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HETEROCYCLIC ANALOGS OF 5,12-NAPHTHACENEQUINONE. 2*. SYNTHESIS OF 4,11-DIHYDROXYNAPHTHO[2,3-*f*]INDAZOLE-5,10-DIONE AND ITS N-METHYL DERIVATIVES

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On methylating 4,11-dimethoxynaphtho[2,3-f]indazole-5,10-dione with methyl iodide in the presence of base a mixture is formed of its 1- and 2-methyl derivatives. Demethylation of the methoxy groups of the starting material and of the products of its alkylation leads to the formation of 4,11-dihydroxynaphtho[2,3-f]indazole-5,10-dione (pyrazoloquinizarine) and its 1- and 2-methyl derivatives.

Keywords: 4,11-dihydroxynaphtho[2,3-*f*]indazole-5,10-dione, pyrazoloquinizarine, demethylation, Stokes shift, fluorescence.

The synthesis of heterocyclic derivatives of quinizarine, analogs of 5,12-naphthacenequinone, derivatives of which (anthracycline antibiotics) possess antitumor activity [2], is promising for the further search for new chemotherapeutic agents. Consequently 4,11-dihydroxynaphtho[2,3-*f*]indazole-5,10-dione (pyrroloquinizarine), was synthesized by us previously [3], the aminoalkyl derivatives of which possess high antiproliferative activity [4], and also methods have been developed for the synthesis of 4,11-dihydroxy-anthra[2,3-*d*]imidazole-5,10-dione (imidazoloquinizarine), 4,11-dihydroxyanthra[2,3-*d*][1,2,3]triazole-5,10-dione (triazoloquinizarine), and 5,12-dihydroxynaphtho[2,3-*g*]quinoxaline-6,11-dione (pyrazinoquinizarine) [1]. In addition a method was developed by us previously for the synthesis of 4,11-dimethoxynaphtho[2,3-*f*]-indazole-5,10-dione [5], an O-dimethyl derivative of pyrazoloquinizarine, consequently the aim of the present work was the search for convenient methods for demethylating it to obtain 4,11-dihydroxynaphtho[2,3-*f*]-indazole-5,10-dione (pyrazoloquinizarine), and also a synthesis of its N-alkyl derivatives.

The N-alkylation reaction in the naphtho[2,3-*f*]indazole-5,10-dione series is most promising for the introduction of pharmacophoric groups, consequently first of all we studied the alkylation of 4,11-dimethoxynaphtho[2,3-*f*]indazole-5,10-dione (**1**) in the presence of base. We established that the alkylation of naphthoindazole **1** with methyl iodide in the presence of NaH in DMF at room temperature leads to the

* For Part 1 see [1].

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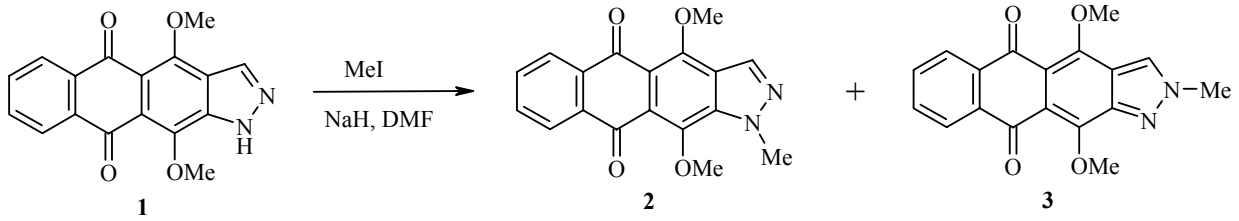
formation of a mixture of 4,11-dimethoxy-1-methyl-1H-naphtho[2,3-*f*]indazole-5,10-dione (**2**) and 4,11-dimethoxy-2-methyl-2H-naphtho[2,3-*f*]indazole-5,10-dione (**3**) in yields of 57 and 37% respectively. The use of potassium or lithium *tert*-butylate as base has practically no influence on the ratio of the products formed, but reduces their yield. The ratio of the 1-methyl and 2-methyl products of the alkylation of 4,11-dimethoxynaphtho[2,3-*f*]indazole-5,10-dione (**1**) is therefore close to the ratio of the alkylation products of unsubstituted indazole in the presence of base [6].



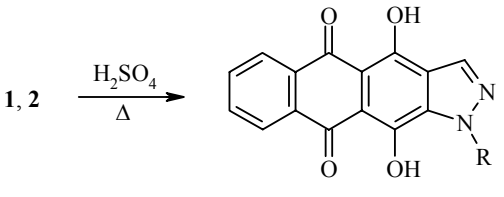
1 **2** **3**

In the ^{1}H NMR spectra of indazoles **2** and **3** the proton signals of the NH group were absent and signals for the methyl groups appeared at 4.27 and 4.34 ppm respectively. The signals of the N-methyl group and the H-3 proton in the spectrum of the $N_{(2)}$-methyl derivative **3** were observed as weakly broadened singlets. Broadening of the methyl group signal disappears on irradiating with a second radiofrequency field at the frequency of the H-3 proton signal. This indicates the presence of an interaction between them with a small coupling constant $J \leq 0.3$ Hz. This is in agreement with the ^{1}H NMR spectral data for the 2-methyl derivative of indazole [7]. Similar effects were not recorded in the spectrum of the 1-methyl derivative **2**.

Peaks were observed in the mass spectra of compounds **2** and **3** for the molecular ions with M^+ 322, which corresponds to the molecular mass of these compounds. The main directions of breakdown of the molecular ions of compounds **2** and **3** were practically the same, the spectra differed only in the relative intensity of the fragment ions. In addition to M^+, peaks were observed for ions 307 $[M\text{-}CH_3]^+$, 293 $[M\text{-}NCH_3]^+$, and 279 $[M\text{-}CH_3\text{-}N_2]^+$.

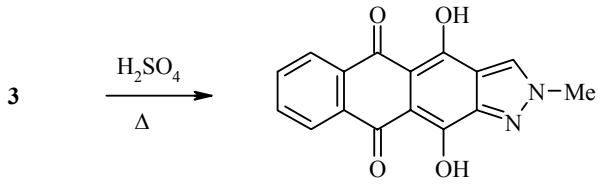
The electronic absorption spectrum (EAS) of compound **2** was practically identical to the spectrum of the starting material **1** [5], while in the spectrum of compound **3** a bathochromic shift of 10 nm was observed for the long-wave absorption maximum, but an additional discontinuity was observed in the region of 377 nm. These data are in agreement with the data of [8, 9], in which it was shown that the absorption spectra of indazole and its 1-methyl derivative were close, while the spectrum of the 2-methyl derivative was different.

The pyrazole ring is stable to the action of acids, consequently for demethylation of the obtained pyrazoloquinizarine O-dimethyl derivatives we used demethylation with sulfuric acid, a method used frequently in the chemistry of anthraquinone [10].



4, **5**

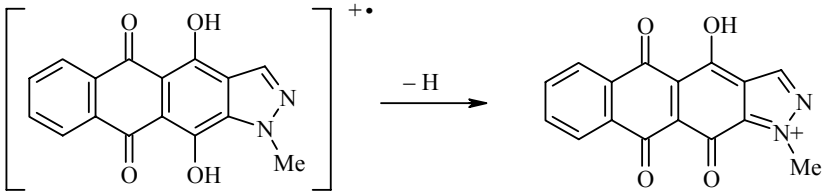
4 R = H, **5** R = Me



6

The synthesized hydroxy derivatives **4-6** possess extremely low solubilities in the majority of solvents, consequently recording of the ^{1}H NMR spectra was carried out at 80°C in DMSO. On cooling solutions to room temperature the substances being investigated crystallized practically completely as needle-like crystals. The singlet signals of the methoxy groups of the initial compounds were absent from the ^{1}H NMR spectra of these compounds, and the signals of the OH group protons were displayed at ~15.0 ppm.

In the mass spectra of compounds **4-6** intense peaks were observed for the molecular ions with M^+ 280 (**4**) and 294 (**5**, **6**), which corresponds to their molecular masses. It should be noted that the mass spectra of derivatives **5** and **6** differed cardinally in the intensity of the $[M-H]^+$ ion peaks. In the spectrum of compound **5**, probably due to the *ortho* disposition of the OH and NMe groups, leading to a favorable stabilization of charge on the $N_{(1)}$ atom, the intensity of the $[M-H]^+$ ion was 86%. In the spectrum of compound **6** the peak for the $[M-H]^+$ ion was absent.



$M^{+\bullet}$ 294 (100%) $[M^+ - H]$ 293 (86%)

Absorption bands were observed in the IR spectra of compounds **4-6** at 3400 cm^{-1} for the stretching vibrations of the OH group, but the bands for the vibrations of the carbonyl groups of the anthraquinone fragment were found at 1600, which is somewhat lower than for bands of the CO groups of quinizarine (1625 cm^{-1} [11]).

Demethylation of the methoxy groups causes a bathochromic shift and an increase in the intensity of the long-wave absorption bands in the EAS of compounds **4-6** in comparison with the spectra of the starting materials **1-3** (Fig. 1). The greatest displacement of the long-wave band was observed on demethylating the 1-methyl derivative **2** (~90 nm), and the least in the case of the 2-methylindazole **3** (~60 nm). In addition it is necessary to mention the significant increase in the intensity of the long-wave absorption bands on methylation of the heterocyclic fragment. The 2-methyl derivative **6** possesses the greatest absorption intensity.

In conclusion it should be noted that all the derivatives of naphtho[2,3-*f*]indazole-5,10-dione synthesized by us possess an intense fluorescence (Table 1). The data obtained show that the dimethoxy derivatives of naphtho[2,3-*f*]indazole-5,10-dione **1-3** have a greater Stokes shift ($\Delta\lambda$ 150 nm). The close photochemical properties of the N-methyl derivatives **2** and **3** and the initial indazole **1** show that high values of the Stokes shift are not connected with the tautomerism of the heterocyclic fragment and are probably explained by the changes in the geometry of the chromophores on transition to the excited state. In contrast to this the Stokes shift of the dihydroxy derivatives of naphtho[2,3-*f*]indazole-5,10-dione **4-6** are significantly less.

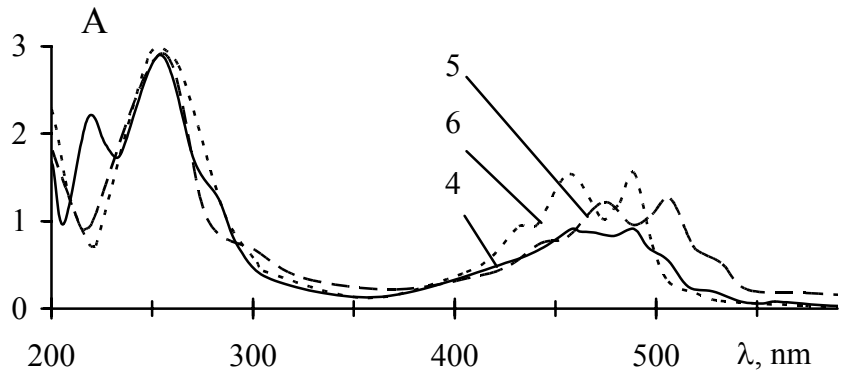


Fig. 1. Electronic absorption spectra of compounds **4-6** in ethanol.

TABLE 1. Electronic Absorption and Fluorescence Spectra of Naphtho-[2,3-*f*]indazole-5,10-diones **1-6** in Ethanol

Compound	λ_{max}, nm		Δλ, nm
	absorption	fluorescence	
1	405	552	147
2	405	552	147
3	414	560	146
4	(435)	(550)	71
	459	530	
	488	510	
5	(443)	(570)	73
	474	547	
	507	515	
6	(435)	(555)	69
	458	527	
	489	498	

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian VXR 400 (400 MHz) spectrometer, internal standard was TMS. The mass spectra were recorded on a Finnigan-MAT SSQ 710 chromato-mass spectrometer, USA, energy of ionizing voltage 70 eV, direct insertion of samples into the ion source, heating of samples to 350°C, temperature of ionization chamber 150°C. The IR spectra were obtained on a Perkin-Elmer 599 spectrometer in KBr disks. The absorption spectra were recorded on a Hitachi U2000 spectrometer. The fluorescence spectra were obtained on a Elyumin 2M instrument. A check on the progress of reactions and the purity of compounds was carried out by TLC on Silufol UV 254 plates.

4,11-Dimethoxy-1-methyl-1H-naphtho[2,3-*f*]indazole-5,10-dione (2) and 4,11-Dimethoxy-2-methyl-2H-naphtho[2,3-*f*]indazole-5,10-dione (3). A suspension of NaH (50 mg, 60%, 1.3 mmol) in mineral oil was added with stirring in a current of argon to a solution of 4,11-dimethoxynaphtho[2,3-*f*]indazole-5,10-dione (**1**) (0.1 g, 0.33 mmol) in anhydrous DMF (10 ml). After 10 min methyl iodide (0.05 ml, 8.0 mmol) was

added with stirring to the violet colored reaction mixture. When the reaction mixture acquired a yellow color (after 15-20 min) ethanol (1 ml) was added dropwise, and the mixture was poured into water. The reaction product was extracted with ethyl acetate (3 × 30 ml), the extract washed with water (2 × 20 ml), dried over $MgSO_4$, and evaporated in vacuum. The residue was purified chromatographically (silica gel, benzene–ethyl acetate, 10:1 → 1:2) and yellow needle-like crystals of naphthoindazoledione **2** (60 mg, 57%), R_f 0.6 (benzene–ethyl acetate, 1:2), mp 187-189°C (benzene–hexane) and yellow crystals of naphthaindazoledione **3**, R_f 0.1 (benzene–ethyl acetate, 1:2), mp 222-224°C (benzene) were isolated.

4,11-Dimethoxy-1-methyl-1H-naphtho[2,3-*f*]indazole-5,10-dione (2). IR spectrum, ν, cm^{-1}: 1660 (C=O). ^1H NMR spectrum (in $CDCl_3$), δ, ppm: 8.30 (1H, s, H-3); 8.24 (2H, m, H-6, 9); 7.74 (2H, m, H-7, 8); 4.40 (3H, s, NCH_3); 4.27 (3H, s, 11-OCH_3); 4.10 (3H, s, 4-OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 322 (100) $[M]^+$, 307 (34) $[M\text{-}CH_3]^+$, 293 (53), 279 (20), 264 (18). Found, %: C 67.30; H 4.53; N 8.57. $C_{18}H_{14}N_2O_4$. Calculated, %: C 67.07; H 4.38; N 8.69.

4,11-Dimethoxy-2-methyl-2H-naphtho[2,3-*f*]indazole-5,10-dione (3). IR spectrum, ν, cm^{-1}: 1660 (C=O). ^1H NMR spectrum (in $CDCl_3$), δ, ppm: 8.27 (1H, s, H-3); 8.23 (2H, m, H-6, 9); 7.72 (2H, m, H-7, 8); 4.40 (3H, s, 11-OCH_3); 4.29 (3H, s, NCH_3); 4.18 (3H, s, 4-OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 322 (100) $[M]^+$, 307 (22) $[M\text{-}CH_3]^+$, 293 (57). 279 (42), 263 (15). Found, % C : 67.15; H 4.60; N 8.86. $C_{18}H_{14}N_2O_4$. Calculated, %: C 67.07; H 4.38; N 8.69.

4,11-Dihydroxynaphtho[2,3-*f*]indazole-5,10-dione. (4). Compound **1** (0.15 g, 0.5 mmol) was dissolved in 80% sulfuric acid (10 ml) with heating and stirring, and the mixture was maintained at 100°C for 30 min. The mixture was cooled, and poured into water (50 ml), the solid was filtered off, washed with water, dried, recrystallized from DMF, and dried. Brown crystals (0.95 g, 70%) were obtained having mp >250°C. IR spectrum, ν, cm^{-1}: 3400 (OH), 3200 (NH), 1605 (C=O). ^1H NMR spectrum (in DMSO-d_6, 80°C), δ, ppm: 14.99 (1H, br. s, OH); 14.81 (1H, br. s, OH); 8.54 (1H, s, H-3); 8.39 (2H, m, H-6, 9); 7.92 (2H, m, H-7, 8). Mass spectrum, *m/z* (I_{rel}, %): 280 (100) $[M]^+$, 251 (4) $[M\text{-}N_2]^+$, 195 (3), 184 (7). Found, %: C 64.12; H 2.63; N 9.87. $C_{15}H_8N_2O_4$. Calculated, %: C 64.29; H 2.88; N 10.00.

4,11-Dihydroxy-1-methyl-1H-naphtho[2,3-*f*]indazole-5,10-dione (5) was obtained analogously to pyrazinoquinizarine **4** from compound **2** on heating in sulfuric acid for 1 h. Yield 75%; mp >250°C. IR spectrum, ν, cm^{-1}: 3400 (OH), 1605 (C=O). ^1H NMR spectrum (in DMSO-d_6, 80°C), δ, ppm: 15.00 (2H, br. s, OH); 8.44 (2H, m, H-6, 9); 8.29 (1H, s, H-3); 7.97 (2H, m, H-7, 8); 4.36 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 294 (100) $[M]^+$, 293 (86) $[M\text{-}H]^+$, 265 (3), 239 (7).

4,11-Dihydroxy-2-methyl-2H-naphtho[2,3-*f*]indazole-5,10-dione (6) was obtained analogously to pyrazinoquinizarine **4** from compound **3**. Yield 79%; mp >250°C. IR spectrum, ν, cm^{-1}: 3400 (OH), 1590 (C=O). ^1H NMR spectrum (in DMSO-d_6, 80°C), 15.00 (2H, br. s, OH); 8.71 (1H, s, H-3); 8.44 (2H, m, H-6, 9); 7.94 (2H, m, H-7, 8); 4.16 (3H, s, CH_3). Mass spectrum, *m/z* (I_{rel}, %): 294 (100) $[M]^+$, 265 (3), 209 (3), 184 (5).

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