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NAPHTHOINDOLES. 9*. SYNTHESIS OF N-DERIVATIVES OF 4,11-DIMETHOXYNAPHTHO-[2,3-*f*]INDOLE-5,10-DIONE

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N-Acetylation and several N-alkylation reactions have been carried out for the previously synthesized 4,11-dimethoxynaphtho[2,3-f]indole-5,10-dione.

Keywords: N-derivatives of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione, N-alkylation, N-acetylation.

The synthesis of new compounds combining anthraquinone and indole fragments in their structure are of significant interest in the search for new therapeutic agents. Several methods of synthesizing naphthoindolediones (pyrroloanthraquinones) have been described in the literature [2-4], however electrophilic substitution reactions at the nitrogen atom of the pyrrole ring have not been studied in practice up to the present. This type of reaction is the most promising in the naphthoindoledione series since it permits the synthesis of a large number of derivatives to be effected. Consequently we have studied the possibility of obtaining 1-derivatives of the previously synthesized 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**1**).

Acetylation of indole by boiling in acetic anhydride in the presence of sodium acetate gives a mixture of mono- and diacetyl derivatives [5]. On acylation of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **1** under analogous conditions we obtained the mono substituted 1-acetyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**2**).

N-Alkylation of indole compounds enables the preparation of N derivatives of indole in high yield. The salt formed in anhydrous medium by the action on the indole of a strong base (NaH, $NaNH_2$, KOH, etc.) is usually subjected to alkylation.

In our work we used the sodium salt of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **1** obtained by the interaction of the initial naphthoindoledione with an excess of NaH in DMF and also by an interphase catalysis procedure. The salt formed in this way has a bright violet color, disappearing under the action of alkyl halides. On using methyl iodide and allyl bromide as alkylating agents we obtained 4,11-dimethoxy-1-methylnaphtho[2,3-*f*]-indole-5,10-dione (**3**) and 1-allyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**4**) (Scheme 1).

Alkylation of the sodium salt of indoles with various haloalkylamines enables the preparation of a wide spectrum of N-alkylamino derivatives of indole, individual representatives of which possess high biological activity. We synthesized 1-(2-dimethylaminoethyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (**5**) by the N-aminoalkylation of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **1** with 1-chloro-2-(N,N-dimethylamino)-ethane in the presence of an excess of NaH in DMF at 50°C.

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* For Part 8 see [1].

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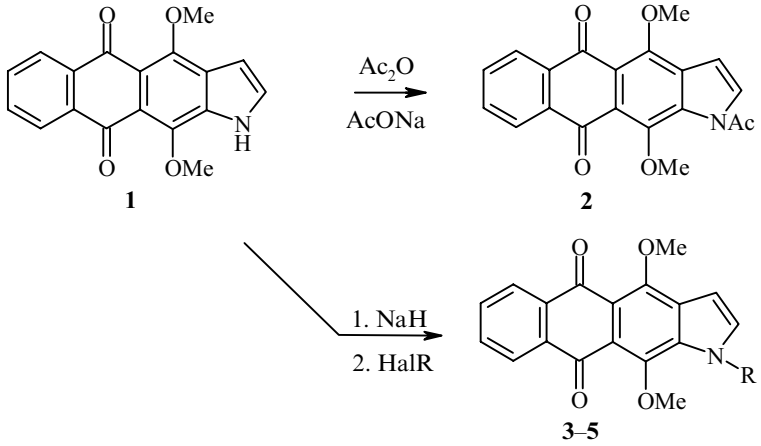
Scheme 1



3 R = Me, **4** R = $CH_2CH{=}CH_2$, **5** R = $(CH_2)_2NMe_2$

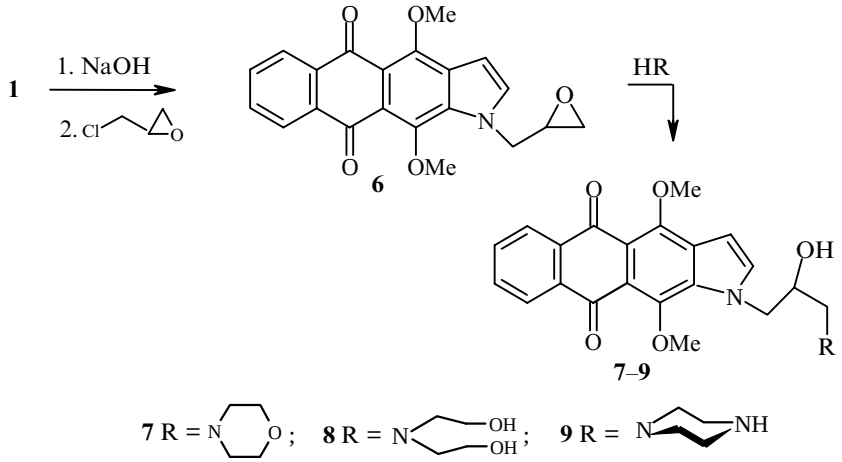
According to the model of Hansch [6] one of the key parameters influencing the biological activity of a compound is its hydrophobicity, which is described by the logarithm of the distribution coefficient (lipophilicity) log *P* in an octanol–water system and strongly affects its penetration, transport, and binding to a receptor [7]. A dependence exists between the cytotoxicity of anthracycline antibiotics and other antitumor intercalators and their distribution coefficient *P* [8]. The optimum lipophilicity of a preparation for antitumor activity lies in the region of log *P* values of 0 to 2.

There is therefore considerable interest in the search for new chemotherapeutic agents by synthesizing compounds possessing solubility in both aqueous media and organic solvents. To impart ambident solubility to N-alkylaminonaphthoindoledione we have synthesized derivatives of 1-(2,3-epoxypropyl)-4,11-dimethoxynaphtho-[2,3-*f*]indole-5,10-dione **6** having a 3-amino-2-hydroxypropyl group in the side chain to increase the water solubility.

The synthesis of 1-(2,3-epoxypropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **6** was effected by us by alkylation using interphase catalysis, used in the synthesis of epoxypropyl derivatives of indole possessing antihistamine [9] and antitumor [10] activity. 1-(2,3-Epoxypropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **6** was obtained by the alkylation of naphthoindoledione **1** with epichlorhydrin in a system of benzene–50% sodium hydroxide solution in the presence of tetraethylbenzylammonium chloride at 60°C.

The synthesis of oxirane **6** by the oxidation of 1-allyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **4** with trifluoroperacetic, perbenzoic, and perphthalic acid was unsuccessful, probably due to the higher inclination of the pyrrole or quinonoid fragments to be oxidized than of the double bond of the allyl substituent.

We synthesized several 3-amino-2-hydroxypropyl derivatives of naphthoindoledione **1** by fission of the oxirane fragment of the epoxy derivative **6** by the action of secondary amines.



7 R = N O; **8** R = N OH OH; **9** R = N NH

1-(2-Hydroxypropyl-3-morpholino)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **7** was obtained by the action of morpholine in butanol at 50°C on the epoxy derivative **6**. 1-[3-Bis(2-hydroxyethyl)amino-2-hydroxypropyl]-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **8** was synthesized by the alkylation of naphthoindoledione **6** with diethanolamine in butanol. Fission of the oxirane fragment of epoxide **6** with an excess of piperazine gave a synthesis of 1-(2-hydroxypropyl-3-piperazino)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **9**.

There was no signal for the proton of the N–H group of the indole fragment in the ^{1}H NMR spectra of the synthesized N-derivatives of 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-diones **2-6**, but signals were observed for the appropriate substituents. The absorption band characteristic of the N–H group was also absent in the IR spectra of these compounds, but intense absorption bands were observed at 1680 cm^{-1} caused by the stretching vibrations of the carbonyl groups of the anthraquinone fragment. Signals were observed for the protons of the amino substituents in the ^{1}H NMR spectra of the N-propanolamine derivatives **7-9** in the form of two multiplet signals and broad absorption bands were displayed in their IR spectra at 3350-3400 cm^{-1} characteristic of the OH group, which confirms fission of the oxirane ring. There were molecular ion peaks in the mass spectra of compounds **2-9** at M^+ 349, 321, 347, 378, 363, 450, 469, and 449, which correspond to their calculated values.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Varian Unity + 400 spectrometer. Chemical shifts were measured relative to TMS as internal standard. The mass spectra were taken on a Varian MAT 112 chromato-mass spectrometer. The IR spectra of the compounds obtained were taken on a Perkin-Elmer 599 spectrometer in nujol. A check on the progress of reactions and the purity of compounds was effected by TLC on Silufol plates. Preparative chromatography of compounds was carried out on type L 40/100 silica gel.

1-Acetyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (2). Acetic anhydride (10 ml) and anhydrous CH_3COONa (1 g) were added to 4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **1** (0.1 g, 0.33 mmol) and the mixture was boiled for 24 h. The reaction mixture was poured into water and 12 h later the resulting mixture was extracted with ethyl acetate. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. The residue was chromatographed (silica gel, benzene–ether, 20 : 1), and 1-acetyl-4,11-dimethoxynaphtho[2,3-*f*]-indole-5,10-dione (0.09 g, 75%) was obtained as yellow crystals; mp 156-157°C (benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.23 (2H, m, 6-H, 9-H); 7.74 (2H, m, 7-H, 8-H); 7.71 (1H, d, 2-H); 6.92 (1H, d, 3-H); 4.11 (3H, s, OCH_3); 3.95 (3H, s, OCH_3); 2.76 (3H, s, N-$COCH_3$). IR spectrum, cm^{-1}: 1690, 1660 (C=O). Mass spectrum*: 349 (100), 307 (57), 278 (69), 260 (53), 248 (48), 206 (21), 193 (28), 164 (35), 150 (30). Found, %: C 69.0; H 4.2; N 4.1. $C_{20}H_{15}NO_5$. Calculated, %: C 69.0; H 4.2; N 4.0.

4,11-Dimethoxy-1-methylnaphtho[2,3-*f*]indole-5,10-dione (3). Sodium hydride (0.05 g, 2 mmol) was added in a stream of argon to a solution of naphthoindole **1** (0.1 g, 0.33 mmol) in freshly distilled DMF (10 ml). The violet colored reaction mixture was heated to 30°C with stirring and methyl iodide (0.05 ml, 8 mmol) was added. When the mixture acquired a yellow color, ethanol (1 ml) was added dropwise, and the obtained mixture was poured into water. The reaction product was extracted three times with toluene, the extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. 4,11-Dimethoxy-1-methylnaphtho[2,3-*f*]indole-5,10-dione **3** (0.085 g, 90%) was obtained by crystallization from benzene as yellow crystals; mp 180-182°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.24 (2H, s, 6-H, 9-H); 7.71 (2H, m, 7-H, 8-H); 7.13 (1H, m, 2-H); 6.79 (1H, m, 3-H); 4.14 (3H, s, NCH_3); 4.11 (3H, s, OCH_3); 4.06 (3H, s, OCH_3). IR spectrum, cm^{-1}: 1660 (C=O). Mass spectrum: 321 (100), 306 (25), 292 (31), 278 (22), 262 (29), 178 (14), 96 (20). Found, %: C 71.0; H 4.7; N 4.4. $C_{19}H_{15}NO_4$. Calculated, %: C 71.0; H 4.7; N 4.4. M^+ 321.

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* Here and subsequently values of *m/z* are given for ion peaks, and the intensities of ion peaks relative to the maximum are given in parentheses.

1-Allyl-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (4) was obtained analogously. Yellow crystals. Yield 85%; mp 134-135°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.23 (2H, s, 6-H, 9-H); 7.70 (2H, m, 7-H, 8-H); 7.21 (1H, d, 2-H); 6.85 (1H, d, 3-H); 6.12 (1H, m, –CH=); 5.15 (2H, d, NCH_2–); 5.10 (2H, m, $=CH_2$); 4.12 (3H, s, OCH_3); 4.03 (3H, s, OCH_3). IR spectrum, cm^{-1}: 1660 (C=O); 1610 (C=C). Mass spectrum: 347 (100), 317 (40), 301 (37), 278 (35), 248 (30), 204 (20), 105 (25). Found, %: C 72.8; H 4.6; N 4.1. $C_{21}H_{17}NO_4$. Calculated, %: C 72.6; H 4.9; N 4.0.

1-(2-Dimethylaminoethyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (5). Sodium hydride (0.1 g, 4 mmol) was added in a stream of argon to naphthoindole **1** (0.1 g, 0.33 mmol) in anhydrous DMF (10 ml). The violet colored reaction mixture was heated with stirring to 50°C and 1-chloro-2-(N,N-dimethylamino)ethane hydrochloride (0.15 g, 1 mmol) added. When the mixture had acquired a yellow color, ethanol (1 ml) was added dropwise, the reaction mixture was poured into 5% acetic acid (50 ml), and extracted with ethyl acetate. The aqueous phase was brought to pH 7 with 10% KOH solution, and extracted three times with ethyl acetate. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. The residue was chromatographed (silica gel, acetone), and 1-(2-dimethylaminoethyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **5** (0.077 g, 63%) was obtained as yellow crystals of mp 133-135°C (methanol–benzene, 1 : 1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.08 (2H, s, 6-H, 9-H); 7.77 (2H, m, 7-H, 8-H); 7.58 (1H, m, 2-H); 7.03 (1H, m, 3-H); 4.62 (2H, t, N–CH_2–); 4.01 (3H, s, OCH_3); 3.97 (3H, s, OCH_3); 3.89 (2H, t, –C<u>H</u>$_2$N$(CH_3)_2$); 3.2 (6H, s, $N(CH_3)_2$). IR spectrum, cm^{-1}: 1660 (C=O). Mass spectrum: 378 (84), 346 (82), 229 (100). Found, %: C 69.8; H 5.6; N 7.5. $C_{22}H_{22}N_2O_4$. Calculated, %: C 69.8; H 5.9; N 7.4.

1-(2,3-Epoxypropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (6). Benzene (10 ml), epichlorhydrin (5 ml, 76 mmol), compound **1** (0.2 g, 0.65 mmol), and triethylbenzylammonium chloride (0.05 g) were added to 50% NaOH solution (20 ml). The reaction mixture was heated to 60°C, stirred until disappearance of the violet color of the organic phase (approximately 30 min), and poured into water. The solution was extracted three times with toluene, the extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. The residue was chromatographed (silica gel, benzene–ether, 10 : 1), and 1-(2,3-epoxypropyl)-4,11-dimethoxynaphtho-[2,3-*f*]indole-5,10-dione **6** (0.14 g, 62%) was obtained as a yellow oil. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.25 (2H, s, 6-H, 9-H); 7.73 (2H, m, 7-H, 8-H); 7.28 (1H, d, 2-H); 6.86 (1H, d, 3-H); 4.92 (2H, d, NCH_2–); 4.29 (1H, m, –CH); 4.12 (3H, s, OCH_3); 4.07 (3H, s, OCH_3); 3.82 (2H, m, $=CH_2$). IR spectrum, cm^{-1}: 1660 (C=O). Mass spectrum: 363 (22), 349 (53), 320 (65), 278 (100). Found, %: C 69.9; H 5.1; N 3.6. $C_{21}H_{17}NO_5$. Calculated, %: C 69.4; H 4.7; N 3.9.

1-(2-Hydroxy-3-morpholinopropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione. (7). Morpholine (0.1 ml, 1.1 mmol) was added to a solution of 1-(2,3-epoxypropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **6** (0.1 g, 0.28 mmol) in butanol (3 ml). The mixture obtained was heated at 50°C for 8 h. The reaction mixture was evaporated in vacuum, the residue dissolved in 20% acetic acid (10 ml), and extracted with ethyl acetate. A 10% KOH solution was added to the aqueous phase to pH 7, and the mixture extracted three times with ethyl acetate. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. The residue was purified chromatographically (silica gel, benzene–acetone, 1 : 5), and 1-(2-hydroxy-3-morpholinopropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **7** (0.08 g, 65%) was obtained as yellow crystals; mp 165-167°C (benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.17 (2H, s, 6-H, 9-H); 7.66 (2H, m, 7-H, 8-H); 7.33 (1H, m, 2-H); 6.78 (1H, m, 3-H); 4.05 (3H, s, OCH_3); 3.98 (3H, s, OCH_3); 4.61 (2H, m, NCH_2–); 4.30 (1H, m, –C<u>H</u>OH–); 3.62 (4H, m, $(–CH_2–)_2O$); 2.53 (2H, m, $–CH_2N=$); 2.32 (4H, m, $N(–CH_2–)_2$). IR spectrum, cm^{-1}: 3360 (OH), 1660 (C=O). Mass spectrum: 450 (40), 422 (44), 405 (51), 319 (100), 292 (62), 130 (87). Found, %: C 66.6; H 5.9; N 6.6. $C_{25}H_{26}N_2O_6$. Calculated, %: C 66.7; H 5.8; N 6.2.

1-[3-Bis(2-hydroxyethyl)amino-2-hydroxypropyl]-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione Acetate (8). Diethanolamine (0.1 g, 9.5 mmol) was added to a solution of 1-(2,3-epoxypropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **6** (0.1 g, 0.28 mmol) in butanol (3 ml) and the mixture was heated at 50°C for 8 h. The reaction mixture was evaporated in vacuum, the residue was dissolved in 20% acetic acid (10 ml), and the solution extracted with ethyl acetate. A 10% solution of KOH was added to the aqueous phase to pH 7, and the mixture was extracted three times with butanol. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. The residue was chromatographed (silica gel, benzene–acetone, 1 : 5) and the

yellow oily product obtained was treated with glacial acetic acid (0.1 ml) in methanol (2 ml). Absolute ether (30 ml) was added to the obtained solution, the precipitate was filtered off, and recrystallized from a methanol–benzene (4 : 1) mixture. 1-[3-Bis(2-hydroxyethyl)amino-2-hydroxypropyl]-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione acetate **8** (0.08 g, 53%) was obtained as yellow crystals; mp 153-155°C (alcohol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 8.08 (2H, s, 6-H, 9-H); 7.77 (2H, m, 7-H, 8-H); 7.58 (1H, m, 2-H); 7.03 (1H, m, 3-H); 4.01 (3H, s, OCH_3); 3.97 (3H, s, OCH_3); 2.62 (2H, m, NCH_2–); 4.56 (1H, m, –C<u>H</u>OH–); 3.62 (4H, m (–C<u>H</u>$_2$OH)$_2$); 2.7 (3H, s, $COCH_3$); 2.51 (6H, m, N(–CH_2–)$_3$). IR spectrum, cm^{-1}: 3370 (OH), 1690, 1660 (C=O). Mass spectrum: 469 (100), 454 (42), 439 (48), 425 (20), 306 (21), 235 (31), 157 (100), 118 (80). Found, %: C 61.3; H 6.2; N 5.4. $C_{27}H_{32}N_2O_9$. Calculated, %: C 61.4; H 6.1; N 5.3.

1-(2-Hydroxy-3-piperazinopropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione (9). Piperazine (0.5 g, 5.8 mmol) was added to a solution of 1-(2,3-epoxypropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **6** (0.1 g, 0.28 mmol) in butanol (3 ml) and the mixture was heated at 50°C for 6 h. The solution was evaporated in vacuum, the residue was dissolved in 20% acetic acid (10 ml), and the solution extracted with ethyl acetate. A 10% KOH solution was added to the aqueous phase to pH 7, and the mixture extracted three times with ethyl acetate. The extract was washed with water, dried over $MgSO_4$, and evaporated in vacuum. The residue was purified chromatographically (silica gel, acetone–ammonia, 10 : 1). 1-(2-Hydroxy-3-piperazinopropyl)-4,11-dimethoxynaphtho[2,3-*f*]indole-5,10-dione **9** (0.6 g, 45%) was obtained as yellow crystals; mp 122-123°C (methanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 8.30 (2H, s, 6-H, 9-H); 7.70 (2H, m, 7-H, 8-H); 7.20 (1H, m, 2-H); 6.71 (1H, m, 3-H); 4.56 (1H, m, –C<u>H</u>OH–); 4.13 (2H, m, NCH_2–); 4.05 (3H, s, OMe); 3.98 (3H, s, OMe); 3.48 (4H, m, (–C<u>H</u>$_2$–)$_2$NH); 3.47 (6H, m, N(–CH_2–)$_3$). IR spectrum, cm^{-1}: 3350-3380 (OH), 1660 (C=O). Mass spectrum: 449 (10), 393 (20), 290 (15), 260 (47). Found, %: C 66.9; H 5.9; N 9.6. $C_{25}H_{27}N_3O_5$. Calculated, %: C 66.8; H 6.1; N 9.4.

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