SYNTHESIS OF THIOPHENO-QUINIZARINE DERIVATIVES

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4,11-Dihydroxyanthra[2,3-b]thiophene-5,10-dione (thiophenoquinizarine) and its 3-methyl derivative were obtained by the cyclization of quinizarin-2-yl derivatives of mercaptoacetaldehyde or mercaptoacetone in acid medium. 4,11-Dimethoxy- and 4,11-dibutoxyanthra[2,3-b]thiophene-5,10-dione were synthesized by the alkylation of the hydroxyl group in the synthesized anthrathiophenes with dimethylformamide dimethyleacetal or butyl iodide respectively. Radical bromination of 4,11-dimethoxy-3-methylanthra[2,3-b]thiophene-5,10-dione, depending on the amount of N-bromo-succinimide taken, leads to the formation of 3-bromomethyl- or 3-dibromomethyl-4,11-dimethoxy-anthra[2,3-b]thiophene-5,10-diones. The action of sodium acetate on the obtained bromo derivatives with subsequent hydrolysis of the intermediate acetates led to the synthesis of 3-hydroxymethyl- or 3-formyl-4,11-dimethoxy-anthra[2,3-b]thiophene-5,10-diones.

Keywords: 4,11-dihydroxyanthra[2,3-b]thiophene-5,10-dione, 4,11-dimethoxy-3-methylanthra[2,3-b]-thiophene-5,10-dione, 2-mercaptoquinizarine, alkylation, hydrolysis, radical bromination, cyclization.

Several derivatives of heterocyclic analogs of 5,12-naphthacenequinone possess high biological activity and are promising in the search for new antitumor preparations with improved chemotherapeutic properties [1-4]. However some of them are little studied, which is mainly explained by the absence of convenient methods for their synthesis and modification. One of such little studied classes are the derivatives of anthra[2,3-b]-thiophene-5,10-dione. There is information in the literature on the preparation of some compounds of this class, however in the majority of studies [5-8] the synthesis is reported of derivatives of anthra[2,3-b]thiophene-5,10-dione having no substituents in the peri positions of the quinonoid ring, important both for functionalization of the chromophore and also in the search for new biologically active compounds. The exception is a patent in which the synthesis of 4,11-diphenoxanthra[2,3-b]thiophene-5,10-dione is described, patented as a photo-chromic dyestuff for rerecording compact disks [1]. However the key compound for its preparation, 4,11-dihydroxanthra[2,3-b]thiophene-5,10-dione (thiophenoquinizarine), to which the authors assigned the structure 5,10-dihydroxanthra[2,3-b]thiophene-4,11-dione with a complete absence of physicochemical and spectral characteristics, is formed in 22% yield from difficultly available compounds. In addition, the preparation of 4,11-dihydroxanthra[2,3-b]thiophene-5,10-dione is described in [9], however its synthesis is carried out in ten stages. The further search for biologically active compounds in the anthra-

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[2,3-\(b\)]thiophene-4,11-dione series therefore requires the development of preparative methods of synthesis of its \textit{peri}-substituted derivatives. The aim of our work is the development of a new method of synthesis and the modification of derivatives of 4,11-dihydroxy[2,3-\(b\)]thiophene-5,10-dione (thiophenoquinizarine).

For the synthesis of thiophenoquinizarine we used one of the methods of synthesis of benzo[\(b\)]thiophenes based on the cyclization of derivatives of \(\alpha\)-arylthiocarbamoyl compounds in an acidic medium [10-12]. \(\alpha\)-Arylthiocarbonyl compounds, key for the annelation of the thiophene nucleus to the quinizarine residue, were obtained from 2-mercaptoquinizarine, formed by the action of sodium sulfide on 2-bromoquinizarine (1) in DMF. Subsequent treatment with the diethylacetal of bromoacetaldehyde or bromoacetone leads to the formation of \(\alpha\)-arylthio derivatives of acetaldehyde 2 or acetone 3. The traditional method of cyclization of \(\alpha\)-arylthiocarbonyl compounds into benzo[\(b\)]thiophenes on heating in polyphosphoric acid (PPA) proved to be unsuitable for the cyclization of derivatives 2 and 3. However the cyclization of the mercaptoacetaldehyde derivative 2 into thiophenoquinizarine 4 was successfully effected on heating it in a mixture of sulfuric and acetic acids, and the best yield (85\%) of the target compound was obtained on slow addition of a solution of derivative 2 to a boiling mixture of acids. For the cyclization of the mercaptoacetone derivative 3, heating in 73\% \(\text{H}_2\text{SO}_4\) proved to be optimal, and led to the formation of 3-methylthiophenoquinizarine 5 in 84\% yield.

The synthesized thiophenoquinizarine 4 and its 3-methyl derivative 5 possess extremely low solubilities in the majority of solvents, which in the main hinders their identification by NMR spectroscopy and the study of their chemical properties. Recording their \(^1\text{H}\) NMR spectra was unsuccessful in DMSO-\(\text{d}_6\) at 100\({\degree}\text{C}\), since at lower temperatures these compounds practically completely crystallize out from solution. In the \(^1\text{H}\) NMR spectrum of thiophenoxyquinizarine the signals of the protons at positions 2 and 3 are observed as doublets at 8.21 and 7.79 ppm with \(J = 5.6\) Hz, close to the value of the coupling constant for benzothiophene [13].

Evidently we were unsuccessful in obtaining the O-methyl derivatives of hydroxy compounds 4 and 5 under the usual conditions for alkylating hydroxyanthraquinones, by boiling in acetone with dimethyl sulfate in the presence of potassium carbonate, due to their low solubility [14]. However their O,O-dimethyl derivatives were successfully obtained by the procedure of [15] on heating thiophenoquinizarines 4 and 5 with dimethylformamide dimethylacetal in DMF.