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HETEROCYCLIC ANALOGS OF 5,12-NAPHTHACENEQUINONE 7*. SYNTHESIS OF NAPHTHO-[2,3-*f*]ISATIN-5,10-DIONE DERIVATIVES

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On chlorination of 4,11-dimethoxynaphtho[2,3-f]indole-5,10-dione with sulfuryl chloride in chloroform, its mono-, di-, and trichloro derivatives are formed depending on the conditions. Hydrolysis of the di- and trichloro derivatives gives a new polycondensed derivative of isatin, 4,11-dimethoxynaphtho-[2,3-f]isatin-5,10-dione. Its demethylation occurs effectively on extended heating with HBr in acetic acid and leads to 4,11-dihydroxynaphtho[2,3-f]isatin-5,10-dione (4,11-di-hydroxynaphtho[2,3-f]indole-2,3,5,10-tetraone).

Keywords: 4,11-dihydroxynaphtho[2,3-*f*]indole-2,3,5,10-tetraone, 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione, hydrolysis, demethylation, chlorination.

Certain heterocyclic analogs of 5,12-naphthacenequinone, such as derivatives of naphtho[2,3-*f*]indole-5,10-dione, possess high biological activity and are promising in the search for chemotherapeutic agents [2]. For the further study of this class of compound it is expedient to continue to develop methods of synthesis and the modification of new naphtho[2,3-*f*]indole-5,10-diones. It is also known that compounds of the isatin series are encountered in nature and for a long time have attracted the attention of synthesizers, since in it are found numereous dyestuffs, analytical reagents, and biologically active substances [3]. In addition, isatin and its analogs have an important synthetic value, since the reactivity of the pyrroledione fragment enables them to be used as intermediates for obtaining various classes of compound [4]. Consequently the synthesis of isatin analogs of 5,12-naphthacenequinone (derivatives of naphtho[2,3-*f*]isatin-5,10-dione) is of interest both for the search for biologically active substances, and also for the synthesis of new heterocyclic derivatives of anthraquinone.

* For Communication 6 see [1].

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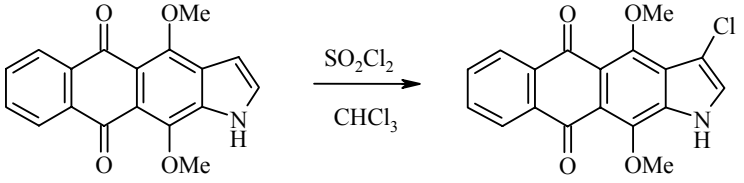
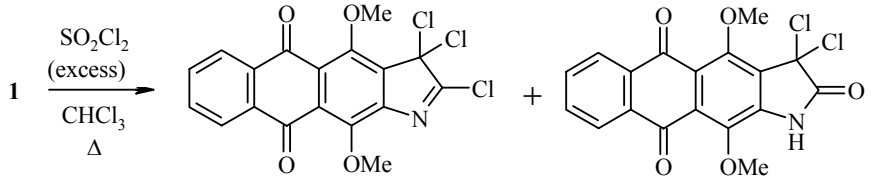
Analysis of the literature data showed that only unsubstituted naphtho[2,3-*f*]isatin-5,10-dione (naphtho[2,3-*f*]indole-2,3,5,10-tetraone) is known up to the present time. This was synthesized in a study of the chlorination of naphtho[2,3-*f*]indole-5,10-dione [5]. In addition, in patents [6, 7] naphthoisatindione analogs of indigoid dyestuffs were proposed as chelating agents for obtaining photochromic complexes, however procedures for their synthesis were not given. Naphtho[2,3-*f*]isatin-5,10-dione described in [5] does not contains substituents in the *peri* positions of the quinonoid fragment, important for biological activity [8], consequently we obtained its 4,11-dihydroxy derivative applying the method for the synthesis of naphthoisatin-diones developed by N. N. Suvorov and coworkers.

Initially we studied the chlorination of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione [9] under the action of sulfuryl chloride. Like the unsubstituted naphtho[2,3-*f*]indole-5,10-dione its 4,11-dimethoxy derivative **1** was readily chlorinated under mild conditions, giving the 3-chloro derivative **2**.



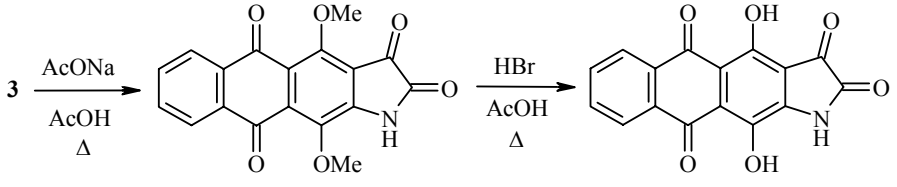
1 **2** (74%)

However on heating naphthoindoledione **1** with an excess of sulfuryl chloride in chloroform the main reaction product (78%) was a compound identified as 2,3,3-trichloro-4,11-dimethoxy-3H-naphtho[2,3-*f*]indole-5,10-dione (**3**), and also trace quantities (less than 7%) of 3,3-dichloro-4,11-dimethoxy-1H-naphtho[2,3-*f*]indole-2,5,10(3H)-trione (**4**). We noted that the proportion of dichloro derivative **4** in the reaction mixture grew significantly on using as solvent moist chloroform or chloroform stabilized with alcohols for storage. These results differ from the data published in [5], where the didemethoxy analog of dichloro derivative **4** is described as the main chlorination product of naphtho[2,3-*f*]indole-5,10-dione by the action of an excess of sulfuryl chloride. Seemingly its formation in this reaction must be explained by the presence in the reaction mixture of water or alcohols leading to hydrolysis of the intermediate trichloro derivative.



3 **4**

The trichloro derivative **3** is stable on storage as crystals, but is readily hydrolyzed under conditions of base or acid catalysis. For example, by the action of sodium acetate in acetic acid 3,3-dichloro-naphthoindoletrione **4** is formed from it in 87% yield. More extended hydrolysis leads to 4,11-dimethoxy-naphtho[2,3-*f*]indole-2,3,5,10-tetraone (naphtho[2,3-*f*]isatindione) **5**.



5 **6**

Demethylation of naphthoisatindione **5** occurs under rigid conditions on heating with HBr in acetic acid. Demethylation of derivative **5** proceeds stepwise, and after several hours boiling the intermediate monomethyl derivative is detected in the reaction mixture (by TLC), passing on extended heating into 4,11-dihydroxynaphtho[2,3-*f*]indole-2,3,5,10-tetraone (**6**).

Comparison of the electronic absorption spectra of 1,4-dimethoxynaphthoindoledione **1** (λ_{max} 421 [9]) and its 3-chloro derivative **2** (λ_{max} 417) shows that the introduction of chlorine has a weak effect on the spectrum of the compound, while for the di- and trichloro derivatives **3** and **4** (λ_{max} 392-404 nm) a hypsochromic shift and a reduction of the intensity of the long wave absorption maximum were observed. This is explained by the loss of the electron-donating properties of the heterocycle and by the emergence in the chromophore, as a result of the exhaustive halogenation, of electron-withdrawing groups (Fig. 1). Subsequent hydrolysis of halogen derivatives **3** and **4**, leading to the generation of an additional keto group in isatin derivative **5**, is accompanied by a further reduction in the intensity of the absorption band. Demethylation of the methoxy groups in naphthoisatindione **5** is accompanied by a bathochromic shift with a significant hyperchromic effect, and the absorption maximum in 4,11-dihydroxy derivative **6** therefore lies in the region of 515 nm. As a result of this the pyrroledione derivative of quinizarin **6** is more deeply colored than quinizarin itself [10].

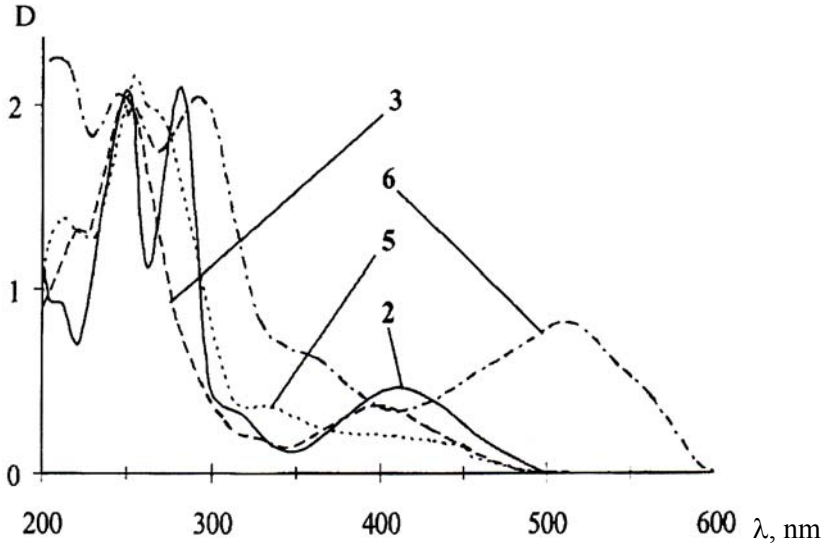


Fig. 1. Electronic absorption spectra of naphthoindoles **2**, **3**, **5**, **6** in ethanol.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz) in $CDCl_3$ (compounds **2**, **3**) and in DMSO-d_6 (compounds **4**-**6**), internal standard was TMS. The mass spectra were recorded on a SSQ 710 chromato-mass spectrometer (Finnigan-MAT, USA), ionizing voltage 70 eV, direct insertion of samples into the ion source, heating of samples to 350°C, ionizing chamber temperature 150°C. The absorption spectra were recorded on a Hitachi-U2000 spectrometer. A check on the progress of reactions and the purity of compounds was carried out by TLC on Silufol UV-254 plates. Preparative chromatography was carried out on Merck 60 silica gel.

3-Chloro-4,11-dimethoxy-1H-naphtho[2,3-*f*]indole-5,10-dione (2). Naphthoindoledione **1** [9] (0.1 g, 0.32 mmol) was dissolved by boiling in chloroform (100 ml), the solution was cooled to 5°C, sulfuryl chloride

(0.06 ml, 0.7 mmol) was added with stirring, and the solution left for 20 min. Water (20 ml) was added to the mixture, which was stirred for 30 min. The organic layer was separated, dried, and evaporated. The residue was purified by column chromatography on SiO_2 (eluent toluene–ethyl acetate, 10:1) and recrystallized from benzene. Chloro derivative **2** (78 mg, 74%) was obtained as yellow crystals; mp 156-157°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 9.87 (1H, br. s, NH); 8.25 (2H, m, H-6,9); 7.75 (2H, m, H-7,8); 7.45 (1H, d, *J* = 2.4, H-2); 4.14 (3H, s, OCH_3); 4.09 (3H, s, OCH_3). ^{13}C NMR spectrum, δ, ppm: 183.29 (C=O); 183.05 (C=O); 153.15*; 145.23; 134.86; 134.36; 133.73; 133.54 (CH); 133.20 (CH); 126.69 (CH); 126.39 (CH); 126.29 (CH); 124.09; 119.75; 118.88; 108.42; 63.29 (CH_3); 62.40 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 343 $[M]^+$ (31), 341 (100), 306 (64). Found, %: C 63.12; H 3.43; N 4.24. $C_{18}H_{12}ClNO_4$. Calculated, %: C 63.26; H 3.54; N 4.10.

2,3,3-Trichloro-4,11-dimethoxy-3H-naphtho[2,3-*f*]indole-5,10-dione (3). A mixture of naphthoindoledione **1** [9] (0.20 g, 0.65 mmol) and sulfuryl chloride (0.4 ml, 5 mmol) in chloroform (50 ml) was boiled for 2 h, after which water (30 ml) was added, and the mixture stirred for 30 min. The organic layer was separated, dried, and evaporated. The residue was purified by column chromatography on SiO_2 (eluent toluene) and recrystallized from a benzene–hexane mixture. Trichloro derivative **3**, (0.21 g, 78%), was obtained as light-yellow crystals, darkening in the air; mp 163-165°C. ^{1}H NMR spectrum, δ, ppm: 8.15 (2H, m, H-6,9); 7.77 (2H, m, H-7,8); 4.26 (3H, s, OCH_3); 4.17 (3H, s, OCH_3). ^{13}C NMR spectrum, δ, ppm: 182.59 (C=O); 181.75 (C=O); 168.34; 152.43; 148.53; 144.98; 136.89; 133.96 (CH); 133.86; 133.85 (CH); 133.40; 131.62; 127.54; 126.60 (CH); 126.59 (CH); 79.31; 63.91 (CH_3); 63.32 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 410 $[M]^+$ (36), 409 (40), 374 (100), 310 (62), 175 (64), 162 (94). Found, %: C 52.60; H 2.37; N 3.30. $C_{18}H_{10}Cl_3NO_4$. Calculated, %: C 52.65; H 2.45; N 3.41.

3,3-Dichloro-4,11-dimethoxy-1H-naphtho[2,2-*f*]indole-2,5,10(3H)-trione (4). A mixture of 2,3,3-trichloro derivative **3** (55 mg, 0.25 mmol), glacial acetic acid (20 ml), and $NaOAc·3H_2O$ (0.4 g, 3.0 mmol) was boiled for 1 h, cooled, and water (50 ml) added. The solid was filtered off, washed with water, dried and recrystallized from a benzene–hexane mixture. Light-yellow crystals (41 mg, 87%) of dichloro derivative **4** were obtained, mp 244-246°C. ^{1}H NMR spectrum, δ, ppm: 12.27 (1H, s, NH); 8.06 (2H, m, H-6,9); 7.85 (2H, m, H-7,8); 4.00 (3H, s, OCH_3); 3.83 (3H, s, OCH_3). ^{13}C NMR spectrum, δ, ppm: 182.29 (C=O); 180.90 (C=O); 169.21 (C=O); 154.93: 141.19; 140.66; 134.49 (CH); 134.10 (CH); 133.64; 133.38; 131.56; 126.47 (CH); 126.45; 126.34 (CH); 122.31; 72.89; 62.39 (CH_3); 62.15 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 393 $[M]^+$ (33), 391 (53), 355 (90), 264 (100). Found, %: C 55.40; H 2.65; N 3.32. $C_{18}H_{11}Cl_2NO_5$. Calculated, %: C 55.12; H 2.83; N 3.57.

4,11-Dimethoxy-1H-naphtho[2,3-*f*]indole-2,3,5,10-tetraone (5). Sodium acetate trihydrate (0.8 g, 6 mmol) was added with stirring to a hot solution of 2,3,3-trichloro derivative **3** (0.11 g, 0.5 mmol) in glacial acetic acid (40 ml). The mixture was boiled for 12 h, cooled, and poured into water (50 ml). The solid was filtered off, washed with water, dried, and recrystallized from a toluene–dioxane mixture. Bright-red crystals of naphthoisatindione **5** (78 mg, 86%) were obtained, mp >270°C. ^{1}H NMR spectrum, δ, ppm: 11.83 (1H, br. s, NH); 8.04 (2H, m, H-6,9); 7.85 (2H, m, H-7,8); 3.98 (3H, s, OCH_3); 3.82 (3H, s, OCH_3). ^{13}C NMR spectrum, δ, ppm:182.12 (C=O); 180.74 (C=O); 180.01 (C=O); 159.30; 155.27; 150.88; 140.19; 134.32 (CH); 134.31; 133.89; 133.69 (CH); 133.28; 126.15 (CH); 126.04 (CH); 121.68; 115.09; 62.36 (CH_3); 61.76 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 337 $[M]^+$ (100), 309 (22), 264 (42), 252 (93). Found, %: C 63.87; H 3.30; N 4.31. $C_{18}H_{11}NO_6$. Calculated, %: C 64.10; H 3.29; N 4.15.

4,11-Dihydroxy-1H-naphtho[2,3-*f*]indole-2,3,5,10-tetraone (6). Naphthoisatindione **5** (50 mg, 0.15 mmol) was boiled for 8 h with stirring in a mixture of glacial acetic acid (10 ml) and conc. HBr (1 ml), the mixture was cooled, and diluted with water (5 ml). The precipitated solid was filtered off, washed with water, and dried. The yield of naphthoisatindione **6** was 38 mg (83%) as a violet-black powder, mp >270° (sublimes).

* Here and subsequently all signals without assignment belong to quaternary carbon atoms.

^{1}H NMR spectrum, δ, ppm: 13.83 (1H, br. s, OH); 12.20 (2H, br. s, OH, NH); 8.24 (2H, m, H-6,9); 7.95 (2H, m, H-7,8). Mass spectrum, *m/z* (I_{rel}, %): 309 $[M]^+$ (11), 281 (100), 253 (61). Found, %: C 61.99; H 2.34; N 4.38. $C_{16}H_7NO_6$. Calculated, %: C 62.15; H 2.28; N 4.53.

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