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HETEROCYCLIC ANALOGS OF 5,12-NAPHTHACENEQUINONE

6.* SYNTHESIS OF 4,11-DIMETHOXY DERIVATIVES OF ANTHRA-[2,3-*b*]THIOPHENE-5,10-DIONE AND ANTHRA[2,3-*d*]ISOTHIAZOLE-5,10-DIONE

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Condensation of 2-formyl- or 2-cyano-3-chloro-1,4-dimethoxyanthraquinone with methyl thioglycolate in the presence of base gave methyl 4,11-dimethoxyanthra[2,3-b]thiophene-5,10-dione-2-carboxylate and its 3-amino derivative respectively. Hydrolysis of the ester group in methyl 4,11-dimethoxy-anthra[2,3-b]thiophene-5,10-dione-2-carboxylate and subsequent decarboxylation of the carboxylic acid formed gave 4,11-dimethoxyanthra[2,3-b]thiophene-5,10-dione. Condensation of 3-chloro-2-formyl-1,4-dimethoxyanthraquinone with ammonia in the presence of sulfur gave 4,11-dimethoxy-anthra[2,3-d]isothiazole-5,10-dione.

Keywords: 3-chloro-1,4-dimethoxyanthracene-9,10-dione-2-carbaldehyde, 4,11-dimethoxy-anthra[2,3-*d*]-isothiazole-5,10-dione, 4,11-dimethoxyanthra[2,3-*b*]thiophene-5,10-dione derivatives, fluorescence spectra, Stokes shift.

Annelation of a heterocyclic fragment with the anthraquinone chromophore significantly affects the photochemical properties of a compound hence the synthesis of heterocyclic analogs of naphthacenequinone and a study of the relationship between chemical structure and spectroscopic properties allows us to direct the synthesis of a compound with targeted spectroscopic and photochemical characteristics. It was found that derivatives of the heterocyclic analogs of naphthacenequinone containing α-alkoxy groups (e.g. 4,11-dimethoxy derivatives of naphtho[2,3-*f*]indazole-5,10-diones [2]) show fluorescence with large Stokes shift values. Continuing a systematic study of heterocyclic analogs of naphthacenequinone analogs we have prepared and studied the spectroscopic properties of the methoxy derivatives of several thio analogs of 5,12-naphtha-cenequinone.

Analysis of the literature data has shown that the most studied class of thio analogs of 5,12-naphtha-cenequinone are anthra[2,3-*d*]thiazole-5,10-diones amongst which series about 40 derivatives have been obtained up to this time. Anthra[2,3-*d*]thiazole-5,10-dione [3] itself and the majority of its derivatives have been patented as vat dyes, but latterly derivatives have found use as dichroic dyes for liquid crystals [4, 5] and its photochromic derivatives have been patented as active media for CD discs [6]. Anthra[2,3-*b*]thiophene-5,10-dione (of which seven derivatives [7-9] have been reported) and anthra[2,3-*d*]isothiazole-5,10-dione [10] have been studied less. The synthesis and study of the spectroscopic properties of derivatives of this series can have

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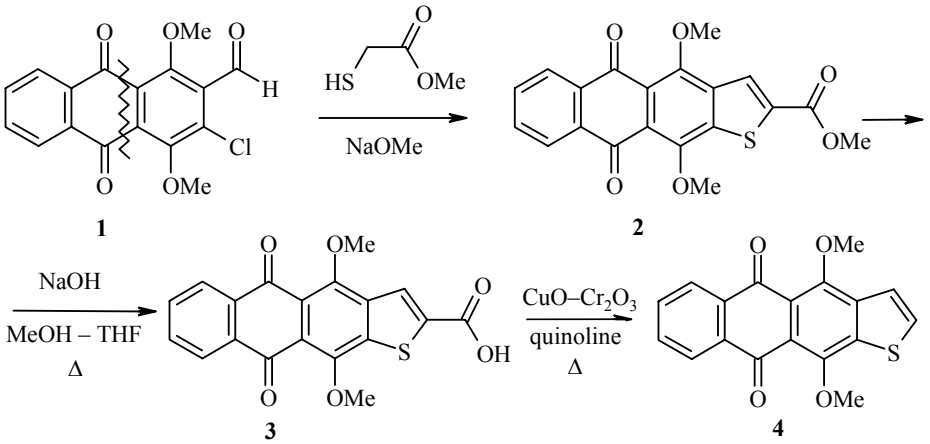
an importance in revealing the overall structure-activity relationship amongst heterocyclic analogs of 5,12-naphthacenequinone. Hence this investigation was connected with developing a method for the synthesis and study of the spectroscopic properties of the previously unknown 4,11-dimethoxy derivatives of anthra[2,3-*d*]isoxazole-5,10-dione and anthra[2,3-*d*]isothiazole-5,10-dione.

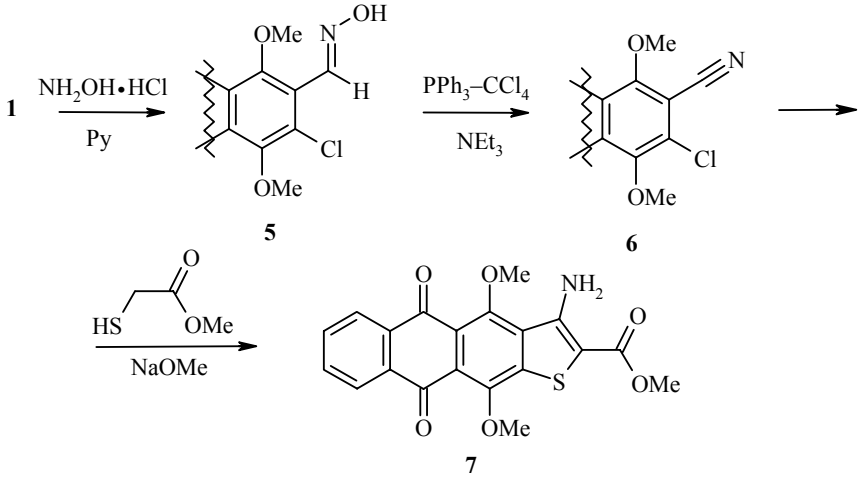
One of the convenient methods for the synthesis of benzothiophenes is the condensation of thiols with available aromatic carbonyl compounds containing a good leaving groups in the *ortho* position (e.g. halogens) [11, 12]. 3-chloro-2-formyl-1,4-dimethoxyanthraquinone (**1**) has been prepared before [13] hence we have studied the possible synthesis from it of 4,11-dimethoxy derivatives of anthra[2,3-*b*]thiophene-5,10-dione. Condensation of *ortho* chloroaldehyde **1** with methyl glycolate in the presence of base gave a high yield (89%) of methyl 4,11-dimethoxyanthra[2,3-*b*]thiophene-5,10-dione-2-carboxylate (**2**).



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

Hydrolysis of ester **2** gives the carboxylic acid **3**, decarboxylation of which using method [14] by refluxing in quinoline in the presence of copper chromite gave 4,11-dimethoxyanthra[2,3-*b*]thiophene-5,10-dione (**4**).

A further method for the synthesis of benzothiophenes is based on condensation of mercaptans with aromatic nitriles containing good leaving groups in the *ortho* position [15]. To realize this route the formyl group in compound **1** was converted to nitrile. In spite of the fact that aldehyde **1** reacts with powerful O-nucleophiles [13] or S-nucleophiles (as in the synthesis of anthrathiophenedione **2** with principal attack at the carbon atom bound to the halogen, the action of hydroxylamine occurs at the formyl group to give a high yield of the oxime **5**. Dehydration of the latter using the CCl_4-PPh_3 method [16] in the presence of NEt_3 gave the nitrile **6**. Like the aldehyde **1**, the nitrile **6** readily condenses with methyl thioglycolate in the presence of base to give methyl 3-amino-4,11-dimethoxyanthra[2,3-*b*]thiophene-5,10-dione-2-carboxylate (**7**) in high yield (85%).

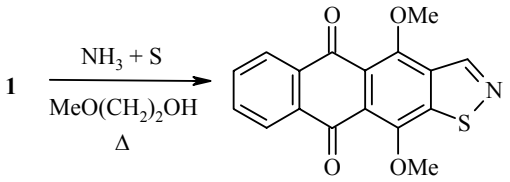


5 **6** **7**

TABLE 1. Electronic Absorption and Fluorescence Spectra of Thio-analogs of 5,12-Naphthacenequinone

Compound	λ_{max}, nm		$\Delta\lambda$, nm
	Absorption	Fluorescence	
2	401	565	164
3	406	554	148
4	400	549	149
7	470	582	112
8	392	549	157

An interesting method has been proposed for the synthesis of benzoisothiazoles based on condensation of aromatic carbonyl compounds containing an *ortho*-positioned halogen with ammonia in the presence of sulfur [10]. Similarly to the unsubstituted anthra[2,3-*b*]isothiazole-5,10-dione reported in this work we prepared 4,11-dimethoxyanthra[2,3-*d*]isothiazole-5,10-dione (**8**) from 3-chloro-2-formyl-1,4-dimethoxyanthraquinone (**1**), although in somewhat lower yield.



8

Comparison of the absorption spectra of 1,4-dimethoxyanthraquinone (λ_{max} 425 [17]) and the synthesized thioanalogs of naphthacenequinone **2-4,8** (λ_{max} 392-404 nm) shows that annelation of a thioarene leads to a hypsochromic shift of the long wavelength absorption maximum and this points to disturbance of the chain of conjugation between the carbonyl and methoxy groups of the chromophore. Introduction of an amino group into position 3 of the anthra[2,3-*b*]thiophene-5,10-dione causes a marked bathochromic shift of the long wavelength absorption band in the spectrum of **8** when compared with the spectrum of the 3-unsubstituted analog.

All of the naphthacenequinone thio analogs obtained show fluorescence in solutions and in the solid state. Study of the fluorescence spectra has shown that compounds **2-4,8** have large Stokes shift values (Table 1). These values are close to the results obtained for 4,11-dimethoxynaphtho[2,3-*f*]indazole-5,10-dione derivatives (147 nm) [2]. Comparison of the spectroscopic parameters for derivatives **2** and **7** shows that introduction of an amino group at position 3 of the anthra[2,3-*b*]thiophene-5,10-dione ring causes a decrease in the Stokes shift value of about 50 nm.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 and 100 MHz respectively) with TMS as internal standard. Mass spectra were recorded on a Finnigan-MAT SSQ 710 chromato mass spectrometer with an ionization energy of 70 eV, direct introduction of the sample into the ion source, sample heating to 350ºC, and an ionization chamber temperature of 150ºC. Absorption spectra were recorded on a Hitachi-U2000 spectrometer using EtOH and fluorescence spectra on Shimadzu RF-500 and Cary Eclipse (Varian) spectrofluorimeters. Monitoring of the course of the reaction and purity of the compounds was carried out by TLC on Silufol UV-254 plates. Preparative chromatography was performed on Merck 60 grade silica gel.

Methyl 4,11-Dimethoxyanthra[2,3-*b*]thiophene-5,10-dione-2-carboxylate (2). Methyl thioglycolate (0.3 ml, 3.3 mmol) was added with stirring to a solution of Na (0.05 g, 2.2 mmol) in MeOH (15 ml) under an argon atmosphere after which a solution of aldehyde **1** (400 mg, 1.2 mmol) in hot dioxane (50 ml) was added rapidly. The reaction mixture was stirred for 30 min and the precipitated solid was filtered off, washed with MeOH and water, and dried to give ester **2** (412 mg, 89%) as yellow crystals. Mp >250ºC (subl.). UV spectrum, λ_{max}, nm (log ε): 236 (4.0), 266 (4.4), 271 (4.4), 279 (4.4), 286 (4.4), (305), 401 (3.8). ^{1}H NMR spectrum (80ºC), δ, ppm: 8.31 (1H, s, H-3); 8.17 (2H, m, H-5,8); 7.89 (2H, m, H-6,7); 4.08 (3H, s, OCH_3); 4.07 (3H, s, OCH_3); 3.97 (3H, s, OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 382 $[M]^+$ (100), 353 (44), 323 (18), 293 (11), 265 (11), 237 (15). Found, %: C 62.90; H 3.76. $C_{20}H_{14}O_6S$. Calculated, %: C 62.82; H 3.69.

4,11-Dimethoxyanthra[2,3-*b*]thiophene-5,10-dione-2-carboxylic Acid (3). Ester **2** (350 mg, 0.9 mmol) was dissolved with refluxing in THF (300 ml), a solution of NaOH (200 mg, 5.0 mmol) in a mixture of methanol (50 ml) and water (20 ml) was added, and the product was refluxed with stirring for 10 min. The reaction product was evaporated to 20-30 ml and the solution obtained was neutralized with 5% HCl. The precipitate was filtered off, washed with water, and dried. Yield of acid **3** 317 mg (94%) as a yellow powder with mp >250ºC (subl.). UV spectrum, λ_{max}, nm (log ε): 231 (4.0), 263 (4.4), (284), 406 (3.7). ^{1}H NMR spectrum, δ, ppm: 8.18 (1H, s, H-3); 8.10 (2H, m, H-5,8); 7.87 (2H, m, H-6,7); 4.02 (6H, s, OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 368 $[M]^+$ (100), 339 (43), 321 (11), 265 (12), 219 (25). Found, %: C 61.99; H 3.34. $C_{19}H_{12}O_6S$. Calculated, %: C 61.95, H 3.28.

4,11-Dimethoxyanthra[2,3-*b*]thiophene-5,10-dione (4). Copper chromite (0.4 g, 1.3 mmol) was added to a solution of acid **3** (200 mg, 0.54 mmol) in quinoline (3 ml) and stirred for 30 min at reflux. The reaction mixture was poured into water and neutralized with 5% HCl and the precipitate was filtered off, washed with water, and dried. The residue was dissolved at reflux in a mixture of toluene and dioxane (1 : 1) and the hot solution was filtered through a layer of silica and evaporated to 5-7 ml. The precipitate was filtered off, recrystallized from DMSO, and the crystals formed were filtered off, washed with water, and dried *in vacuo* to give the anthrathiophene **4** (75 mg, 42%) as yellow, needle-like crystals with mp 193-195ºC. UV spectrum, λ_{max}, nm (log ε): 251 (4.4), 275 (4.3), (317), 400 (3.7). ^{1}H NMR spectrum (60ºC), δ, ppm (*J*, Hz): 8.12 (3H, d, H-3,5,8); 7.85 (2H, m, H-6,7); 7.75 (2H, d, *J* = 5.3, H-2); 4.03 (3H, s, OCH_3); 4.02 (3H, s, OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 324 $[M]^+$ (100), 295 (44), 265 (24), 253 (12). Found, %: C 66.46; H 3.76. $C_{18}H_{12}O_4S$. Calculated, %: C 66.65; H 3.73.

3-Chloro-1,4-dimethoxyanthracene-9,10-dione-2-carbaldehyde Oxime (5). Hydroxylamine hydrochloride (150 mg, 2.1 mmol) was added with stirring to a suspension of aldehyde **1** (400 mg, 1.2 mmol) in pyridine (20 ml) and the mixture obtained was stirred for 30 min and poured with stirring into a mixture of water (100 ml), ice (200 g), and conc. HCl (25 ml). The precipitate was filtered off, washed with water, dried, and recrystallized from toluene to give oxime **5** (397 mg, 95%) as yellow crystals with mp 226-228ºC. UV spectrum, λ_{max}, nm (log ε): 215 (4.3), 258 (4.4), (338), 367 (3.7). ^{1}H NMR spectrum (30ºC), δ, ppm: 11.95 (1H, s, OH); 8.26 (1H, s, CHN); 8.07 (2H, m, H-5,8); 7.87 (2H, m, H-6,7); 3.89 (3H, s, OCH_3); 3.82 (3H, s, OCH_3); ^{13}C NMR spectrum (30ºC), δ, ppm: 181.16 (C=O); 181.09 (C=O); 155.19*; 152.19; 135.13; 133.67; 133.53; 133.32; 127.75; 125.84; 142.45 (CHN); 134.05 (CH); 133.95 (CH); 126.10 (CH); 126.07 (CH); 62.59 (CH_3); 62.36 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 345 $[M]^+$ (100), 328 (51), 301 (22), 284 (38). Found, %: C 59.11; H 3.59; N 4.11. $C_{17}H_{12}ClNO_5$. Calculated, %: C 59.06; H 3.50; N 4.05.

3-Chloro-1,4-dimethoxyanthracene-9,10-dione-3-carbonitrile (6). Nitrile **5** (300 mg, 0.9 mmol) was dissolved with refluxing in acetonitrile. The solution was cooled to room temperature and Et_3N (0.3 ml, 2.3 mmol), CCl_4 (1.0 ml, 10.4 mmol), and triphenylphosphine (300 mg, 1.1 mmol) were added with stirring. After 30 min the reaction product was diluted with an equivalent volume of petroleum ether and the precipitate of Ph_3PO was filtered off. The filtrate was diluted with EtOAc and the solution was washed with 5% HCl,

* Here and subsequently all of the unassigned signals are from quaternary carbon atoms.

water, dried, and evaporated. The residue was purified by column chromatography on silica (eluent toluene-ethyl acetate, 5 : 1). Recrystallization from toluene gave the nitrile **6** (207 mg, 73%) as yellow crystals with mp 241-243ºC. ^{1}H NMR spectrum (30ºC), δ, ppm: 8.12 (2H, m, H-5,8); 7.91 (2H, m, H-6,7); 4.06 (3H, s, OCH_3); 3.96 (3H, s, OCH_3). ^{13}C NMR spectrum (30ºC), δ, ppm: 180.48 (C=O); 179.83 (C=O); 158.24: 151.87; 137.40; 132.98; 132.90; 131.12; 126.22; 115.11; 111.83; 133.91 (CH); 133.83 (CH); 125.88 (CH); 125.78 (CH); 62.78 (CH_3); 61.44 (CH_3). Mass spectrum, *m/z* (I_{rel}, %): 327 $[M]^+$ (100), 310 (22), 298 (28), 284 (41), 263 (21), 255 (19). Found, %: C 62.44; H 3.13. $C_{17}H_{10}ClNO_4$. Calculated, %: C 62.30; H 3.08; N 4.27.

Methyl 3-Amino-4,11-dimethoxyanthra[2,3-*b*]thiophene-5,10-dione-2-carboxylate (7) was prepared from nitrile **6** and methyl thioglycolate similarly to ester **2**. Yield of ester **7** 85% as orange-red crystals with mp >250ºC. UV spectrum, λ_{max}, nm (log ε): 274 (4.4), (309), 470 (3.7). ^{1}H NMR spectrum (60ºC), δ, ppm: 8.16 (2H, m, H-5,8); 7.90 (2H, m, H-6,7); 7.08 (2H, m, NH_2); 4.03 (3H, s, OCH_3); 4.00 (3H, s, OCH_3); 3.86 (3H, s, OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 397 $[M]^+$ (100), 382 (18), 350 (19), 336 (20), 308 (11). Found, %: C 60.55; H 3.93; N 3.61. $C_{20}H_{15}NO_6S$. Calculated, %: C 60.45; H 3.80; N 3.52.

4,11-dimethoxyanthra[2,3-*d*]isothiazole-5,10-dione (8). A mixture of aldehyde **1** (200 mg, 0.6 mmol), aqueous ammonia (25%, 0.2 ml, 1.1 mmol), and powdered sulfur (32 mg, 1.0 mmol) in methyl cellosolve (2 ml) was heated in a sealed ampule with vigorous stirring (magnetic stirrer) at 100ºC and held for 20 min. The reaction mixture was cooled, diluted with water, and extracted with EtOAc. The extract was washed with water, dried over sodium sulphate, and evaporated. The residue was purified chromatographically (silica gel, benzene-EtOAc, 10 : 1) to give the anthraisothiazole **8** (84 mg, 43%) as yellow crystals with mp 228-230ºC (a mixture benzene and hexane, 1 : 2). UV spectrum, λ_{max}, nm (log ε): 252 (4.4), 308 (3.3), 392 (3.6). ^{1}H NMR spectrum, δ, ppm: 9.22 (1H, s, H-3); 8.26 (2H, m, H-5,8); 7.79 (2H, m, H-6,7); 4.21 (3H, s, OCH_3); 4.19 (3H, s, OCH_3). Mass spectrum, *m/z* (I_{rel}, %): 325 $[M]^+$ (100), 310 (11), 296 (44), 282 (25), 266 (24), 254 (15). Found, %: C 62.81; H 3.55; N 4.22. $C_{17}H_{11}NO_4S$. Calculated, %: C 62.76; H 3.41; N 4.31.

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