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4-HYDROXY-2-QUINOLONES. 32.* SYNTHESIS AND ANTITHYROID ACTIVITY OF THIO ANALOGS OF 1H-2-OXO-3-(2-BENZIMIDAZOLYL)-4-HYDROXYQUINOLINE

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We propose preparative synthesis methods for 2-thio-4-hydroxy-, 2-oxo-4-mercapto-, and 2-thio-4-mercapto-1H-3-(2-benzimidazolyl)quinolines. We have studied the antithyroid activity of the synthesized compounds.

As we know, the basis for the arsenal of the most effective modern drugs for treatment of thyrotoxicosis is provided by thio(mercapto) derivatives of some heterocycles: uracil, barbituric acid, imidazole, triazole, thiazole, and others [2].

Earlier we noted the high antithyroid activity of 1-R-2-oxo-3-(2-benzimidazolyl)-4-hydroxyquinolines [3], the most promising of which proved to be the 1H derivative I [4], having greater specific activity and toxicity than the drug mercazolyl used in medical practice.

This investigation was devoted to synthesis and study of the antithyroid properties of thio analogs of quinolone I. 2-Thio-4-mercapto- (II) and 2-oxo-4-mercapto- (III) 1H-3-(2-benzimidazolyl) quinolines were obtained by the simple scheme of treatment of ethyl esters of respectively 2,4-dichloro (IV) and 2-oxo-4-chloro- (V) quinoline-3-carboxylic acids with thiourea in acetone. Base hydrolysis of the thiouronium salts VI and VII formed in this case yields thio-substituted 3-carbethoxyquinolines VIII and IX (it is interesting that the ester groups are not involved here), thermolysis of which with an equimolar amount of *o*-phenylenediamine leads to the target benzimidazolylquinolones II and III.

The synthesis of 1H-2-thio-3-(2-benzimidazolyl)-4-hydroxyquinoline (X) seems somewhat more complicated, in our opinion, especially due to the tendency of 2- and 4-hydroxyquinoline-3-carboxyl acids toward facile decarboxylation under thermolysis conditions [5, 6], which predetermines the need for esterification of the starting 2-chloro-4-hydroxyquinoline-3-carboxylic acid in this case [7]. However, we unexpectedly found a rather simple solution to this problem. MMX calculations for quinolone I show that the most energetically favorable arrangement for it is the arrangement of the quinolone and benzimidazole heterocyclic systems in the same plane, stabilized by two intramolecular hydrogen bonds. Evidence for the presence of strong intramolecular hydrogen bonds also comes from the singlet signals of 2H intensity from the protons of the 4-OH groups of the quinolone and the NH groups of the benzimidazole in the PMR spectra of these compounds [3, 8] and in addition the extremely low solubility of quinolone I and its 1-alkyl analogs in aqueous bases. If there are differences between the strength of the intramolecular hydrogen bonds, this fact allows us to suggest the possibility of obtaining reactions of quinolone I with the phosphorus oxychloride of the monochloro-substituted derivative. In fact, for relatively brief heating of quinolone I in $POCl_3$, the monochloro-substituted quinoline is formed according to the mass spectrum. In order to unambiguously resolve the question of its structure, we synthesized a compound with known 2-oxo-4-chloroquinoline structure XII. Comparison of the electronic absorption spectra of these compounds (see Fig. 1) shows that the first of these can be identified only as the 2-chloro-3-(2-benzimidazolyl)-4-hydroxyquinoline (XIII), which in turn through the thiouronium salt XIV was also converted to 1H-2-thio-3-(2-benzimidazolyl)-4-hydroxyquinoline (X). We should however note that formation of the 2-chloro derivative XIII is only the first step of the reaction of quinolone I with $POCl_3$. With an increase in the reaction time, we see a regular increase in the fraction of 2,4-dichloro-substituted product XV, used to confirm the structure of the dithio-substituted quinolone II by an alternate synthesis.

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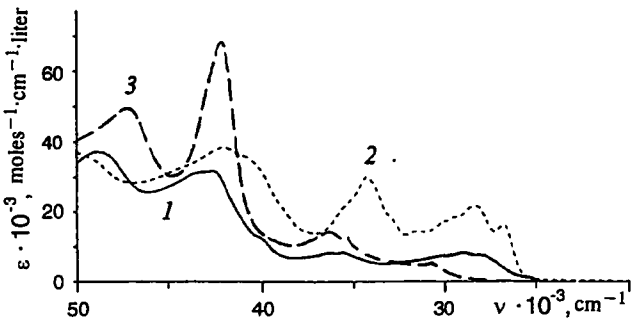
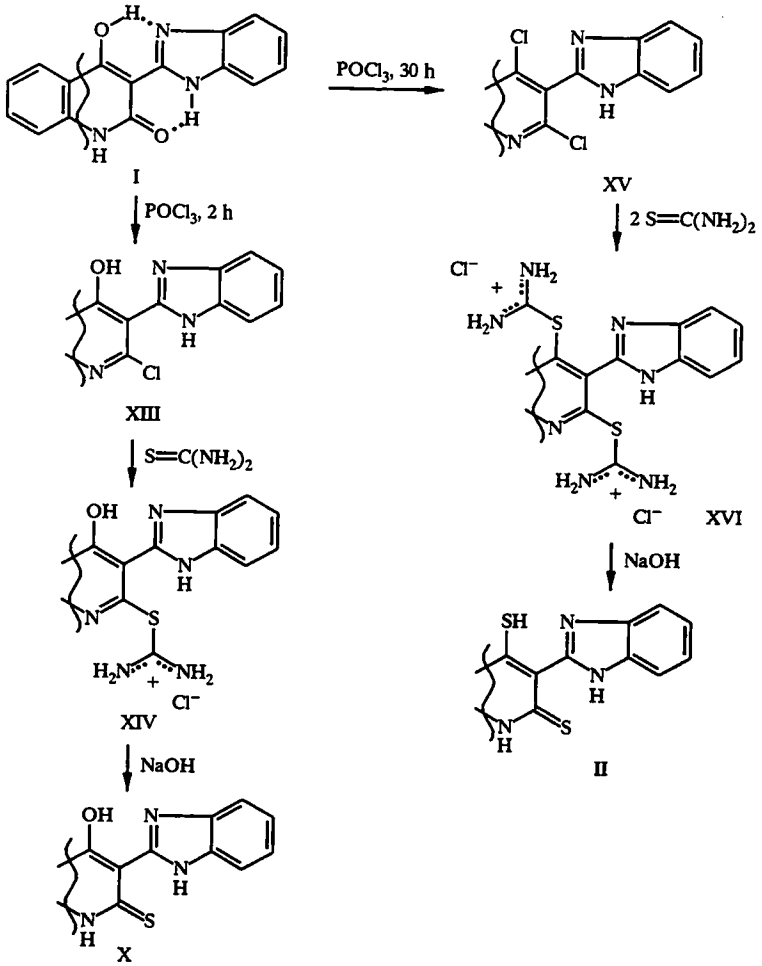
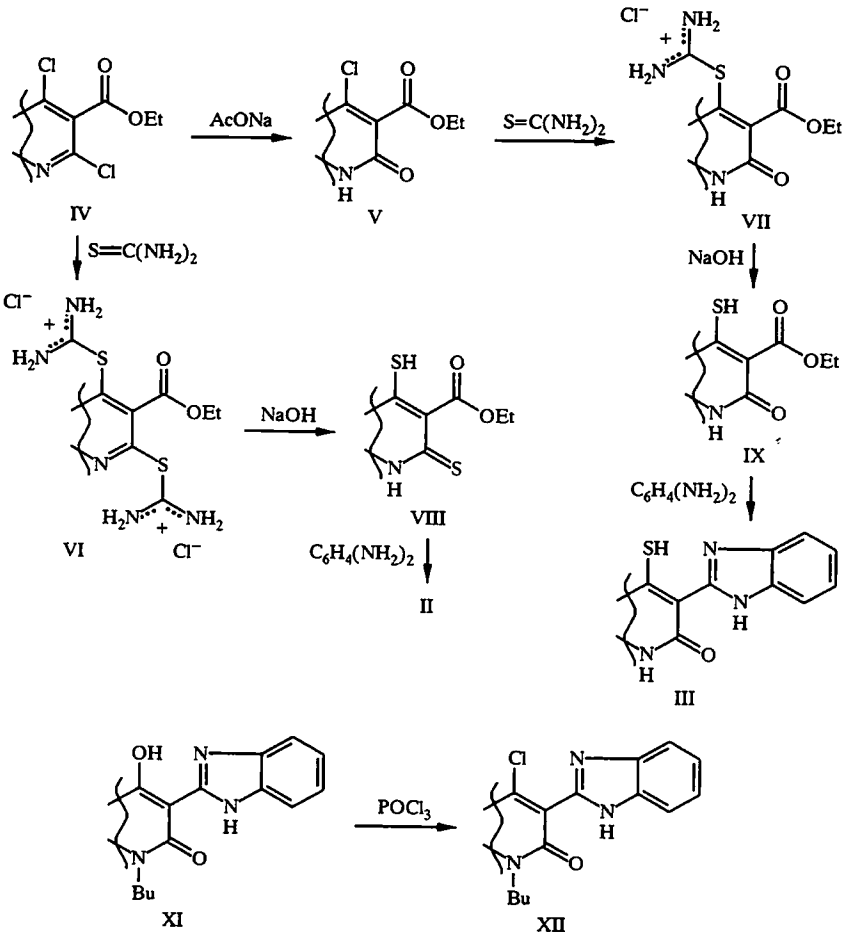


Fig. 1. Electronic absorption spectrum in 2-propanol of: *1*) 1-butyl-4-chloroquinoline (XII); *2*) 2-chloro-4-hydroxyquinoline (XIII); *3*) 2,4-dichloroquinoline (XV).

We studied the antithyroid properties of the synthesized thioquinolines II, III, and X by the generally accepted method in [9], comparing with quinolone I and mercazolyl by determining the triiodothyronine (T_3) and thyroxine (T_4) level in blood serum of experimental animals using standard radioimmunoassay kits (Rio-T_3-PG Minsk and Rio-T_4-PG Minsk). Analysis of the results obtained shows that only dithio-substituted quinoline II in a dose of 10 mg/kg approaches the activity of mercazolyl.



It is interesting that the mechanism of action of all the thio derivatives (stimulation of the thyroid gland) is analogous to the action of mercazolyl, while quinolone I in the same dose depresses the function of the thyroid gland.



EXPERIMENTAL

The electronic absorption spectra were obtained on a Specord M-40 spectrometer in a 2-propanol solution (10^{-4} to 10^{-3} moles/liter). The PMR spectra were recorded on a Bruker WP-100 SY in DMSO-D_6, internal standard TMS. The mass spectra were obtained on a Finnigan MAT-4615 B, ionizing potential 70 eV with ballistic heating of the sample.

Ethyl esters of 2-oxo-4-chloro- (V) and 2,4-dichloro- (IV) quinoline-3-carboxylic acids were obtained according to the familiar method in [7]. Synthesis of 3-(2-benzimidazolyl)-1H- (I) and 1-butyl- (XI) -2-oxo-4-hydroxyquinolines was done respectively according to the procedures in [3, 8].

1H-2-Thio-3-(2-benzimidazolyl)-4-mercaptoquinoline (II). A. A mixture of 2.65 g (0.01 moles) ester VIII and 1.08 g (0.01 moles) *o*-phenylenediamine was allowed to stand at a temperature of 250°C for 20 min. This was cooled and crystallized from dioxane. Yield, 2.81 g (91%). T_{mp} 326-328°C. PMR spectrum: 14.52 (2H, s, SH+NH of benzimidazole); 12.41 (1H, s, NH of quinolone); 8.52 (1H, d, J = 8.0 Hz, 5-H); 7.78 (2H, m, J = 3.0 Hz, 4,7-H of benzimidazole); 7.62-7.43 (4H, m, 7,8-H quinolone + 5,6-H of benzimidazole); 7.23 ppm (1H, t, J = 7.0 Hz, 6-H). Mass spectrum, *m/z* (relative intensity, %): 309 (100) $[M]^+$, 276 (33) $[M-SH]^+$, 149 (22), 119 (28). Found, %: C 62.11; H 3.63; N 13.57; S 20.73. $C_{16}H_{11}N_3S_2$. Calculated, %: C 62.13; H 3.59; N 13.59; S 20.69.

B. A mixture of 2.95 g (0.01 moles) of 2,4-dichloro-substituted quinoline XV and 2.28 g (0.03 moles) thiourea in 50 ml acetone was boiled for 5 h. The acetone was driven off and 40 ml 10% aqueous NaOH solution was added to the residue and this was boiled for 1 h. This was cooled and then acidified by HCl up to pH 3. The residue of quinolone II was filtered off, washed with water, and dried. Yield, 2.68 g (87%).

A mixed sample with the material obtained according to method A did not yield a depression of the melting point. The PMR spectra and the mass spectra of these compounds are identical.

1H-2-oxo-3-(2-benzimidazolyl)-4-mercaptoquinoline (III). The ethyl ester of 2-oxo-4-chloroquinoline-3-carboxylic acid (V) was treated with thiourea in acetone according to the procedure of the preceding experiment. The ethyl ester of 2-oxo-4-mercaptoquinoline-3-carboxylic acid (IX) obtained after base hydrolysis with phenylenediamine under conditions analogous to those for the synthesis of the dithio-substituted quinolone II (method A) yields the target mercaptoquinoline III. Yield, 74% (calculation based on the starting ester V). T_{mp} 348-350°C (from DMF). PMR spectrum: 15.47 (2H, s, SH+NH of benzimidazole); 11.63 (1H, s, NH of quinolone); 8.75 (1H, d, J = 8.4 Hz, 5-H); 7.99 (2H, m, J = 3.0 Hz, 4,7-H of benzimidazole); 7.56 (1H, t, J = 7.8 Hz, 7-H); 7.41 (2H, m, J = 3.0 Hz, 5,6-H of benzimidazole); 7.32 (1H, d, J = 7.2 Hz, 8-H); 7.21 ppm (1H, t, J = 7.3 Hz, 6-H). Mass spectrum: 293 (100) $[M]^+$, 260 (43) $[M-SH]^+$, 146 (27). Found, %: C 65.54; H 3.80; N 14.31; S 10.98. $C_{16}H_{11}N_3OS$. Calculated, %: C 65.52; H 3.78; N 14.33; S 10.91.

Ethyl Ester of 2-Thio-4-mercaptoquinoline-3-carboxylic Acid (VIII). Obtained from the ethyl ester of 2,4-dichloroquinoline-3-carboxylic acid (IV) according to the procedure for synthesis of quinolone II (method B). Yield, 80%. T_{mp}, 194-196°C (from ethanol). PMR spectrum: 14.09 (1H, s, OH); 10.35 (1H, s, NH); 8.20-7.15 (4H, m, H arom.); 4.21 (2H, q, CH_2); 1.13 ppm (3H, t, CH_3). Found, %: C 54.37; H 4.19; N 5.24; S 24.10. $C_{12}H_{11}N_2O_2S_2$. Calculated, %: C 54.33; H 4.18; N 5.28; S 24.13.

1H-2-Thio-3-(2-benzimidazolyl)-4-hydroxyquinoline (X). Obtained from 2-chloro-3-(2-benzimidazolyl)-4-hydroxyquinoline (XIII) according to the general procedure. Yield, 91%. T_{mp} 286-288°C (DMF). PMR spectrum: 14.45 (2H, s, OH+NH of benzimidazole); 13.64 (1H, s, NH of quinolone); 8.22 (1H, d, J = 8.0 Hz, 5-H); 7.80-7.65 (3H, m, 7-H+4,7-H of benzimidazole); 7.60-7.20 ppm (4H, m, 6,8-H of quinolone + 5,6-H of benzimidazole). Mass spectrum: 293 (100) $[M]^+$, 248 (15), 146 (24), 120 (41). Found, %: C 65.51; H 3.83; N 14.30; S 10.88. $C_{16}H_{11}N_3OS$. Calculated, %: C 65.52; H 3.78; N 14.33; S 10.91.

1-Butyl-2-oxo-3-(2-benzimidazolyl)-4-chloroquinoline (XII). A solution of 3.33 g (0.01 moles) benzimidazolylquinolone XI in 20 ml $POCl_3$ was boiled for 5 h. The excess $POCl_3$ was driven off under reduced pressure. Finely crushed ice was added to the residue and this was thoroughly stirred. The reaction mixture was neutralized with sodium carbonate. The residue of chloroquinoline XI was filtered off, washed with water, and dried. Yield, 3.37 g (96%). T_{mp} 258-260°C (from ethanol). PMR spectrum: 12.69 (1H, s, NH); 8.15 (1H, d, J = 8.0 Hz, 5-H); 7.90-7.72 (2H, m, 7,8-H); 7.65 (2H, m, J = 3.0 Hz, 4,7-H of benzimidazole); 7.47 (1H, t, J = 7.0 Hz, 6-H); 7.24 (2H, m, J = 3.0 Hz, 5,6-H of benzimidazole); 4.34 (2H, t, NCH_2); 1.70 (2H, q, $NCH_2C\underline{H}_2$); 1.46 (2H, m, $C\underline{H}_2CH_3$); 0.94 ppm (3H, t, CH_3). Mass spectrum: 351 (87) $[M]^+$, 322 (31), 309 (60), 295 (54), 280 (32), 267 (47), 260 (100). Here and later, for the chloro-substituted quinolines we present the m/z values only for the ^{35}Cl isotope. Electronic absorption spectra: $\nu \cdot 10^{-3}$, cm^{-1} (λ, nm), $\varepsilon \cdot 10^{-3}$, $moles^{-1} \cdot cm^{-1} \cdot liter$; 48.8 (205) 37.1; 42.6 (235) 31.8; 35.9 (278) 8.2; 28.9 (346) 8.3. Found, %: C 68.34; H 5.16; Cl 9.94; N 11.95. $C_{20}H_{18}ClN_3O$. Calculated, %: C 68.35; H 5.17; Cl 9.96; N 11.96.

2-Chloro-3-(2-benzimidazolyl)-4-hydroxyquinoline (XIII). A solution of 2.77 g (0.01 moles) benzimidazolylquinoline I in 20 ml $POCl_3$ was boiled for 2 h. Then it was treated according to the procedure for the preceding experiment. 15 ml DMF and 5 ml water were added to the product and this was thoroughly stirred. After 1 h, the residue was filtered off, washed with water, and dried. Obtained: 0.37 g (12%) 2,4-dichloroquinoline XV. The filtrate was diluted with a ten-fold amount of water and cooled. The precipitate of 2-chloroquinoline XII was filtered off, washed with water, and dried. Yield, 1.83 g (62%). T_{mp} 230-232°C (from aqueous ethanol). PMR spectrum: 8.27 (1H, d, J = 8.0 Hz, 5-H); 7.86 (2H, m, J = 3.0 Hz, 4,7-H of benzimidazole); 7.79-7.60 (2H, m, 7,8-H); 7.54 (1H, t, J = 7.0 Hz, 6-H); 7.42 ppm (2H, m, J = 3.0 Hz, 5,6-H of benzimidazole). Mass spectrum: 295 (100) $[M]^+$, 259 (50), 231 (34). Electronic absorption spectrum: 42.1 (238) 38.5; 34.3 (292) 30.2; 28.4 (352) 21.7; 26.8 (373) 16.3. Found, %: C 65.10; H 3.39; Cl 11.90; N 14.27. $C_{16}H_{10}ClN_3O$. Calculated, %: C 65.07; H 3.42; Cl 11.85; N 14.24.

2,4-Dichloro-3-(2-benzimidazolyl)quinoline (XV). Obtained according to the procedure for synthesis of the 2-chloro derivative XIII. Boiling time in $POCl_3$, 30 h. Yield, 87%. T_{mp} 280-282°C (from ethanol). PMR spectrum: 1299 (1H, s, NH); 8.32 (1H, dd, J = 7.9 and 2.0 Hz, 5-H); 8.14 (1H, td, J = 6.9 and 1.7 Hz, 7-H); 8.02 (1H, d, J = 6.9 Hz, 8-H); 7.90 (1H, td, J = 7.0 and 2.0 Hz, 6-H); 7.71 (2H, m, J = 3.0 Hz, 4,7-H of benzimidazole); 7.29 ppm (2H, m, J = 3.0 Hz, 5,6-H of benzimidazole). Mass spectrum: 313 (100) $[M]^+$, 277 (31), 242 (20). Electronic absorption spectrum: 47.3 (212) 49.5; 42.1 (238) 68.4; 36.3 (275) 14.4; 30.7 (326) 5.5. Found, %: C 61.33; H 2.94; Cl 22.30; N 13.46. $C_{16}H_9Cl_2N_3$. Calculated, %: C 61.34; H 2.90; Cl 22.34; N 13.42.

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