

NAPHTHOINDOLES.

1. SYNTHESIS OF NAPHTHO[2,3-e]INDOLE-4,9-DIONE AND NAPHTHO[2,3-f]INDOLE-5,10-DIONE

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Naphtho[2,3-e]indole-4,9-dione and naphtho[2,3-f]indole-5,10-dione were synthesized by the Friedel-Crafts reaction from phthalic anhydride and N-acetylin-doline and by the Fischer reaction by cyclization of 2-anthraquinonyl hydrazone of ethyl pyruvate.

Despite the numerous publications relating to anthraquinone derivatives, practically no information is available in the literature up to the present time on the synthesis of naphthoindolediones [1, 2]. Among the anthraquinone derivatives, several antibiotics have recently been discovered, which have high antitumorigenic activity [3, 4], and, therefore, compounds of this class, containing both indole and anthraquinone fragments, can undoubtedly be of interest in the search for various physiologically active compounds in this series. The aim of the present work was to develop a practical method for the preparation of naphtho[2,3-f]indole-5,10-dione (VII) and naphtho[2,3-e]indole-4,9-dione (VIII), and to study their physicochemical properties.

Compounds VII and VIII were synthesized by the Friedel-Crafts reaction of phthalic anhydride with N-acetylin-doline in a melt of aluminum chloride and sodium chloride salts, followed by conversion of the N-acetyl derivatives of naphtho[2,3-f]- and naphtho[2,3-e]-indolinediones III and IV in quantitative yield into the corresponding naphthoindolinediones V and VI by boiling in hydrochloric acid. The latter were converted into the end compounds VII and VIII by dehydration with manganese dioxide. The overall yield of compounds III and IV is 60%, whereby the linear and angular isomers are formed in a 1:1 ratio. They could not be separated by column chromatography on silica gel.

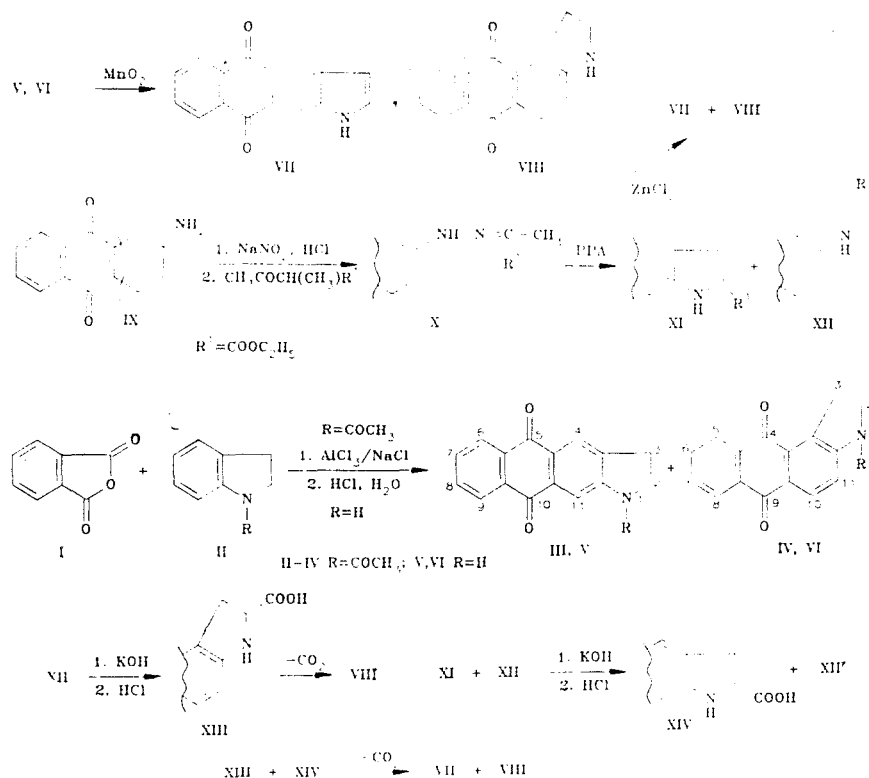
For an alternative synthesis of naphthoindolediones VII and VIII by the Fischer reaction involving the diazotization of 2-aminoanthraquinone IX and coupling the diazonium salt formed with methylacetoacetic ester, we obtained a 2-anthraquinonyl hydrazone of ethyl pyruvate (X) in the anti-form. Cyclization of compound X in the presence of anhydrous zinc chloride at 240°C results in a mixture of naphthoindolediones VII and VIII in an overall yield of 8%, with a 1:3 ratio of the isomers. Isomers VII and VIII were separated by recrystallization from alcohol.

Cyclization of hydrozone X in polyphosphoric acid (PPA) at 125°C gave a mixture of compounds XI and XII in a yield of 29% with a 1:3 ratio between the linear and angular isomers according to the PMR spectroscopy data. Only the angular ester XII could be isolated in a pure state by column chromatography on silica gel. Compound XI could be obtained in a pure state by chromatographic separation of the mixture only on plates with a stationary layer of silica gel DS - Fertigplatten Kieselgel 40 F₂₅₄.

Hydrolysis of ester XII and decarboxylation of acid XIII by boiling in dimethylformamide in the presence of copper salts and acetyl acetone gave the angular naphthoindoledione VIII. The linear naphthoindoledione VII was isolated by recrystallization from alcohol of a mixture of compounds VII and VIII obtained by hydrolysis of esters XI and XII, followed by decarboxylation of the corresponding acids (see scheme below).

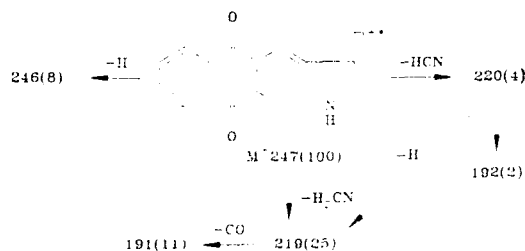
The use of other condensing agents, such as a PPA ester, solutions of hydrogen chloride in alcohol and butanol, concentrated H₂SO₄, solution of sulfuric acid in glacial acetic acid

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for the cyclization of hydrazone X does not give the desired results: At low temperatures and in the presence of mild cyclizing agents, the reaction does not proceed, while under rigorous conditions the hydrazone splits from the initial amine. Compounds VII and VIII obtained by the Friedel-Crafts and by the Fischer reaction are identical.

In the mass spectra of compounds VII and VIII, there are intense peaks of molecular ions M^+ 247,* while the character of further fragmentation, confirmed by metastable transitions, does not contradict the structures attributed to them:



The mass spectrum of the angular naphthoindole-dione VIII is similar.

The PMR spectra of the linear (VII) and the angular (VIII) isomers are characterized by the absence or presence of SSCC of the ortho-protons of the benzene ring of the indole fragment (for compound VIII, $J_{1011} \sim 8$ Hz) and also by a weak-field shift of the 3-H proton signal of the angular isomer due to the anisotropic influence of the nearby located carbonyl group of the quinoid ring in compound VIII (6.87 and 7.63 ppm for compounds VII and VIII, respectively). The benzene ring spectrum of the naphtho fragments of the compounds (the ABCD system) is located in the shifts range of 7.8-8.3 ppm. (The PMR spectra of compounds III-VIII and XI-XIII are given in Table 1.)

In the IR spectra of the obtained compounds there is an intense absorption band in the $1640-1720 \text{ cm}^{-1}$ region due to the stretching vibrations of the C=O group, while the characteristic absorption frequencies of the N-H groups are present in the $3300-3380 \text{ cm}^{-1}$ region, which coincides with the corresponding band in the spectrum of indole.

*Here and below the m/z values are given for the ion peaks, while the relative intensities of the ion peaks in % with respect to the maximal value are given in brackets.

TABLE 1. PMR Spectra of Compounds III-VIII, XI-XIII*

Com- pound	Chemical shifts, δ , ppm						SSCC, J, Hz
	1-R, s	2-H	3-H	4-H (1H, s)	10-H (1H)	11-H (1H)	
III	2.31** (3H)	4.20 (2H, t)	3.34 (2H, t)	8.09		8.96**	$J_{23}=8,55$
IV	2.32** (3H)	4.25 (2H, t)	3.79 (2H, t)		8,29 d	7,78	$J_{23}=8,79; J_{1011}=8,30$
V	4.50 (1H)	3.77 (2H, t)	3.20 (2H, t)	8,01		7,30	$J_{23}=8,79$
VI	4.55 (1H)	3.83 (2H, t)	3.65 (2H, t)		8,12 d	6,79	$J_{23}=7,81; J_{1011}=8,30$
VII	11,21 (1H)	7,78 (1H, dd)	6,87 (1H, dd)	8,61		8,41	$J_{12}=2,50; J_{23}=3,29;$ $J_{13}=2,19$
VIII	11,03 (1H)	7,76 (1H, dd)	7,63 (1H, dd)		8,12 d	7,93	$J_{12}=1,93; J_{23}=2,92;$ $J_{13}=1,83; J_{1011}=8,57$
XI	11,80*** (1H)	4,44 (2H, q);	7,52 (1H, s)	8,50		8,74	$J_{\text{CH}_2\text{CH}_3}=6,95$
XII	11,94 (1H)	1,11 (3H, t)	~8,2 (1H)		8,30 d	8,02	$J_{\text{CH}_2\text{CH}_3}=7,08$
XIII	11,60 (1H)	4,45 (2H, q);	~8,3 (1H)		~8,3	8,04	$J_{1011}=8,77$

*The spectra of compounds VII, VIII, XI-XIII were obtained in acetone-D₆, and those of compounds III-VI in CDCl₃.

**A broadening of the signal due to the rotation of the amide bond is observed.

***Partially NH → ND.

****The COOH group is not observed as a result of intermolecular exchange.

The UV spectra of compounds VII and VIII are typical for anthraquinone compounds having an electron-donor substituent at the 2-position, and are characterized by the presence of three intense bands in the short-wave region and a less-intense and broad band in the longwave region with the absorption maximum in the visible region. The small hypsochromic shift (20 nm) to the shortwave region for the angular isomer can be explained by the partial removal of the unshared electron pair of nitrogen atom from the conjugation with the anthraquinone π -system due to steric factors.

EXPERIMENTAL

The UV spectra were run on a Specord UV-vis spectrophotometer (in ethanol), IR spectra on a UR-20 spectrophotometer with NaCl and LiF prisms (in mineral oil), rate of scanning 160 at a spectral slit width of 4 cm⁻¹. The mass spectra were run on a Varian MAT-311A spectrometer at an ionizing voltage of 70 eV, a cathode emission current of 1 mA, and accelerating voltage of 3 kV. The evaporation temperatures of the samples were from 30 to 300°C in a linearly-programmed regime. The PMR spectra were obtained on a WP-200-SY Bruker spectrometer, using TMS as internal standard. The course of the reaction and the purity of the compounds was monitored on Silufol UV-254 plates with a stationary silica gel layer. The preparative chromatography of the compounds was carried out on L 40/100 brand silica gel. The data of the elemental analyses for C, H, and N correspond to the calculated values.

N-Acetylnaphtho[2,3-f]indoline-5,10-dione (III) and N-Acetylnaphtho[2,3-e]indoline-4,9-dione (IV, C₁₈H₁₃NO₃). A mixture of 20 g (150 mmoles) of dry aluminum chloride and 4 g (68 mmoles) of sodium chloride is fused at 160°C, the melt is then cooled to 140°C, and a mixture of 2 g (13.5 mmoles) of phthalic anhydride and 2 g (12.7 mmoles) of N-acetylindoline is added to it. The temperature is raised to 180°C, and the mixture is held at this temperature for 3 min. The mixture thus formed is stirred vigorously with 300 ml of a saturated aqueous solution of oxalic acid, the precipitate is filtered, washed with water, and dried. The obtained mixture of compounds III and IV is purified by chromatography (silica gel, benzene-acetone, 9:1) and the two compounds are separated. Compound IV. R_F 0.44 (Silufol UV-254, benzene-acetone, 4:1). Yield 1.1 g (30%), mp 241-242°C (from alcohol). IR spectrum: 1340 (N-C), 1680 cm⁻¹ (C=O). UV spectrum, λ_{max} (log ϵ): 206 (4.154), 253 (4.362), 282 (4.179), 299 (4.179), 408 nm (3.742). M⁺ 291. Compound III. R_F 0.33 (Silufol UV-254, benzene-ace-

tone, 4:1). Yield 1.1 g (30%), mp 271-272°C (from alcohol). IR spectrum: 1340 (N-C), 1680 cm^{-1} (C=O). UV spectrum, λ_{max} (log ϵ): 204 (4.320), 244 (4.294), 299 (4.547), 385 nm (3.564).

Naphtho[2,3-f]indoline-5,10-dione (V, $\text{C}_{16}\text{H}_{11}\text{NO}_2$). A mixture of 0.6 g (2 mmoles) of compound III and 60 ml of concentrated HCl is boiled for 3 h. The reaction mixture is cooled to room temperature and aqueous ammonia is added to pH 8. The precipitate that separates is extracted with chloroform, the extract is washed with water, dried over CaCl_2 , and evaporated to dryness. Yield 0.49 g (95%), mp 280°C (from alcohol). IR spectrum: 1680 (C=O), 3380 cm^{-1} (N-H). UV spectrum, λ_{max} (log ϵ): 207 (4.238), 246 (4.320), 309 (4.268), 358 (3.726), 495 nm (3.450). M^+ 249.

Naphtho[2,3-e]indoline-4,9-dione (VI, $\text{C}_{16}\text{H}_{11}\text{NO}_2$) is obtained in a similar manner as compound V. Yield 97%, mp 200°C (from alcohol). IR spectrum: 1640 (C=O), 3370 cm^{-1} (N-H). UV spectrum λ_{max} (log ϵ): 207 (4.200), 248 (4.410), 262-272 (4.128), 312 (4.055), 370 (3.650), 500 nm (3.650). M^+ 249.

2-Anthraquinonyl Hydrazone of Ethyl Pyruvate (X, $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_4$). A 16-ml portion of concentrated HCl is added to a boiling solution of 4.46 g (20 mmoles) of 2-aminoanthraquinone in 150 ml of glacial acetic acid. The mixture obtained is cooled to 40°C, 6 g (87 mmoles) of NaNO_2 in 15 ml of water are added with stirring, and the mixture is stirred for another 30 min at 40°C. Excess of nitrous acid is decomposed by adding 3.75 g (63 mmoles) of urea, the mixture is filtered, and sodium acetate is added to the filtrate to pH 5. The solution is cooled to 0°C, 3 ml (20 mmoles) of methylacetoacetic ester in 12 ml of acetic acid are added, and the mixture obtained is allowed to stand for 2 h. The yellow precipitate of the hydrazone is filtered, washed with water, and dried. Yield 4.9 g (73%), mp 248°C (from chloroform). IR spectrum: 1235 (C-O-C), 1680, 1715 (C=O), 3310 cm^{-1} (N-H). PMR spectrum (CDCl_3): 7.90 (1H, d, 1-H, $J_{1,3} = 2.55$ Hz), 7.73 (1H dd, 3-H, $J_{1,3} = 2.55$, $J_{3,4} = 8.40$ Hz), 8.31 (1H, d, 4H, $J_{3,4} = 4.80$ Hz), 8.05 (1H, s, N-H), 2.19 (3H, s, CH_3), 4.36 (2H, q, CH_2 , $J_{\text{CH}_2\text{CH}_3} = 6.95$ Hz), 1.42 (3H, t, CH_3 , $J_{\text{CH}_2\text{CH}_3} = 6.95$ Hz), 7.7-8.3 ppm (4H, 5-, 6-, 7-, 8-H). M^+ 336.

2-Carbethoxynaphtho[2,3-f]indole-5,10-dione (XI) and 2-Carbethoxynaphtho[2,3-e]indole-4,9-dione (XII, $\text{C}_{19}\text{H}_{13}\text{NO}_4$). A mixture of 4 g (12 mmoles) of hydrazone X and 66 g of (PPA) is stirred for 5 min at 125°C. The reaction mixture is cooled to room temperature and poured into 200 ml of water. The precipitate that separates is filtered, washed with water, dried, and the mixture of compounds XI and XII obtained is purified by chromatography (silica gel, carbon tetrachloride-ethyl acetate, 10:1). Yield 1.1 g (29%) of a mixture of compounds XI and XII. Compound XII is separated by chromatography (silica gel, carbon tetrachloride-2-propanol, 10:1). Yield 0.6 g (16%), mp 240°C (from alcohol). IR spectrum: 1260 (C-O-C), 1690 (C=O), 3300 cm^{-1} (N-H). M^+ 319.

Compound XI is separated chromatographically on plates with a stationary layer of silica gel DC-Fertigplatten Kieselgel 40 F_{254} (carbon tetrachloride-2-propanol, 9:1). Compound XI was obtained in an amount of a few milligrams sufficient for PMR and mass spectra, mp 290°C (from alcohol). M^+ 319.

2-Carboxy[2,3-e]indole-4,9-dione (XIII, $\text{C}_{17}\text{H}_9\text{NO}_4$). A mixture of 1 g (3 mmoles) of compound XII in 50 ml of 10% alcoholic solution of KOH is boiled for 2 h. The mixture is cooled, poured into 200 ml of water, and acidified with 0.1 N HCl to pH 7. The precipitate that separated is filtered, washed with water, and dried. Yield 0.7 g (77%), mp 320°C (decomposition, from methanol). IR spectrum: 1680, 1720 (C=O), 3300 cm^{-1} (N-H). M^+ 291.

Naphtho[2,3-f]indole-5,10-dione (VII, $\text{C}_{16}\text{H}_9\text{NO}_2$). A 2-g portion of MnO_2 is added to a solution of 0.4 g (1.4 mmoles) of compound V in 100 ml of chloroform, and the mixture obtained is boiled for 30 min. The precipitate is filtered, washed with 50 ml of chloroform, the solutions are combined and evaporated to dryness. Yield 0.36 g (90%), mp 320°C (from alcohol). IR spectrum: 1680 (C=O), 3300 cm^{-1} (N-H). UV spectrum, λ_{max} (log ϵ): 210 (4.320), 248 (4.482), 294 (4.542), 416 nm (3.674). M^+ 247.

Naphtho[2,3-e]indole-4,9-dione (VIII, $\text{C}_{16}\text{H}_9\text{NO}_2$) is obtained in a similar way as compound VII. Yield 88%, mp 246°C (from alcohol). IR spectrum: 1675 (C=O), 3330 cm^{-1} (N-H). UV spectrum, λ_{max} (log ϵ): 218 (4.345), 250 (4.220), 286 (4.247), 407 nm (3.520). M^+ 247.

B. A mixture of 0.6 g (2 mmoles) of compound XIII, 20 ml of dimethylacetamide, 5 ml of acetylacetone, and 0.15 g (1 mmole) of CuCl_2 is boiled for 30 h. The reaction mixture is poured into 100 ml of cold water, the precipitate is filtered, dried, and purified by chromatography (silica gel, benzene-acetone, 9:1). Yield 0.22 g (43%), mp 246°C (from al-

cohol). Compound VII is identical to a sample from experiment A according to IR, UV, PMR, and mass spectra.

Naphtho[2,3-f]indole-5,10-dione (VII) and Naphtho[2,3-e]indole-4,9-dione (VIII). A. A 2-g portion (6 mmoles) of a mixture of compounds XI and XII (a 1:3 content of isomers according to PMR data) in 50 ml of 10% ethanolic solution of KOH is boiled for 2 h. The mixture is cooled, poured into 200 ml of cold water, and acidified with 0.1 N HCl to pH 7. The separated precipitate is filtered, washed with water, dried and recrystallized from acetic acid. The yield of the mixture of acids XIII and XIV is 1.82 g (77%).

A suspension of 0.8 g (2.7 mmoles) of a mixture of compounds XIII and XIV, 0.2 g (1.5 mmole) of CuCl_2 , 25 ml of dimethylacetamide and 5 ml of acetylacetone is boiled for 30 h. The reaction mixture is poured into 150 ml of cold water, the precipitate is filtered, dried, and purified by chromatography (silica gel, benzene-acetone, 9:1), and the residue after the removals of solvents, is recrystallized from alcohol. The yield of compound VII is 0.07 g (10%), mp 320°C (from alcohol). The yield of compound VIII is 0.23 g (34%), mp 246°C (from alcohol). Compounds VII and VIII are identical according to IR, UV, PMR, and mass spectra, to samples obtained before.

B. A mixture of 4 g (12 mmoles) of hydrazone X and 15 g (110 mmoles) of anhydrous zinc chloride is heated to 240°C and the mixture is left to stand at this temperature for 5 min. The melt is cooled to room temperature, and poured into water with vigorous stirring. The precipitate is filtered, washed with water, dried, dissolved in chloroform, and the solution mixed with 6 g of silica gel. The solvent is distilled off in vacuo, the precipitate is deposited on a column and eluted with benzene to yield 0.22 g (8%) of a mixture of compounds VII and VIII, which is partitioned by recrystallization from alcohol. The yield of compound VII is 0.06 g (2%), mp 320°C (from alcohol). The yield of compound VIII is 0.16 g (6%), mp 246°C (from alcohol). Compounds VII and VIII are identical to the obtained previous samples, according to IR, UV, PMR, and mass spectra.

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