4-HYDROXY-2-QUINOLONES.

18.* SYNTHESIS AND ANTITHYROID ACTIVITY OF 1-R-2-OXO-3-(4-OXO-3H-QUINAZOLIN-2-YL)-4-HYDROXYQUINOLINES

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Preparative methods for the synthesis of 1-R-2-oxo-3-(4-oxo-3H-quinazolin-2-yl)-4-hydroxyquinolines based on ethyl esters or nitriles of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids and anthranilamide or ethyl anthranilate correspondingly were proposed. The antithyroid activity of the compounds synthesized was studied.

Continuing previous investigations [2] into the production of potential antithyroid agents based on two-membered ensembles of heterocycles, containing the 2-oxo-4-hydroxyquinoline system as one of the structural fragments, we conducted the synthesis of the 1-R-2-oxo-3-(4-oxo-3H-quinazolin-2-yl)-4-hydroxyquinolines (I) and studied their biological properties.

The interaction of the ethyl esters of the corresponding quinoline-3-carboxylic acids (II) with anthranilamide under conditions of thermolysis led to high yields of the 2-carbamylanilides of 1-R-2-oxo-4-hydroxyquinoline-3-carboxylic acids (III). It is known [3] that the amides or anilides of N-acylanthranilic acids may be readily converted to 2-substituted 4-quinazolones by means of cyclodehydration. The dehydration agents utilized for this are acid chlorides of organic and inorganic acids, polyphosphoric and formic acids, phosphorus pentoxide, and orthoesters, but more frequently acetic anhydride. Nevertheless, after the prolonged (6-7 h) boiling of the 2-carbamylanilides (III) in acetic anhydride, the initial compounds were separated instead of the expected quinazolones (I) or their 4-O-acetyl derivatives. After the treatment of these compounds with aqueous solutions of alkalis, the quinazolones (I) were obtained in virtually quantitative yield. The given case favors the conclusion that the base-catalyzed cyclization of the 2-carbamylanilides (III) evidently includes the intramolecular nucleophilic attack by the phenolate anion in (IV) on the carbonyl group of the terminal amide fragment. The resulting eight-membered cyclic compounds (V), which undergo a second intramolecular cyclization, are converted, in the end, to the anions (VII), the acidification of which leads to the quinazolones (I).

An alternative method for the synthesis of the quinazolones (I) is the condensation of the alkyl anthranilates with 2-oxo-3-cyano-4-hydroxyquinolines (IX) obtained, in turn, by the Dieckmann reaction of the 2-methoxycarbonylcyanacetanilides (VIII). An advantage of this method is the formation of the quinazolone ring in one stage. However, this advantage is only realized practically in the synthesis of the quinazolone (Ia) since difficulties in the isolation of the corresponding initial cyanacetanilides (VIII) arise in the case of the 1-alkyl-substituted derivatives (Ib, c).

Both the quinazolones (I) and their synthetic precursors — the anilides (III) — were subjected to pharmacological screening for antithyroid properties. As the results of investigations, performed analogously [4], showed, the intragastric application of the 2-carbamylanilides (III) at the dose of 10 mg/kg induces a marked decrease in the concentration of triiodothyronine (T_3) in the blood serum of experimental animals; the effect is comparable with that of Mercazole [5]. All the compounds lower the level of the other thyroid hormone — thyroxine (T_4). However, this effect is more marked for the quinazolones (I), particularly the 1H-derivative (Ia), which surpasses the reference preparation according to this indicator.

*For Communication 17, see [1].

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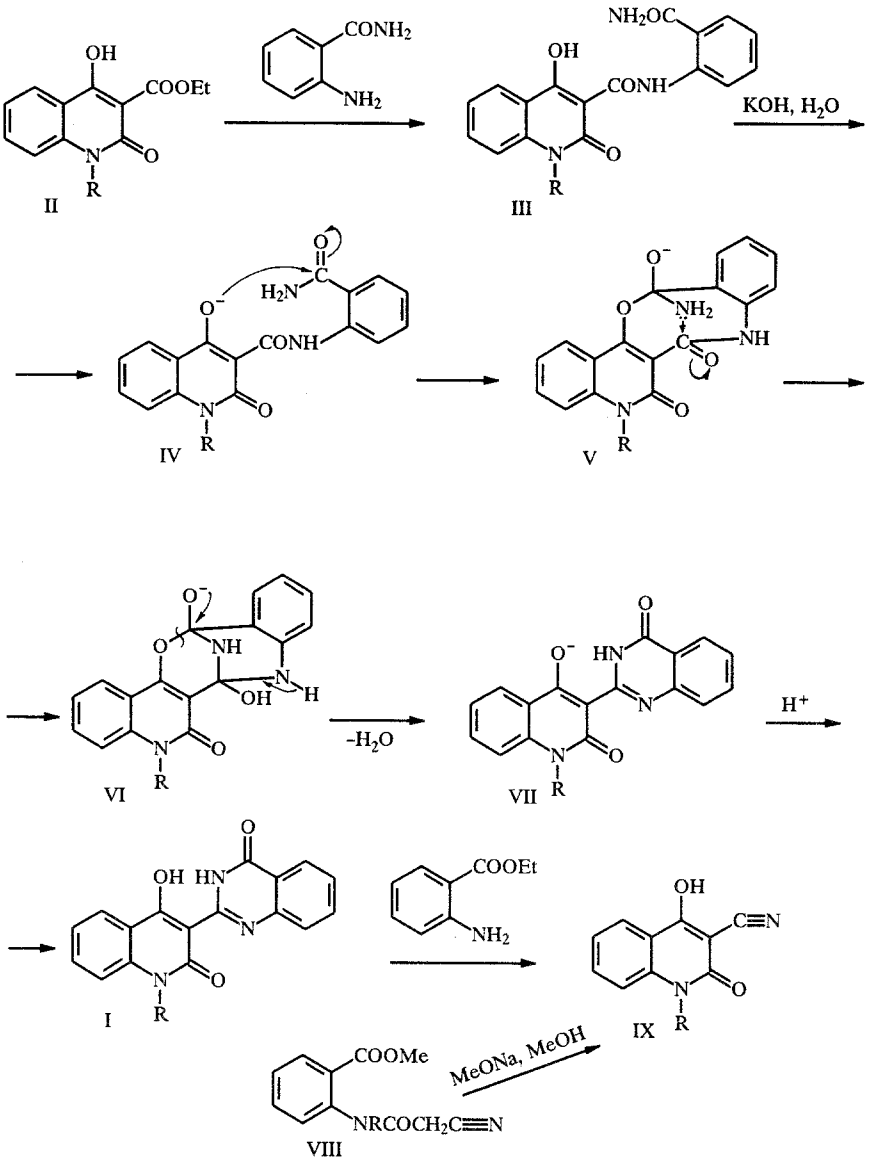

I - IIIa R = H, b R = Me, c R = Et

EXPERIMENTAL

The IR spectra of the compounds synthesized were registered on the Specord M-80 instrument using tablets of KBr. The PMR spectra were recorded on the Bruker WP 100 SY instrument using DMSO-D_6 and with TMS as the internal standard.

The data of the elemental analysis for C, H, and N correspond with the calculated data.

The ethyl 1-R-2-oxo-4-hydroxyquinoline-3-carboxylates (IIa-c) were obtained by methods previously described [6].

General Method for the Isolation of the 1-R-2-Oxo-3-(4-oxo-3H-quinazolin-2-yl)-4-hydroxyquinolines (I). A. The mixture of the corresponding 2-carbamylanilide (III) (0.01 mole) and 30 ml of the 10% aqueous solution of KOH is boiled using a reflux condenser for 2.5-3 h. The mixture is cooled and acidified with HCl to the pH 4. The residue of the quinazolone (I), which was separated out, is filtered off, washed with water, dried, and recrystallized from DMF.

B. The mixture of 1.86 g (0.01 mole) of the nitrile (IX) and 5 ml of ethyl anthranilate is boiled using a reflux condenser for 30 min. The mixture is cooled prior to the addition of 20 ml of hexane. The residue of the quinazolone (Ia) is filtered off, washed with hexane, and dried. Yield 2.80 g (92%).

The mixed test with the quinazolone (Ia), obtained according to method **A**, does not give a depression of the melting temperature. Their IR spectra were identical.

TABLE 1. Characteristics of the Compounds Synthesized

Compound	Empirical formula	mp, °C	IR spectrum, cm^{-1} C=O, C≡N	PMR spectra,* δ, ppm			Yield, %
				OH 1H,	Harom, m	R	
Ia	$C_{17}H_{11}N_3O_3$	338...340	1700, 1632	16,02	8,17...7,04 (8H)	11,33 (1H, s, NH)	96
Ib	$C_{18}H_{13}N_3O_3$	282...284	1693, 1635	16,00	8,23...7,21 (8H)	3,62 (3H, s, CH_3)	96
Ic	$C_{19}H_{15}N_3O_3$	244...246	1689, 1634	15,92	8,22...7,18 (8H)	4,27 (2H, q, CH_2) 1,29 (3H, t, CH_3)	95
IIIa	$C_{17}H_{13}N_3O_4$	276...278	1651, 1628	16,54	8,49...7,15 (10H)**	11,83 (1H, s, NH)	97
IIIb	$C_{18}H_{15}N_3O_4$	232...234	1646, 1629	16,78	8,45...7,11 (10H)**	3,65 (3H, s, CH_3)	98
IIIc	$C_{19}H_{17}N_3O_4$	261...263	1645, 1627	16,50	8,49...7,13 (10H)**	4,35 (2H, q, CH_2) 1,30 (3H, t, CH_3)	96

*The signals of the protons of the NH groups in the quinazolone ring of the compounds (Ia-c) appear as a broad singlet in the region of 14.85-14.81 ppm. The signals of the protons of the NH groups of the anilide residue in the compounds (IIIa-c) appear as a singlet in the region of 12.95-12.81 ppm.

**The signals of the protons of the NH_2 group appear in the same region.

General Method for the Isolation of the 2-Carbamylanilides of 1-R-2-Oxo-4-hydroxyquinoline-3-carboxylic Acids (III). The mixture of 0.01 mole of the corresponding ethyl ester (II) and 1.36 g (0.01 mole) of anthranilamide is maintained at 150°C for 10-15 min. The mixture is cooled prior to the addition of 20 ml of alcohol and the careful trituration. The residue of the 2-carbamylanilide (III) is filtered off, washed with alcohol, and dried. It is recrystallized from DMF.

2-Methoxycarbonylcyanacetanilide (VIII) ($C_{11}H_{10}N_2O_3$). The mixture of 1.51 g (0.01 mole) of cyanacetic ester is maintained at 160-170°C for 1 h. The reaction mixture is then cooled, and the residue is triturated with 20 ml of hexane. The residue of the aniline (VIII) is filtered off, washed with hexane, and dried. Yield 1.32 g (61%); mp 110-111°C (ethanol). IR spectrum (cm^{-1}): 3319 (NH), 2260 (C≡N), 1700 (C=O), 1683 (C=O), 1608 (C=C). PMR spectrum (ppm): 10.69 (1H, s, NH), 8.06 (1H, dd, J = 8.4 and 1.5 Hz, 3-H), 7.90 (1H, dd, J = 8.0 and 1.6 Hz, 6-H), 7.63 (1H, td, J = 8.0 and 1.9 Hz, 5-H), 7.26 (1H, td, J = 7.0 and 1.5 Hz, 4-H), 4.05 (2H, s, CH_2), 3.86 (3H, s, CH_3).

1H-2-Oxo-3-cyano-4-hydroxyquinoline (IX) ($C_{10}H_6N_2O_2$). To the solution of 2.18 g (0.01 mole) of the 2-methoxycarbonylcyanacetanilide (VIII) in 5 ml of absolute methanol is added the solution of sodium methoxide [from 0.46 g (0.02 mole) of metallic sodium and 5 ml of methanol], and the mixture is left for 10 h at room temperature. To the reaction mixture are then added 50 ml of water prior to the acidification with HCl to pH 4. The separated residue of the nitrile (IX) is filtered off, washed with water, and dried. Yield 1.71 g (92%); mp 286-288°C (ethanol). According to the data of [7], mp 292-295°C; according to the data of [8], mp 189°C. IR spectrum (cm^{-1}): 3440 (OH), 2239 (C≡N), 1642 (C=O), 1599 (C=C). PMR spectrum (ppm): 11.73 (1H, s, NH), 8.03 (1H, dd, J = 8.0 and 1.6 Hz, 5-H), 7.64 (1H, td, J = 7.8 and 1.6 Hz, 7-H), 7.30 (1H, d, J = 8.2 Hz, 8-H), 7.23 (1H, td, J = 7.0 and 1.2 Hz, 6-H).

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