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SYNTHESIS AND FUNCTIONALIZATION OF 7-HYDROXYANTHRA[2,1-*b*]BENZO[*d*]FURAN-8,13-DIONES

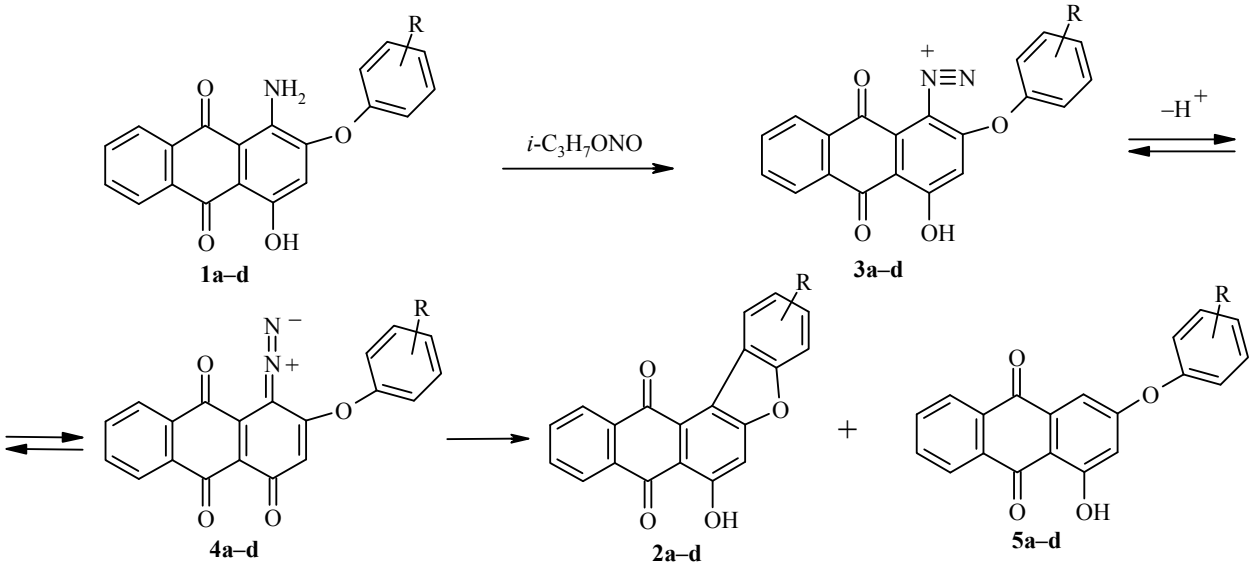
L. M. Gornostaev[1]*, E. V. Arnold[1], E. V. Lykova[1], and M. V. Sadoschenko[1]

The diazotization of 1-amino-2-aryloxy-4-hydroxy-9,10-anthraquinones in various solvents and subsequent heating of the diazotization products lead to 7-hydroxyanthra[2,1-b]benzo[d]furan-8,13-diones. When consecutively treated with benzenesulfonyl chloride and amines, the products form 7-aminoanthra[2,1-b]benzo[d]furan-8,13-diones.

Keywords: anthraquinones, benzofurans, quinone diazide, diazotization.

Oxygen-containing heterocyclic derivatives of 9,10-anthraquinone of natural and synthetic origin are promising for practical use as antitumor preparations [1, 2].

There are relatively few methods for the production of 9,10-anthraquinones condensed with a furan ring at positions 1 and 2. A method for the production of anthra[2,1-*d*]-4-*tert*-butylbenzo[*b*]furan-8,13-dione as a result of the photolysis of a solution of 2-diazo-1-(4-*tert*-butylphenoxy)-9,10-anthraquinone was described in



1, 3–5 a R = H, **b** R = 4-*t*-Bu, **c** R = 4-Cl, **d** R = 2-Me

* To whom correspondence should be addressed, e-mail: gornostaev@kspu.ru.

[1]V. P. Astaf'ev Krasnoyarsk State Pedagogical University, Krasnoyarsk 660049, Russia.

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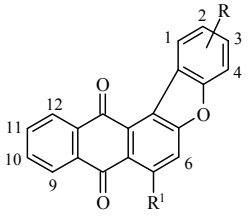
[3]. In [4] certain anthra[2,1-*b*]furan-6,11-diones, obtained by nucleophilic substitution of hydrogen or halogen in 2,3-dichloro-1,4-dihydroxyanthraquinone by the action of the carbanions generated from CH-acids (cyanoacetic ester or malononitrile) followed by cyclization of the substitution products, were described. Anthra[2,1-*b*]benzo[*d*]furan-8,13-dione was synthesized by the reaction of dibenzofuran with phthalic acid or phthalic anhydride [5].

We developed a method for the production of 7-hydroxyanthra[2,1-*b*]benzo[*d*]furan-8,13-diones on the basis of the readily obtainable [6] 1-amino-2-aryloxy-9,10-anthraquinones **1a-d**.

The amines **1a-d** were diazotized with isopropyl nitrite in acetic acid or in an aprotic solvent (DMSO) at 20-25°C. The obtained diazotized products were heated, without isolation, to 50-90°C. Cyclization to 7-hydroxyanthra[2,1-*b*]benzo[*d*]furan-8,13-diones **2** with the release of nitrogen occurred here with yields of 60-80%. It is likely that the precursors of the benzofurans **2a-d** are both diazo compounds **3a-d** and quinone diazides **4a-d**. In a separate experiment we isolated and identified 4-diazo-3-phenoxyanthracene-1,9,10(4H)-trione (**4a**).

TABLE 1. The ^{1}H NMR Spectra of 7-R-Anthra[2,1-*b*]benzo[*d*]furan-8,13-diones **2** and **8**



2a–d R^1 = OH, **a** R = H, **b** R = 2-*t*-Bu, **c** R = 2-Cl, **d** R = 4-Me; **8a–d** R = H, **a** $R^1 = N(CH_2CH_2)_2O$, **b** $R^1 = N(CH_2)_5$, **c** $R^1 = NHCH(CH_2)_5$, **d** R^1 = NHBn

Compound	Chemical shifts,* δ, ppm (*J*, Hz)
2a	7.55 (1H, t, *J* = 8.0, H-2); 7.65 (1H, t, *J* = 8.0, H-3); 7.66 (1H, s, H-6); 7.68 (1H, d, *J* = 8.0, H-4); 7.78–8.22 (2H, m, H-10,11); 8.34 (1H, d, *J* = 8.0, H-9,12); 8.36 (1H, d, *J*= 8.0, H-9,12); 9.20 (1H, d, *J* = 8.0, H-1); 13.5 (1H, s, OH)
2b	1.45 (9H, s, $3CH_3$); 7.47 (1H, s, H-6); 7.52 (1H, d, *J* = 8.0, H-4); 7.67 (1H, d, *J* = 8.0, H-3); 7.88 (2H, br. s, H-10,11); 8.12 (1H, br. s, H-9,12); 8.16 (1H, br. s, H-9,12); 9.2 (1H, s, H-1); 13.4 (1H, s, OH)
2c	7.69 (1H, d, *J* = 6.0, H-4); 7.71 (1H, s, H-6); 7.79 (1H, br. d, *J* = 8.0 H-3); 8.00 (2H, br. t, *J* = 6.0, H-10,11); 8.32 (1H, br. d, *J* = 6.0, H-9,12); 8.38 (1H, br. d, *J* = 6.0, H-9,12); 9.25 (1H, s, H-1); 13.25 (1H, s, OH)
2d	2.45 (3H, s, CH_3); 7.39 (1H, t, *J* = 8.0, H-2); 7.48 (1H, d, *J* = 8.0, H-3); 7.71 (1H, s, H-6); 7.95-8.02 (2H, m, H-10,11); 8.28 (1H, d, *J*= 6.0, H-9,12); 8.31 (1H, d, *J*= 6.0, H-9,12); 9.03 (1H, d, *J* = 8.0, H-1); 13.4 (1H, s, OH)
8a	3.23 (4H, t, *J* = 4.0, 2',6'-CH_2); 3.88 (4H, t, *J* = 4.0, 3',5'-CH_2); 7.48 (1H, t, *J* = 8.0, H-2); 7.62 (1H, t, *J* = 7.0, H-3); 7.73 (1H, d, *J* = 7.0, H-4); 7.81 (1H, s, H-6); 7.86-7.94 (2H, m, H-10,11); 8.18 (1H, d, *J* = 7.0, H-9,12); 8.24 (1H, d, *J* = 7.0, H-9,12); 9.05 (1H, d, *J* = 8.0, H-1)
8b	1.64-1.69 (2H, m, 4'-CH_2); 1.76-1.81 (4H, m, 3',5'-CH_2); 3.20-.24 (4H, m, 2',6'-CH_2); 7.46 (1H, t, *J* = 7.0, H-2); 7.59 (1H, t, *J* = 7.0, H-3); 7.69 (1H, d, *J* = 7.0, H-4); 7.75 (1H, s, H-6); 7.85-7.93 (2H, m, H-10,11); 8.18 (1H, d, *J* = 7.0, H-9,12); 8.25 (1H, d, *J* = 7.0, H-9,12); 9.05 (1H, d, *J* = 7.0, H-1)
8c	1.34–2.11 (10H, m, 2',3',4',5',6'-CH_2); 3.51 (1H, br. s, H-1'); 7.03 (1H, s, H-6); 7.33 (1H, t, *J* = 7.0, H-2); 7.38-7.48 (2H, m, H-3,4); 7.68 (1H, t, *J* = 7.0, H-10,11); 7.72 (1H, t, *J* = 7.0, H-10,11); 8.23 (1H, d, *J* = 8.0, H-9,12); 8.25 (1H, d, *J* = 8.0, H-9,12); 9.15 (1H, d, *J* = 7.0, H-1); 10.31 (1H, d, *J* = 6.0, NH)
8d	4.54 (2H, d, *J* = 5.0, CH_2); 6.93 (1H, s, H-6); 7.27-7.44 (8H, m, H-2,3,4,2',3',4',5',6'); 7.66-7.73 (2H, m, H-10,11); 8.21 (1H, d, *J*= 7.0, H-9,12); 8.24 (1H, d, *J*= 7.0, H-9,12); 9.13 (1H, d, *J* = 8.0, H-1); 10.53 (1H, br. s, NH)

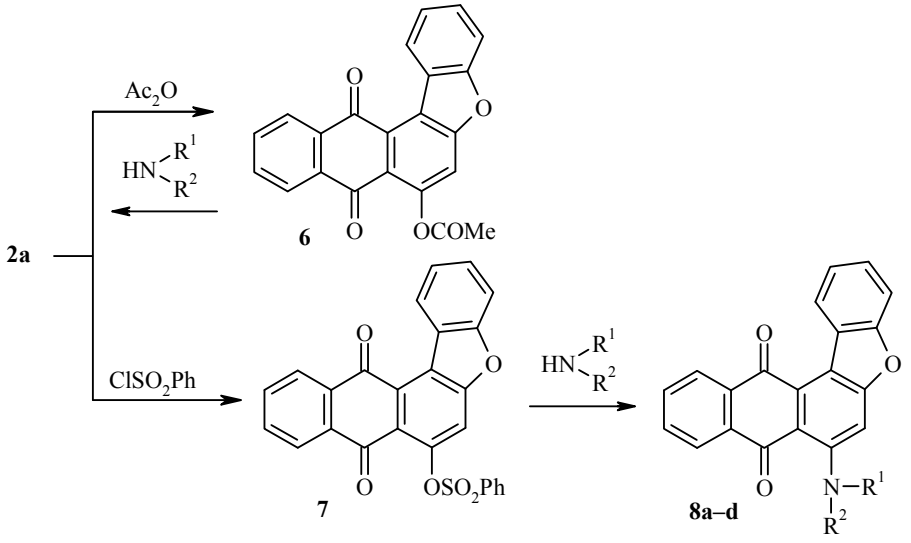
* The ^{1}H NMR spectra were obtained in DMSO-d_6 (compounds **2a-d**, **8a**,**b**) and in $CDCl_3$ (compounds **8c**,**d**).

Side products – 3-aryloxy-1-hydroxy-anthracene-9,10-diones **5a-d** – are formed with smaller yields together with the benzofurans **2a-d**, and we confirmed this for the case of compound **1a**.

The cyclization of the diazo compounds **4** to the benzofurans **2** can also be realized by photochemical means (see Experimental) but without any advantages compared with the thermal method.

In the ^{1}H NMR spectra compounds **2a-d** (Table 1) the signal of the H-1 proton is in the downfield region (9.0-9.2 ppm), which is apparently due to the anisotropic effect of the carbonyl group.

We studied the possibility of modifying compounds **2a-d** by substituting the hydroxyl group by amines. Direct substitution of the hydroxyl group by amines was not observed even under rigorous conditions (boiling in DMF). The product from the acetylation of 7-hydroxyanthra[2,1-*b*]benzo[*d*]furan-8,13-dione (**2a)**, i.e., 7-acetoxyanthra[2,1-*b*]benzo[*d*]furan-8,13-dione (**6**), is converted by the action of amines into the initial furan **2a**. At the same time the product from benzenesulfonylation, 8,13-dioxo-8,13-dihydroanthra-[2,1-*b*]benzo-[*d*]furan-7-benzenesulfonate (**7**), reacted when heated with amines by nucleophilic substitution of the benzene-sulfonate ion.



8 a $R^1+R^2 = (CH_2CH_2)_2O$; **b** $R^1+R^2 = (CH_2)_5$; **c** $R^1 = H$, $R^2 = CH(CH_2)_5$; **d** $R^1 = H$, $R^2 = Bn$

In this way, we developed convenient approaches to a difficultly obtainable group of heterocyclic derivatives of 9,10-anthraquinone having potential biological activity.

EXPERIMENTAL

The ^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer (500 MHz) with TMS as internal standard. The reactions and the individuality of the obtained compounds were monitored by TLC on Silufol UV-254 plates. The melting points were determined on Boetius apparatus.

7-Hydroxyanthra[2,1-*b*]benzo[*d*]furan-8,13-dione (2a) and 1-Hydroxy-3-phenoxy-9,10-anthra-quinone (5a). To a mixture of the amine **1a** (0.99 g, 3 mmol) in acetonitrile (6 ml), we added with stirring isopropyl nitrite (1 ml) at 20°C. The mixture was kept for 30 min and heated at 90°C for 30-60 min. After cooling the precipitate was filtered off, washed with ethanol, dried, and chromatographed on a column of silica gel with toluene as eluent. We obtained compound **2a** (Table 2). The filtrate was poured onto ice, and the precipitate was filtered off and dried. The product was then chromatographed on a column of silica gel with toluene as eluent, and compound **5a** was obtained. The yield 0.26 g (27%); mp 154°C. ^{1}H NMR spectrum

TABLE 2. The Physicochemical Characteristics of Anthra[2,1-*b*]benzo-[*d*]furan-8,13-diones **2** and **8**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{20}H_{10}O_4$	76.23 / 76.43	3.23 / 3.18		251-252	68
2b	$C_{24}H_{18}O_4$	77.78 / 77.84	4.86 / 4.86		232	52
2c	$C_{20}H_9ClO_4$*	69.13 / 68.87	2.54 / 2.58		335	65
2d	$C_{21}H_{12}O_4$	77.05 / 76.83	3.56 / 3.66		230	68
8a	$C_{24}H_{17}NO_4$	75.11 / 75.20	4.34 / 4.43	3.68 / 3.66	211	69
8b	$C_{25}H_{19}NO_3$	78.81 / 78.74	4.95 / 4.99	3.92 / 3.67	227	63
8c	$C_{26}H_{21}NO_3$	79.03 / 79.19	5.30 / 5.33	3.80 / 3.55	193-194	73
8d	$C_{27}H_{17}NO_3$	79.80 / 80.40	4.13 / 4.22	3.70 / 3.47	196	68

* Found, %: Cl 9.90. Calculated, %: 10.19.

(DMSO-d_6), δ, ppm (*J*, Hz): 6.82 (1H, d, *J* = 3.0, H-3); 7.15 (1H, d, *J* = 3.0, H-1); 7.25 (2H, d, *J* = 7.0, H-3',5'); 7.36 (1H, t, *J* = 7.0, H-4'); 7.53-7.56 (2H, m, H-2',6'); 7.91-7.98 (2H, m, H-6,7); 8.16 (1H, d, *J* = 7.0, H-5,8); 8.24 (1H, d, *J* = 7.0, H-5,8); 12.6 (1H, br. s, OH). Found, %: C 76.07; H 3.81. $C_{20}H_{12}O_4$. Calculated, %: C 75.95; H 3.80.

Compounds **2b-d** were obtained similarly (Tables 1 and 2).

4-Diazo-3-phenoxyanthracene-1,9,10(4H)-trione (4a). To a mixture of the amine **1a** (0.99 g, 3 mmol) in acetonitrile (6 ml), we added isopropyl nitrite (1 ml). The reaction mixture was stirred at 20°C for 40 min, and the precipitate was filtered off, washed with ethanol, and dried. The yield 0.52 g (50%); mp 148°C (benzene). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 5.58 (1H, s, H-3); 7.33 (2H, d, *J* = 8.0, H-3',5'); 7.39 (1H, t, *J* = 8.0, H-4'); 7.55 (2H, t, *J* = 8.0, H-2',6'); 7.87 (1H, t, *J* = 8.0, H-6,7); 7.95 (1H, t, *J* = 8.0, H-6,7); 8.05 (1H, d, *J* = 7.0, H-5,8); 8.10 (1H, d, *J* = 7.0, H-5,8). Found, %: C 70.02; H 3.34; N 7.04. $C_{20}H_{10}N_2O_4$. Calculated, %: C 70.18; H 2.92; N 8.19.

Photochemical Synthesis of 7-Hydroxyanthra[2,1-*b*]benzo[*d*]furan-8,13-dione (2a). A solution of the diazo compound **4a** (0.10 g, 0.3 mmol) in benzene (800 ml) was exposed to the full spectrum of a DRL-400 mercury lamp at a distance of 30-40 cm at 20-25°C for 6 h until the release of nitrogen had stopped. The solvent was distilled to a volume of 30 ml under vacuum. The precipitate was filtered off, dried, and chromatographed on a column of silica gel with toluene as eluent. The yield 0.06 g (67%).

8,13-Dioxo-8,13-dihydroanthra[2,1-*b*]benzo[*d*]furan-7-acetate (6). To a mixture of compound **2a** (0.94 g, 3 mmol), we added acetic anhydride (10 ml) and conc. H_2SO_4 (0.1 g). The mixture was stirred at 20°C for 2 h. It was then poured onto ice, and the precipitate was filtered off and dried. The yield 0.99 g (88%); mp 249-250°C (toluene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.46 (3H, s, CH_3); 7.55 (1H, t, *J* = 8.0, H-2); 7.71 (1H, t, *J* = 8.0, H-3); 7.82 (1H, d, *J* = 8.0, H-4); 7.91-7.96 (2H, m, H-10,11); 8.10 (1H, s, H-6); 8.12-8.14 (1H, m, H-9,12); 8.25-8.27 (1H, m, H-9,12); 9.22 (1H, d, *J* = 8.0, H-1). Found, %: C 74.11; H 3.27. $C_{22}H_{12}O_5$. Calculated, %: C 74.16; H 3.37.

8,13-Dioxo-8,13-dihydroanthra[2,1-*b*]benzo[*d*]furan-7-benzenesulfonate (7). To a mixture of compound **2a** (0.94 g, 3 mmol) in pyridine (6 ml), we added benzenesulfonyl chloride (12 ml, 94 mmol) at 20°C. The mixture was stirred at 90°C for 4 h. After cooling the precipitate was filtered off, washed with ethanol, and dried. The yield 1.23 g (85%); mp 208°C (toluene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz):

7.55-7.61 (2H, m, H-3,4); 7.58 (1H, s, H-6); 7.70-7.76 (2H, m, H-10,11); 7.84-7.94 (7H, m, H-2,9,2',3',4',5',6'); 8.20-8.22 (1H, m, H-12); 9.22 (1H, br. d, J = 7.0, H-1). Found, %: C 67.42; H 2.99; S 7.09. $C_{26}H_{14}O_6S$. Calculated, %: C 68.72; H 3.08; S 7.05.

7-Aminoanthra[2,1-*b*]benzo[*d*]furan-8,13-diones (8a-d). To compound **7** (1 mmol) in DMF (3 ml) at 20°C we added the amine (3 mmol). The mixture was stirred at 90-100°C for 40-60 min. After cooling the precipitate was filtered off , washed with ethanol, dried, and chromatographed on a column of silica gel with toluene or benzene as eluent (Tables 1 and 2).

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