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NAPHTHOINDOLES. 10.* SYNTHESIS OF 4,11-DIHYDROXYNAPHTHO[2,3-*f*]-INDOLE-5,10-DIONE AND SOME OF ITS DERIVATIVES

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4,11-Dihydroxynaphtho[2,3-f]indole-5,10-dione (pyrroloquinizarin), its 11-dehydroxy derivative, and Mannich base were synthesized by demethylation of previously obtained methoxynaphtho[2,3-f]indole-5,10-diones.

Keywords: 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione, methoxynaphtho[2,3-*f*]indole-5,10-dione, pyrroloquinizarin, demethylation.

The methoxy derivatives of anthracycline antibiotics rubomycin and doxorubicin hardly exhibit any antitumor activity during *in vivo* trials. This is explained by steric factors that arise during intercalation of the chromophoric fragment of the molecule of the antibiotics into the DNA helix [2]. It is therefore of great interest during the search for intercalators with chemotherapeutic characteristics in the series of naphthoindoles to synthesize 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione and its derivatives. The most rational scheme for the synthesis of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione is didemethylation of 4,11-dimethoxy[2,3-*f*]indole-5,10-dione.

An attempt on demethylation by the method employed for the synthesis of anthracyclinones [3] by the action of $AlCl_3$ or $AlBr_3$ on benzene solution of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**1**) led to resinification of the reaction mixture even at 0°C. This was not unexpected, since indole and its derivatives polymerize under such conditions [4].

Another method of demethylation, used for the production of hydroxytetrahydro-5,12-naphthacenediones in the synthesis of anthracyclinones, involves treatment of the methoxy derivatives with BBr_3 or BCl_3 in dichloroethane at -78°C [5]. For demethylation it is also possible to use the less active dimethyl sulfide complexes of BBr_3 or BCl_3, which are used for the cleavage of ethers and do not require continuous treatment at low temperatures [6].

The demethylation of naphthoindoledione **1** was carried out by the action of dimethyl sulfide complex of BCl_3. When 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **1** was boiled with $BCl_3 \cdot SMe_2$ in dichloroethane, 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione (**2**) was obtained with 42% yield.

* For Communication 9, see [1].

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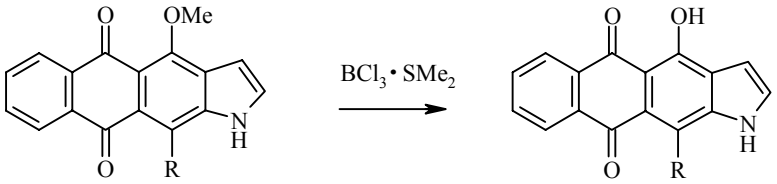


1, **3** **2**, **4**

1 R = OMe; **2** R = OH; **3, 4** R = H

Demethylation of the previously obtained 4-methoxynaphtho[2,3-*f*]indole-5,10-dione (**3**) by the action of $BCl_3 \cdot SMe_2$ gave 4-hydroxynaphtho[2,3-*f*]indole-5,10-dione (**4**) with a yield of 67%.

The ^{1}H NMR spectra of compounds **2** and **4** do not contain signals in the upfield region for the protons of the methoxy groups. There are singlet signals in the downfield region of the spectrum for the protons of the hydroxy groups at 15.23 and 14.93 ppm (pyrroloquinizarin **2**) and 14.5 ppm (hydroxy derivative **4**) respectively. In addition, the broad singlets of the N–H protons and the multiplets of the protons at α-positions of the benzene ring of the anthraquinone fragment are shifted downfield by 0.2-0.3 ppm in comparison with the spectrum of the initial naphthoindolediones. The signals for the 2-H proton of the pyrrole ring are also shifted upfield by 0.1-0.2 ppm. The singlets of the protons of the hydroxy groups in the ^{1}H NMR spectrum of 1,4-dihydroxyanthraquinone (quinizarin) are observed at 13.1 ppm. Thus, it is possible to state that annellation of the pyrrole fragment to quinizarin leads to a shift of the signals for the protons of the hydroxy groups downfield by ~2 ppm.

Comparing the chemical shifts of the N–H proton in the series of synthesized naphthoindolediones, we note the following relationship: the signal of the N–H proton in naphtho[2,3-*f*]indole-5,10-dione is observed in the form of a singlet at 11.6 ppm [7]. The successive introduction of two α-methoxy groups into the molecule of naphtho[2,3-*f*]indole-5,10-dione leads to a downfield shift of the N–H signal (12.12 and 12.38 ppm, naphthoindolediones **3** and **1**) [8]. The introduction of α-hydroxy groups into the molecule of naphtho[2,3-*f*]indole-5,10-dione leads to an even greater downfield shift of the signal for the N–H proton (12.52 and 12.61 ppm, naphthoindolediones **4** and **2**).

In the IR spectra of pyrroloquinizarin **2** and its 11-dehydroxy derivative **4** there are strong absorption bands characteristic of the N–H group in the region of 3150 cm^{-1}. In the IR spectrum of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione **2** the band corresponding to the stretching vibrations of the carbonyl groups of the anthraquinone fragment is observed in the region of 1590-1580 cm^{-1}. In contrast to the spectrum of initial dimethoxy derivative **1** the absorption band of the carbonyl groups is shifted towards the low-frequency region by 75 cm^{-1}, which is due to the formation of the intramolecular hydrogen bond characteristic of the IR spectra of α-hydroxyanthraquinones, but it exceeds the normal values. According to published data [9], in quinizarin the absorption band of the C=O groups lies in the region of 1625 cm^{-1}, while the shift of the absorption band of the carbonyl groups of anthraquinones during the formation of the intramolecular hydrogen bond amounts to 30-40 cm^{-1}. Thus, the data from the IR spectrum of pyrroloquinizarin **2** indicate an increase of intramolecular hydrogen bond compared with quinizarin. In the IR spectrum of 4-hydroxynaphtho[2,3-*f*]indole-5,10-dione **3** there are two absorption bands for C=O groups: the absorption band of the free carbonyl group in the region of 1670-1660 cm^{-1} and the absorption band of the carbonyl involved in formation of the intramolecular hydrogen bond in the region of 1610-1600 cm^{-1}.

In contrast to the electronic absorption spectrum of the initial naphthoindole **1**, in the long-wave region of the spectrum of 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione **2** in ethanol (Fig. 1), as also in the spectra of other α-hydroxy- and α-aminoanthraquinones, there are three absorption bands and a bathochromic shift, explained by the formation of internal and intermolecular hydrogen bonds [10]. The maxima of the long-wave absorption bands of pyrroloquinizarin **2** practically coincide with the absorption maxima of 1,4-dihydroxyanthraquinone (quinizarin) [10].

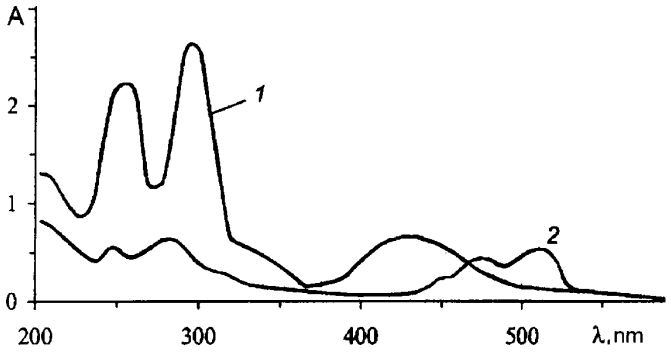
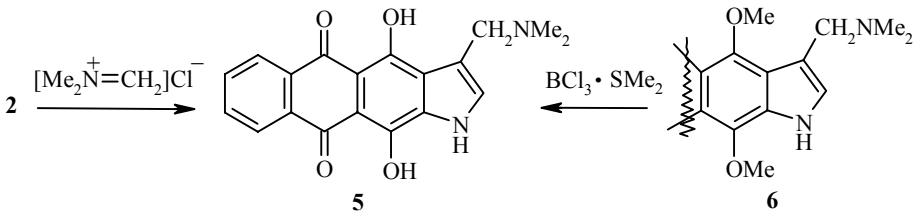


Fig. 1. The electronic absorption spectra of naphthoindoles **1** and **2** in ethanol.

In the mass spectra of the demethylated derivatives **2** and **4** there are strong peaks of the molecular ions M^+ 279 and 263.

The Mannich reaction is one of the most important reactions for the derivatives of indole, since Mannich bases and their quaternary salts are intermediate products in the synthesis of biologically active substances. The direct reaction of pyrroloquinizarin **2** with dimethylamine and formaldehyde in acetic acid could not be realized. However, the action of the more effective aminomethylating agent N,N-dimethyl(methylene)ammonium chloride (the crystalline Mannich reagent) on 4,11-dihydroxynaphtho-[2,3-*f*]indole-5,10-dione **2** gave 3-N,N-dimethylaminomethyl-4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-dione (**5**) with a yield of 50%. In addition, we obtained the Mannich base **5** with a yield of 41% by the didemethylation of the previously synthesized [11] 3-N,N-dimethylaminomethyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**6**) by the action of $BCl_3 \cdot SMe_2$ in dichloroethane.



The reactivity of naphtho[2,3-*f*]indole-5,10-dione [12] and 4,11-dimethoxy- and 4,11-dihydroxynaphtho[2,3-*f*]indole-5,10-diones in the Mannich reaction is approximately equal. Pyrroloquinizarin **2** has significantly lower reactivity in aminomethylation: the synthesis of the Mannich base **5** takes place at a higher temperature, and the reaction requires a longer time and results in a lower yield than for the dimethoxy derivative **1**.

The ^{1}H NMR spectrum of compound **5** confirms that the β-hydrogen atom of the pyrrole ring is substituted by the dimethylaminomethyl group, as demonstrated by the absence of a signal for the 3-H proton and also by the appearance of singlets in the upfield region – for the protons of the methylene group at 4.4 and those of the dimethylamino group at 2.4 ppm.

In the IR spectrum of the Mannich base **5** in the region of 3150-3350 cm^{-1} there is a broad absorption band due to the stretching vibrations of the N–H group. The absorption band of the C=O group lies in the region of 1600-1590 cm^{-1}. In the mass spectrum of compound **5** there is a molecular ion peak M^+ at 336, which corresponds to the calculated value.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 instrument at 400 MHz. The chemical shifts were measured with reference to TMS as internal standard. The mass spectra were recorded on a Varian Mat-112 chromato-mass spectrometer, and the IR spectra were obtained in Vaseline oil on a Perkin-Elmer 599 spectrometer. The reactions and the purity of the compounds were monitored by TLC on Silufol plates. Preparative chromatography was conducted on silica gel L 40/100.

4,11-Dihydroxynaphtho[2,3-*f*]indole-5,10-dione (2). To 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **1** (0.2 g, 0.65 mmol) we added dichloroethane (50 ml) and $BCl_3 \cdot SMe_2$ (0.45 g, 2.5 mmol), and we boiled the mixture for 5 h. The reaction mixture was then evaporated under vacuum, water (50 ml) was added, and the product was extracted with hot ethyl acetate. The extract was washed with water, dried with magnesium sulfate, and evaporated under vacuum. The residue was recrystallized twice from DMF, washed with water, and dried. The compound **2** was obtained in the form of red crystals. Yield 0.079 g (42%); mp >370°C (subl.). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 15.23 (1H, s, OH); 14.93 (1H, s, OH); 12.61 (1H, m, N–H); 8.40 (2H, m, 6-, 9-H); 7.78 (2H, m, 7-, 8-H); 7.25 (1H, m, 2-H); 6.85 (1H, m, 3-H). IR spectrum, ν, cm^{-1}: 3260 (N–H, OH), 1585 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 279 (100), 263 (21), 222 (15), 140 (35). Found, %: C 69.0; H 3.4; N 5.1. $C_{16}H_9NO_4$. Calculated, %: C 68.8; H 3.3; N 5.0. M^+ 279.

4-Hydroxynaphtho[2,3-*f*]indole-5,10-dione (4). To 4-methoxynaphtho[2,3-*f*]indole-5,10-dione **3** (0.1 g, 0.36 mmol) we added dichloroethane (50 ml) and $BCl_3 \cdot SMe_2$ (0.2 g, 1 mmol). The mixture was boiled for 4 h and evaporated under vacuum, water (20 ml) was added, and the product was extracted with ethyl acetate. The extract was washed with water, dried with magnesium sulfate, and evaporated under vacuum. The residue was purified chromatographically (silica gel, 15:1 benzene–ether). We obtained 0.062 g (67%) of compound **4** in the form of red crystals; mp 351-352°C (alcohol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 14.19 (1H, s, OH); 11.51 (1H, m, N-H); 8.31 (2H, m, 6-, 9-H); 8.01 (1H, s, 11-H); 7.77 (2H, m, 7-, 8-H); 7.35 (1H, m, 2-H); 6.86 (1H, m, 3-H). IR spectrum, ν, cm^{-1}: 3260 (N–H, OH), 1665 and 1605 (C=O). Found, %: C 72.9; H 3.6; N 5.2. $C_{16}H_9NO_4$. Calculated, %: C 73.0; H 3.5; N 5.3. Mass spectrum: 263 (100), 247 (25).

3-N,N-Dimethylaminomethyl-4,11-dihydroxynaphtho[2,3-f]indole-5,10-dione (5). A. To solution of compound **2** (0.05 g, 0.17 mmol) in DMF (20 ml) we added N,N-dimethyl(methylene)ammonium chloride (0.05 g, 0.05 mmol). The mixture was heated at 100°C for 8 h, poured into water, and extracted three times with ethyl acetate. 10% solution of sodium bicarbonate was added to the aqueous phase till a neutral reaction, and the product was extracted with ethyl acetate. The extract was washed with water, dried with magnesium sulfate, and evaporated under vacuum. The residue was purified chromatographically (silica gel, 10:1 acetone–ammonia). The yield of compound **5** was 0.031 g (50%) in the form of red crystals; mp 151-152°C (methanol).

B. To 3-N,N-dimethylaminomethyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **6** (0.1 g, 0.27 mmol) we added dichloroethane (50 ml) and $BCl_3 \cdot SMe_2$ (0.3 g, 1.5 mmol). The mixture was boiled for 5 h and evaporated under vacuum, water (20 ml) was added, and the product was extracted with ethyl acetate. The extract was washed with water, dried with magnesium sulfate, and evaporated under vacuum. The residue was chromatographed (silica gel, 10:1 acetone–ammonia). Yield 0.037 (41%); mp 150-152°C (methanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 15.01 (2H, s, OH); 13.45 (1H, m, N–H); 8.24 (1H, d, 2-H); 7.92 (2H, m, 6-, 9-H); 7.51 (2H, m, 7-, 8-H); 4.30 (2H, s, CH_2); 2.46 (6H, s, $N(CH_3)_2$). IR spectrum, ν, cm^{-1}: 3260 (N–H, OH), 1590 (C=O). Found, %: C 67.5; H 4.7; N 8.7. $C_{16}H_9NO_4$. Calculated, %: C 67.8; H 4.8; N 8.3. Mass spectrum: 336 (25), 321 (59), 293 (49), 264 (10), 97(22).

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