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NAPHTHOINDAZOLES. SYNTHESIS OF 4,11-DIMETHOXY-NAPHTHO[2,3-*f*]INDAZOLE-5,10-DIONE

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The previously unknown 4,11-dimethoxynaphtho[2,3-f]indazole-5,10-dione has been obtained by the thermal cyclization of N-nitroso derivative of 2-acetamido-3-methyl-1,4-dimethoxyanthraquinone.

Keywords: substituted N-acetyl-N-nitrosoanthraquinone, naphtho[2,3-*f*]indazoledione, thermal cyclization.

Derivatives of 5,12-naphthacenequinone [1,2] isolated from certain strains of actinomycetes, their glycosylated derivatives, anthracyclins, and also several synthetic analogs possess high biological activity. These compounds contain in their structure an anthraquinone fragment capable of intercalating between nucleotide pairs of the DNA chain, causing disturbance of its matrix function in the processes of replication and transcription, which mainly determines their antitumor activity [3]. Some heterocyclic analogs of anthracyclins [4] and the preparation mitoxanthrone (such as pyrazolanthrones [5] and pyrazolacridines [6]) exceed doxorubicin and its analogs in antitumor activity. A series of condensed systems, in which the anthraquinone fragment is annelated with various heterocycles, is therefore promising in the search for new chemotherapeutic agents. Previously [7,8] we obtained derivatives of naphtho[2,3-*f*]indole-5,10-dione, being the pyrrole analog of the condensed system 5,12-naphthacenequinone. Consequently it seemed of interest to study the dependence of physicochemical and biological properties of heterocyclic analogs of 5,12-naphthacenequinone on the nature of the heterocycle annelated with the anthraquinone fragment.

The aim of the present work is the development of a preparative method of synthesizing the pyrazole analog of 5,12-naphthacenequinone, namely naphtho[2,3-*f*]indazole-5,10-dione. Although indazole derivatives have not been detected in nature [9], a large number of biologically active compounds have been found among indazoles. At the end of the seventies a preparative method was developed for synthesizing 3-indazolecarboxylic acid chloride, 3-formylindazole, and derivatives of them [10], among which compounds were found possessing high fungicidal and antibiotic activity. In the eighties the high antitumor activity of certain derivatives of 3-indazolecarboxylic acid was discovered (the preparation lonidamine) [11].

One of the most widespread methods of synthesizing indazoles is the method [12], according to which N-nitroso derivatives of *o*-acetotoluidines cyclize on heating to the corresponding indazoles. The key compound for making this method useful for the synthesis of 4,11-dimethoxynaphtho[2,3-*f*]indazole-5,10-dione is 2-amino-1,4-dimethoxy-3-methylanthraquinone (**2**), which may be obtained by the reduction of 1,4-dimethoxy-2-methyl-3-nitroanthraquinone (**1**) [8].

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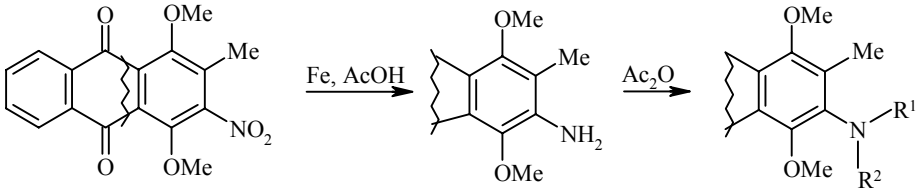
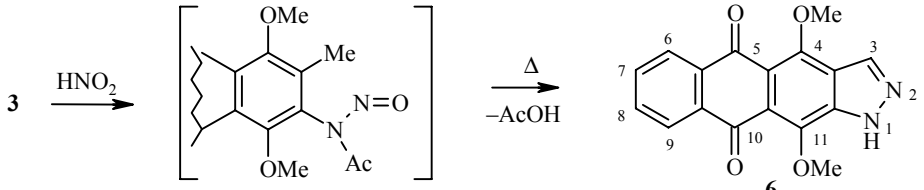


1 **2** **3, 4**

3 R^1 = Ac, R^2 = H; **4** R^1 = R^2 = Ac

The latter is reduced under mild conditions by the action of iron in an ethanol–acetic acid mixture with the formation of 2-amino-1,4-dimethoxy-3-methyl- anthraquinone (**2**). On acylation of aminoanthraquinone **2** with acetic anhydride N-acetyl-2-amino-1,4-dimethoxy-3-methylanthraquinone (**3**) is formed in high yield. Acetylation at a higher temperature (80-90°C) and increasing the reaction time lead to the formation of N,N-diacetyl-2-amino-1,4-dimethoxy-3-methylanthraquinone (**4**). The N,N-diacetyl derivative **4** proved to be a fairly stable compound, it is not hydrolyzed by water, and may be isolated and purified chromatographically or by recrystallization from toluene. However compound **4** is readily hydrolyzed to acetamide **3** on boiling in 10% Na_2CO_3 solution.

Nitrosation of N-acetyl-2-amino-1,4-dimethoxy-3-methylanthraquinone (**3**) in toluene by the action of hydrochloric acid and sodium nitrite leads to the formation of N-acetyl-N-nitroso-2-amino-1,4-dimethoxy-3-methylanthraquinone (**5**). As a rule N-nitrosoacetotoluidines are unstable compounds, consequently N-nitrosoacetamide **5** was converted by thermal cyclization without isolation into the desired 4,11-dimethoxynaphtho[2,3-*f*]indazole-5,10-dione (**6**) in an overall yield of 65% calculated on the initial amide **3**. The intermediate N-nitrosoacetamide **5** proved to be a fairly stable compound for its identification by TLC (in toluene–ethyl acetate, 3:1).



5 **6**

In the ^{1}H NMR spectrum of aminoanthraquinone **2** a singlet signal was displayed for the protons of the amino group at 4.66 ppm. In the spectrum of N-acetyl derivative **3** singlet signals were observed for the protons of the acetyl substituent and for the 3-methyl group (2.29 and 2.28 ppm) together with a low field shift of the singlet signal of the NH group (7.44 ppm). Further acetylation of this compound leads to the disappearance of the signal for the NH group proton and an increase in the intensity of the signal of the acetyl group protons with a small shift of them towards low field (2.32 ppm). As a result of cyclization of the pyrazole fragment the singlet signals of the protons of the acetyl substituent and of the 3-methyl group, observed for the initial anthraquinone **3**, are absent from the spectrum of 4,11-dimethoxynaphtho[2,3-*f*]indazole-5,10-dione (**6**). The signal for the NH group proton is present as a singlet at 14.2 ppm. Displacement towards low field was noted for the singlet signals of the methoxy group protons (4.23 and 4.02 ppm).

Intense absorption bands were observed in the IR spectra of anthraquinones **2-4** at 1660-1690 cm^{-1} corresponding to the stretching vibrations of the carbonyl groups of the anthraquinone fragment and acetyl substituents. In addition, intense absorption bands characteristic of NH groups were observed in the IR spectrum of aminoanthraquinone **2** at 3390 cm^{-1} and of acetylaminoanthraquinone **3** at 3260 cm^{-1}. The lack of an absorption band characteristic of the NH group in the IR spectrum of anthraquinone **4** serves to confirm the formation of N,N-diacetylamide **4**. In the IR spectrum of the desired naphthoindazoledione **6** the absorption band of the C=O group lies at 1640 cm^{-1} and an intense absorption band is observed at 3260 cm^{-1} characteristic of the NH group.

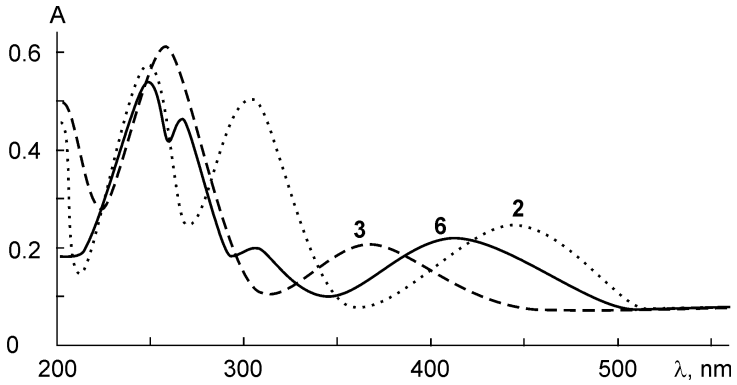


Fig. 1. Electronic absorption spectra of $1 \cdot 10^{-6}$ M solutions of compounds **2**,**3**, and **6** in ethanol.

The electronic absorption spectra of anthraquinones **2** and **3** and also of naphthoindazoledione **6** are shown in Fig. 1. The maximum of the long-wave absorption band of aminoanthraquinone **2** lies at 444 nm. Comparison of the electronic absorption spectra of aminoanthraquinone **2** and of its N-acetyl derivative **3** shows a hypsochromic shift of the long-wave absorption band at 369 nm, which is evidently linked with the electron-withdrawing properties of the acetyl group. This effect disappears in the case of naphthoindazoledione **6**, the maximum of the long-wave absorption of which is found at 414 nm. The small hypsochromic shift of the maximum in the long-wave region of absorption observed on comparing the electronic absorption spectra of 4,11-dimethoxynaphtho[2,3-*f*]indazole-5,10-dione (**6**) and of the previously obtained 4,11-dimethoxynaphtho-[2,3-*f*]indole-5,10-dione, the long-wave maximum for which is at 420 nm, is explained by the weak electron-withdrawing properties of the azole nitrogen atom in the heterocycle.

Peaks were observed in the mass spectra of compounds **2**-**4** and **6** for the molecular ions M^+ at 297, 339, 381, and 308 respectively, which correspond to the calculated values.

EXPERIMENTAL

The NMR spectra were recorded on a Varian UNITY plus 400 (400 MHz) spectrometer, internal standard was TMS. The mass spectra were taken on a Varian Mat 112 chromato-mass spectrometer. The IR spectra of the compounds obtained were recorded on a Perkin-Elmer 599 spectrometer in nujol. The UV spectra were recorded on a Specord M 400 spectrophotometer in ethanol. A check on the progress of reactions and the purity of compounds was carried out by TLC on Silufol plates. Preparative chromatography of compounds was carried out on silica gel type L 40/100.

2-Amino-1,4-dimethoxy-3-methylanthraquinone (2). Solution of 1,4-dimethoxy-2-methyl-3-nitroanthraquinone (**1**) [8] (2.1 g, 6.6 mmol) in mixture of glacial acetic acid (60 ml) and ethanol (60 ml) was heated to 70-75°C and iron powder (1.8 g, 33 mmol) was added with vigorous stirring. After 15 min the solution was filtered, and evaporated in vacuum to 5 ml. The residue was poured into water, and the solid obtained was filtered off. The solid was washed with water, dried, and dissolved in boiling toluene. The solution was filtered and chromatographed (silica gel, toluene–ethyl acetate, 4:1). Yield of compound **2** 1.2 g (61%); mp 165-166°C (toluene). NMR spectrum ($CDCl_3$), δ, ppm: 8.18 (2H, m, 5-H, 8-H); 7.69 (2H, m, 6-H, 7-H); 4.66 (2H, s, NH_2); 3.92 (3H, s, OCH_3); 3.88 (3H, s, OCH_3); 2.21 (3H, s, 3-CH_3). IR spectrum, ν, cm^{-1}: 3390 (NH), 1665 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 297 (100), 283 (15), 282 (68), 280 (32), 268 (25), 264 (17), 250 (20). Found, %: C 68.89; H 5.3; N 4.6. $C_{17}H_{15}NO_4$. Calculated, %: C 68.7; H 5.1; N 4.7.

N-Acetyl-2-amino-1,4-dimethoxy-3-methylanthraquinone (3). Mixture of compound **2** (0.6 g, 2 mmol) and acetic anhydride (10 ml, 0.11 mol) was heated for 1 h at 70°C, after which the reaction mixture was evaporated to 2/3 volume in vacuum. After 20 min the precipitated crystals of compound **3** were filtered off, washed with ethanol, and dried. Yield 0.55 g (85%) of yellow needle-like crystals; mp 234-235°C (toluene). NMR spectrum ($CDCl_3$), δ, ppm: 8.18 (2H, m, 5-H, 8-H); 7.73 (2H, m, 6-H, 7-H); 7.44 (1H, s, NH); 3.95 (3H, s, OCH_3); 3.91 (3H, s, OCH_3); 2.29 (3H, s, $COCH_3$); 2.28 (3H, s, 3-CH_3). IR spectrum, ν, cm^{-1}: 3260 (NH), 1670 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 339 (41), 324 (41), 308 (36), 296 (39), 292 (21), 283 (24), 282 (100), 280 (25), 278 (29), 268 (19), 264 (17). Found, %: C 67.6; H 5.2; N 4.2. $C_{19}H_{17}NO_3$. Calculated, %: C 67.3; H 5.1; N 4.1.

N,N-Diacetyl-2-amino-1,4-dimethoxy-3-methylanthraquinone (4). Compound **2** (0.55 g, 1.85 mmol) was dissolved in acetic anhydride (10 ml, 0.11 mol) and the mixture was heated for 3 h at 90°C. The solution was cooled, and poured into water with ice (100 ml). After 2 h the precipitated crystals were filtered off, washed with water, and dried. After recrystallization from the minimum volume of toluene compound **4** (0.52 g, 76%) was obtained as yellow crystals of mp 176-177°C. NMR spectrum ($CDCl_3$), δ, ppm: 8.2 (2H, m, 5-H, 8-H); 7.76 (2H, m, 6-H, 7-H); 3.96 (3H, s, OCH_3); 3.85 (3H, s, OCH_3); 2.32 [6H, s, $N(COCH_3)_2$]; 2.23 (3H, s, 3-CH_3). IR spectrum, ν, cm^{-1}: 1710, 1700, 1680 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 381 (21), 339 (55), 324 (35), 321 (38), 308 (58), 306 (27), 296 (41), 292 (38), 290 (34), 289 (41), 282 (100), 280 (30), 278 (57), 264 (25). Found, %: C 66.1; H 5.2; N 3.5. $C_{21}H_{19}NO_6$. Calculated, %: C 66.1; H 5.0; N 3.7.

4-11-Dimethoxynaphtho[2,3-*f*]indazole-5,10-dione (6). Compound **3** (0.45 g, 1.33 mmol) was dissolved by heating in toluene (300 ml). The solution was cooled to 0°C and solution of concentrated HCl (0.17 ml, 5.32 mmol) in water (5 ml) was poured in. Solution of $NaNO_2$ (0.45 g, 5.32 mmol) in water (3 ml) was added with vigorous stirring at a temperature below 5°C. The mixture was stirred for 1 h and then washed three times with water. The toluene solution of N-acetyl-N-nitroso-2-amino-1,4-dimethoxy-3-methylanthraquinone (**5**) was dried for 20 min over $MgSO_4$, filtered, and heated to boiling. The mixture was cooled, and left overnight in the refrigerator. The precipitate obtained was filtered off, and compound **6** (0.19 g) was obtained as yellow crystals. Evaporation of the mother liquor and recrystallization of the residue from toluene gave a further 0.08 g of the compound, overall yield was 68%; mp 256-257°C. NMR spectrum (DMSO-d_6), δ, ppm: 14.22 (1H, s, NH); 8.62 (1H, s, 3-H); 8.1 (2H, m, 6-H, 9-H); 7.84 (2H, m, 7-H, 8-H); 4.23 (3H, s, OCH_3); 4.03 (3H, s, OCH_3). IR spectrum, ν, cm^{-1}: 3260 (NH), 1640 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 308 (100), 294 (10), 293 (27), 291 (14), 280 (13), 279 (61), 265 (24), 249 (20), 236 (12), 139 (19), Found, %: C 66.7; H 3.6; N 9.2. $C_{17}H_{12}N_2O_4$. Calculated, %: C 66.2; H 3.9; N 9.1.

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