t, NCH_2); 1,70 (2H, m, NCH_2CH_2); 1,00 (3H, t, CH_3)	92
III d	$C_{20}H_{19}N_3O_2$	182...184	1627, 1593	4,26 (2H, t, NCH_2); 1,65 (2H, m, NCH_2CH_2); 1,25 (2H, s, CH_2CH_3); 0,83 (3H, t, CH_3)	90
IIIe	$C_{21}H_{21}N_3O_2$	170...172	1625, 1590	4,26 (2H, t, NCH_2); 1,67 (2H, m, NCH_2CH_2); 1,40 (4H, s, $(CH_2)_2CH_3$); 0,90 (3H, t, CH_3)	86
III f	$C_{22}H_{23}N_3O_2$	193...195	1622, 1594	4,26 (2H, t, NCH_2); 1,64 (2H, m, CH_2CH_2); 1,35 (6H, s, $(CH_2)_3CH_3$); 0,88 (3H, t, CH_3)	89
III g	$C_{25}H_{29}N_3O_2$	186...188	1623, 1592	4,27 (2H, t, NCH_2); 1,69 (2H, m, NCH_2CH_2); 1,25 (12H, s, $(CH_2)_6CH_3$); 0,84 (3H, t, CH_3)	86

*Signals for the protons of the 4-OH groups of the quinolone nucleus and the NH groups of the benzimidazole are singlets at 14.58-13.56 ppm with intensity 2H, which, apparently, requires an intramolecular proton exchange. Signals for the aromatic protons of the benzimidazole are in the form of two characteristic multiplets for the spin system AA'BB' at 7.80 and 7.32 ppm. Signals for the aromatic protons of the quinoline rings (spin systems ABCD) are observed in the following regions: 5-H(dd), 8.25-8.08; 7-H(td), 7.66-7.53; 8-H(d), 7.49-7.29; 6-H(td) 7.23-7.14 ppm.

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