Synthesis of substituted benz[*g*]indole-6,9-diones and benzo[*h*]quinoline-7,10-diones by heterocyclization of 6-alkynyl-5-amino-1,4-naphthoquinones

*E. A. Yakovleva, I. D. Ivanchikova, and M. S. Shvartsberg**

Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 3 ul. Institutskaya, 630090 Novosibirsk, Russian Federation. Fax: +7 (383 3) 30 7350. E-mail: shvarts@ns.kinetics.nsc.ru

Substituted benz[*g*]indole-6,9-diones were synthesized by intramolecular cyclization of 6-alkynyl-5-amino-3-diethylamino-1,4-naphthoquinones. A method was developed for the preparation of 2-aryl(or alkyl)-4,9-bis(dialkylamino)benzo[*h*]quinoline-7,10-diones, which involves the addition of a secondary amine to 6-acylethynyl-5-amino-3-diethylamino-1,4-naphthoquinone followed by cyclization of the resulting adduct.

Key words: 6-alkynyl-5-amino-3-diethylamino-1,4-naphthoquinones, heterocyclization, benz[*g*]indole-6,9-diones, 2-aryl(or alkyl)-4,9-bis(dialkylamino)benzo[*h*]quinoline-7,10-diones.

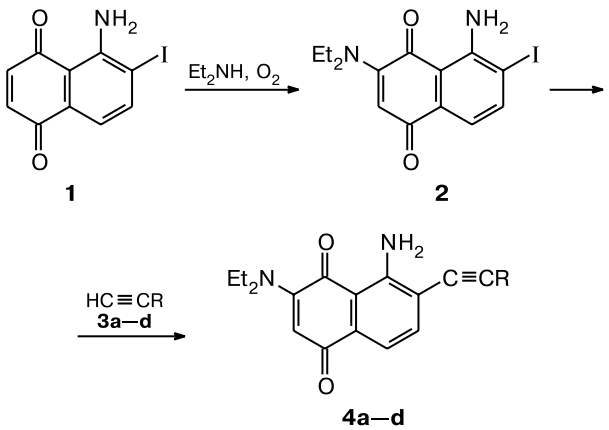
High biological activity of many fused heterocyclic quinone derivatives constantly stimulates researchers to develop procedures for the synthesis of new compounds of this class, study their chemical transformations, and search for new promising pharmacophoric structures.[1—3]

Earlier,[4—8] we have synthesized various N-, O-, and S-containing heterocycles fused to quinones with the use of alkynyl derivatives of anthraquinone as the key precursors. The procedures for the preparation of alkynyl derivatives of naphthoquinone are poorly developed, and these compounds have been used for this purpose only in rare cases.[9—11] It should be noted that heterocyclization of alkynylnaphthoquinones often follows a pathway different from that observed for the analogous reactions of anthraquinone derivatives.[10,12,13] Hence, methods of heterocyclization of alkynylanthraquinones cannot *a priori* be extended to the synthesis of naphthoquinone derivatives.

In the present study, we propose a method for synthesizing previously unknown heterocyclic systems fused to quinones, *viz.*, benz[*g*]indole-6,9-diones and benzo[*h*]quinoline-7,10-diones, by cyclization of 6-alkynyl-5-aminonaphthoquinones.

To prepare the key alkynyl compounds, the starting 5-amino-6-iodo-1,4-naphthoquinone (**1**) was subjected to oxidative amination with diethylamine (Scheme 1). Due to the strong orientation effect of the amino group at position 5,[14] the diethylamino group was directed predominantly at position 3. The yield of 5-amino-3-diethylamino-6-iodonaphthoquinone (**2**) was 89%. The corresponding 2-diethylamino isomer was formed in minor amount. It was necessary to block the quinonoid ring to avoid competitive reactions with nucleophiles in subsequent steps. Condensation of iodide **2** with terminal acetylenes **3a—d** was carried out in aqueous dioxane in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and Na_2CO_3. This modification of cross-coupling, which has been initially proposed for iodoanthraquinones,[15] proved to be also applicable to iodonaphthoquinones containing the protected quinonoid ring.[13] 6-Alkynyl-5-amino-3-diethylaminonaphthoquinones **4a—d** were prepared in 80—95% yields.

Scheme 1



4a—d

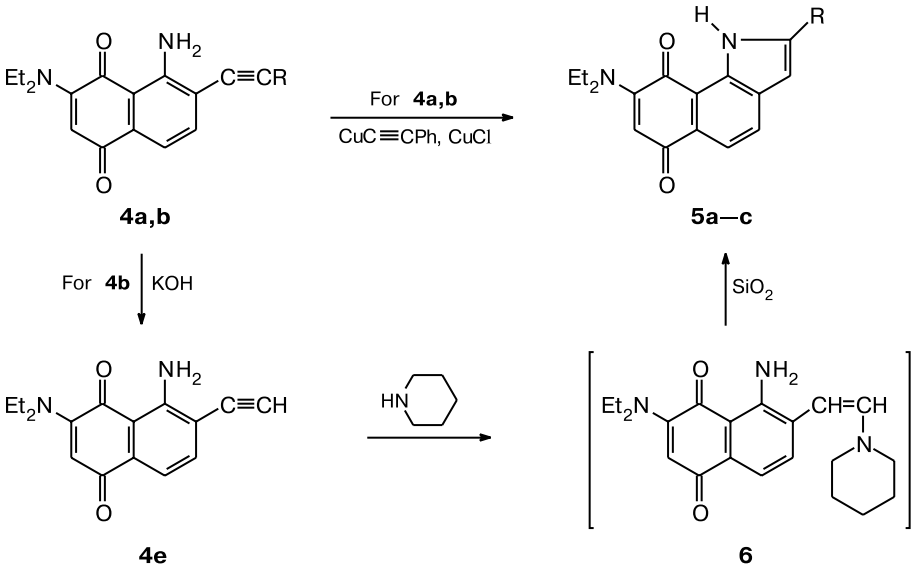
R = Ph (**a**), C(OH)Me_2 (**b**), CH(OH)Ph (**c**), CH(OH)$CHMe_2$ (**d**)

The possibility of the pyrrole ring closure in *vic*-(alkynyl)aminonaphthoquinones **4** giving rise to sub-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 412—418, February, 2005.

1066-5285/05/5402-0421

Scheme 2



R = Ph (**4a**, **5a**), C(OH)Me_2 (**4b**), H (**4e**, **5b**), $CMe{=}CH_2$ (**5c**)

stituted benz[*g*]indole-6,9-diones **5** was exemplified by cyclization of phenylethynyl derivative **4a**, tertiary acetylenic alcohol **4b**, and ethynyl derivative **4e** (Scheme 2). Compound **4e** was prepared by alkaline cleavage of alcohol **4b** (the retro-Favorskii reaction).[5]

Aminoacetylenes **4a,b** were subjected to cyclization in DMF in the presence of PhC≡CCu and CuCl[16] at 155 °C for 4.5—5 h. The yield of 2-phenylbenzindoledione **5a** was as high as 83%. Cyclization of alcohol **4b** was accompanied by dehydration and gave isopropenylbenzindoledione **5c** instead of the expected 2-(1-hydroxy-1-methylethyl)-8-diethylaminobenz[*g*]indole-6,9-dione as the major product (55% yield).

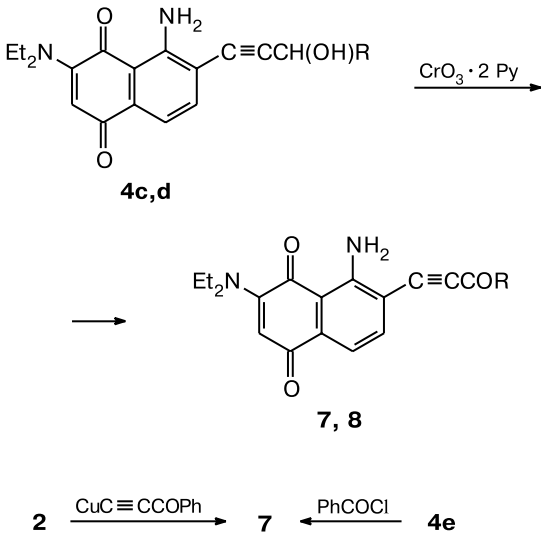
Earlier,[16,17] it has been demonstrated that the pyrrole ring closure in *vic*-(alkynyl)aminoanthraquinones can be performed in the absence of Cu^I compounds and, what is more important, under much milder conditions. This process involves the nucleophilic addition of a secondary amine at the triple bond, which is highly electrophilic in these compounds, followed by cyclization of the adduct in the presence of mineral acids or on SiO_2.

We extended this method to naphthoquinone derivatives. The addition of piperidine to ethynylnaphthoquinone **4e** occurred at 70 °C during 3.5 h to give adduct **6**. Being adsorbed on SiO_2 in $CHCl_3$, adduct **6** underwent cyclization with elimination of piperidine to form 8-diethylaminobenz[*g*]indole-6,9-dione (**5b**) in 80% yield.

Thus, cross-coupling of 5-amino-3-diethylamino-6-iodonaphthoquinone with terminal acetylenes followed by heterocyclization of the resulting acetylenic derivatives provides a convenient route to substituted benz[*g*]indole-6,9-diones.

In intramolecular cyclization giving rise to six-membered heterocycles, *vic*-functionalized acylethynyl derivatives can serve as precursors.[6,7,18] Hence, to prepare naphthoquinones angularly annelated to the pyridine ring, we oxidized secondary alcohols **4c,d** with the Collins reagent at 20 °C to ketones **7** and **8** (Scheme 3) in 94 and 78% yields, respectively.

Scheme 3



R = Ph (**4c**, **7**), $CHMe_2$ (**4d**, **8**)

In addition, ketone **7** was synthesized by condensation of iodide **2** with cuprous benzoylacetylide[19] and by

benzoylation of ethynylnaphthoquinone **4e**.[20] Unfortunately, the acetylide method is applicable only in certain cases because of instability of many acylacetylides. As for catalytic acylation, it is complicated by side reactions and gives products in low yields.

The simplest procedure for the closure of the nitrogen-containing six-membered ring in such compounds, including anthraquinones, is based on cyclization under conditions of hydration of the triple bond.[21]

We attempted to perform cyclization of ketone **7** to the corresponding benzo[*h*]quinolinetrione. To avoid hydrolysis of the diethylamino group, one had to carry out the reaction in dioxane in the presence of $HgSO_4$ and small amounts of 45% H_2SO_4 (1.5% v/v). However, even under these conditions, only hydrolysis of compound **7** occurred to give 5-amino-6-benzoylethynyl-3-hydroxy-1,4-naphthoquinone (**9**), whereas no heterocyclic ring closure was observed. We failed to perform cyclization of hydroxynaphthoquinone **9** by increasing the H_2SO_4 concentration and changing the amount of the mercury catalyst.

A more efficient approach to the construction of the benzo[*h*]quinoline system based on ketones **7** and **8** involves cyclization of aminovinyl ketones, which are prepared by the addition of amines to acetylenic ketones.[18] The formation of adducts leads to changes in the geometry of the unsaturated substituent and, as a consequence, to a decrease in the distance between the reaction centers necessary for the heterocyclic ring closure.

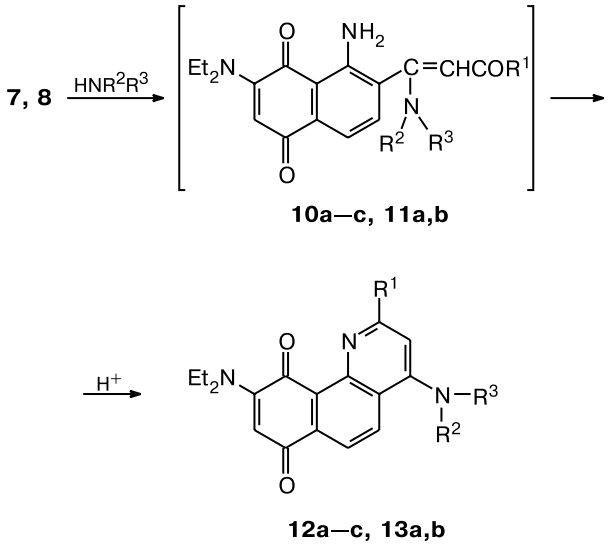
The reactions of acetylenic ketones **7** and **8** with an excess of amine at 20 °C afforded adducts **10a—c** and **11a,b**, which were subjected to cyclization in a biphasic system benzene—12% HCl (Scheme 4).

The yields of substituted benzo[*h*]quinoline-7,10-diones **12a—c** and **13a,b** were 50—90%. No complications associated with hydrolysis of the diethylamino group were observed.

Thus, the method of the construction of the 4-amino-substituted pyridine ring, which involves the vicinal amino- and acylethynyl groups and proceeds *via* the aminovinyl adducts, was extended to naphthoquinone derivatives. This made it possible to prepare substituted benzo[*h*]quinoline-7,10-diones, thus extending the range of compounds, which, like related anthraquinone derivatives, serve as chelating and potentially biologically active compounds.[22,23]

The characteristic differences observed in the ^{1}H NMR spectra of alkynylnaphthoquinones **4**, **7**, and **8**, benz[*g*]indole-6,9-diones **5**, and benzo[*h*]quinoline-7,10-diones **12** and **13** can be used to make assignments of the structures (Tables 1 and 2). The chemical shifts of the protons of the benzenoid ring slightly increase in the series **4**, **7**, **8** → **5** → **12**, **13** (δ 7.3—7.8, 7.8—7.9, and 8.0—8.4, respectively). The involvement of the N atom of the primary amino groups in acetylenic compounds **4**, **7**, and **8** in ring systems brings about a downfield shift of the signal for the proton in the *para* position of the benzenoid ring. The formation of the indole structure leads to the shift of ~0.4—0.6 ppm (for the quinoline structure, the shift is no smaller than 0.6 ppm). It should be noted that the character of substitution in the benzenoid ring is poorly reflected in the chemical shifts of the proton of the quinonoid ring (δ 5.71—5.85). The replacement of the diethylamino group with the hydroxy group leads to an upfield shift of this proton by ~0.5 ppm. The introduction of the phenyl substituent at position 2 of the heterocycle of the benzindoledione and benzoquinolinedione systems causes a downfield shift of the signal for the adjacent proton by ~0.3 and ~0.6 ppm, respectively. The nature of the dialkylamino group at position 4 of quinolines **12** and **13** has virtually no effect on the chemical shift of the proton at position 3.

Scheme 4



R^1 = Ph (**7**, **10**, **12**), $CHMe_2$ (**8**, **11**, **13**);
$R^2 + R^3 = (CH_2)_5$ (**a**), $(CH_2)_2O(CH_2)_2$ (**b**); $R^2 = R^3$ = Et (**c**)

Experimental

The ^{1}H NMR spectra were recorded on a Bruker DPX-200 instrument (200 MHz) in $CDCl_3$ at 25 °C. The IR spectra were measured on a UR-20 spectrometer in $CHCl_3$. The UV spectra were recorded on a Shimadzu 2401PC spectrometer in benzene. The reactions were monitored and the purity of the reaction products was checked by TLC on Silufol UV 254 plates. Compounds **3** were commercial reagents.

5-Amino-3-diethylamino-6-iodo-1,4-naphthoquinone (2). Diethylamine (20 mL) was added with stirring to a solution of iodide **1** (2.60 g, 8.7 mmol) and $Cu(OAc)_2 \cdot H_2O$ (0.60 g, 3.0 mmol) in dioxane (70 mL) for 15 min. Then air was passed through the solution at 20 °C for 2 h. The reaction mixture was poured into water (0.5 L) and extracted with $CHCl_3$ (3×100 mL).

Table 1. Melting points, results of elemental analysis, and ^{1}H NMR and IR spectra of acetylenic derivatives of naphthoquinones **4a—e** and **7—9**

Compound	M.p./°C (toluene—hexane)	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)	IR, ν/cm^{-1}
		C	H	N			
4a	87—88	76.65 76.72	5.68 5.85	8.00 8.13	$C_{22}H_{20}N_2O_2$	1.29 (t, 6 H, 2 Me, *J* = 7.0); 3.52 (q, 4 H, 2 NCH_2, *J* = 7.0); 5.84 (s, 1 H, H(2)); 7.37 (d, 1 H, H(8), *J* = 7.7); 7.62 (d, 1 H, H(7), *J* = 7.7); 7.30—7.45 (m, 3 H, *m*-H arom., *p*-H arom.); 7.45—7.60 (m, 4 H, 2 *o*-H arom. + NH_2)	1620, 1645 (C=O); 2220 (C≡C); 3360, 3485 (NH_2)
4b	85—86	70.04 69.92	6.98 7.02	8.75 8.58	$C_{19}H_{22}N_2O_3$	1.28 (t, 6 H, 2 NCMe, *J* = 7.2); 1.67 (s, 6 H, 2 Me); 2.35 (br.s, 1 H, OH); 3.48 (q, 4 H, 2 NCH_2, *J* = 7.2); 5.78 (s, 1 H, H(2)); 7.00 (br.s, 2 H, NH_2); 7.27 (d, 1 H, H(8), *J* = 7.6); 7.42 (d, 1 H, H(7), *J* = 7.6)	1620, 1650 (C=O); 2220 (C≡C); 3360, 3485 (NH_2); 3620 (OH)
4c	109—110	73.59 73.78	6.18 5.92	7.46 7.48	$C_{23}H_{22}N_2O_3$	1.27 (t, 6 H, 2 Me, *J* = 7.0); 3.51 (q, 4 H, 2 NCH_2, *J* = 7.0); 2.85 (br.s, 1 H, OH); 5.82 (s, 1 H, H(2)); 5.79 (d, 1 H, CHO, *J* = 8.0); 7.34 (d, 1 H, H(8), *J* = 7.7); 7.54 (d, 1 H, H(7), *J* = 7.7); 7.35—7.50 (m, 3 H, *m*-H arom., *p*-H arom.); 7.55—7.65 (m, 2 H, *o*-H arom.); 7.00 (br.s, 2 H, NH_2)	1620, 1645 (C=O); 2220 (C≡C); 3365, 3485 (NH_2); 3600 (OH)
4d	106—107	70.54 70.56	7.21 7.11	8.08 8.23	$C_{20}H_{24}N_2O_3$	1.27 (t, 6 H, 2 NCMe, *J* = 6.8); 1.90—2.20 (m, 1 H, CH); 1.06, 1.08 (both d, 3 H each, 2 MeC, *J* = 6.3); 3.49 (q, 4 H, 2 NCH_2, *J* = 6.8); 2.54 (br.s, 1 H, OH); 4.47 (d, 1 H, CHO, *J* = 5.4); 5.82 (s, 1 H, H(2)); 7.31 (d, 1 H, H(8), *J* = 7.6); 7.46 (d, 1 H, H(7), *J* = 7.6); 7.00 (br.s, 2 H, NH_2)	1620, 1645 (C=O); 2220 (C≡C); 3350, 3490 (NH_2); 3600 (OH)
4e	126—127	71.44 71.62	6.06 6.01	10.51 10.44	$C_{16}H_{16}N_2O_2$	1.25 (t, 6 H, 2 Me, *J* = 6.9); 3.50 (q, 4 H, 2 NCH_2, *J* = 6.9); 3.55 (s, 1 H, C≡CH); 5.82 (s, 1 H, H(2)); 7.34 (d, 1 H, H(8), *J* = 8.2); 7.58 (d, 1 H, H(7), *J* = 8.2); 7.10 (br.s, 2 H, NH_2)	1620, 1650 (C=O); 2100, 3310 (C≡CH); 3350, 3490 (NH_2)
7	143—144	74.12 74.18	5.26 5.41	7.66 7.52	$C_{23}H_{20}N_2O_3$	1.30 (t, 6 H, 2 Me, *J* = 7.0); 3.52 (q, 4 H, 2 NCH_2, *J* = 7.0); 5.85 (s, 1 H, H(2)); 7.41 (d, 1 H, H(8), *J* = 7.8); 7.78 (d, 1 H, H(7), *J* = 7.8); 7.45—7.60 (m, 2 H, *m*-H arom.); 7.60—7.70 (m, 1 H, *p*-H arom.); 8.19 (dd, 2 H, *o*-H arom., $J_{o,m}$ = 8.5, $J_{o,p}$ = 1.5)	1650 (C=O); 2190 (C≡C); 3360, 3495 (NH_2)
8	71—72	70.93 70.98	6.52 6.55	8.41 8.28	$C_{20}H_{22}N_2O_3$	1.27 (d, 6 H, CMe_2, *J* = 6.9); 1.28 (t, 6 H, 2 NCMe, *J* = 7.0); 2.77 (sept, 1 H, CH, *J* = 6.9); 3.51 (q, 4 H, 2 NCH_2, *J* = 7.0); 5.84 (s, 1 H, H(2)); 7.37 (d, 1 H, H(8), *J* = 7.8); 7.66 (d, 1 H, H(7), *J* = 7.8)	1660 (C=O); 2190 (C≡C); 3350, 3470 (NH_2)
9	209—210	71.82 71.92	3.31 3.49	4.21 4.41	$C_{23}H_{20}N_2O_3$	6.30 (s, 1 H, H(2)); 7.48 (d, 1 H, H(8), *J* = 7.7); 7.86 (d, 1 H, H(7), *J* = 7.7); 7.50—7.75 (m, 4 H, OH, *m*-H arom., *p*-H arom.); 8.10—8.25 (m, 2 H, *o*-H arom.)	1610, 1640 (C=O); 2200 (C≡C); 3370, 3490 (NH_2)

The chloroform solution was washed with water (5×70 mL), and $CHCl_3$ was removed *in vacuo* by replacing it with toluene during distillation. The toluene solution (~15 mL) was diluted with hexane (45 mL) and allowed to stand at 0 °C for ~12 h. The precipitate that formed was filtered off. The yield of compound **2** was 2.80 g (87.5%), decomposes at >100 °C (toluene—hexane). Found (%): C, 45.65; H, 4.22; I, 34.20. $C_{14}H_{15}IN_2O_2$. Calculated (%): C, 45.42; H, 4.08; I, 34.28. ^{1}H NMR, δ: 1.25 (t, 6 H, 2 Me, *J* = 6.9 Hz); 3.49 (q, 4 H, 2 NCH_2, *J* = 6.9 Hz); 5.85 (s, 1 H, H(2)); 7.10 (br.s, 2 H, NH_2); 7.11 and 7.93 (both d, 1 H each, H(7), H(8), *J* = 7.6 Hz).

5-Amino-3-diethylamino-6-phenylethynyl-1,4-naphthoquinone (4a). Phenylacetylene (**3a**) (0.17 g, 0.18 mL, 1.7 mmol), $Pd(PPh_3)_2Cl_2$ (18 mg), CuI (18 mg), and a solution of Na_2CO_3 (0.23 g, 2.3 mmol) in water (8 mL), which was preheated to ~80 °C, were successively added to a solution of compound **2** (0.40 g, 1.1 mmol) in dioxane (17 mL) under argon at 70 °C. The reaction mixture was stirred at 87 °C for 15 min, cooled, poured into water (400 mL), and extracted with toluene. The toluene solution was concentrated *in vacuo* and applied on a small Al_2O_3 layer (30×50 mm). Product **4a** was eluted with toluene. The yield was 0.30 g (81.1%) (see Table 1).

Table 2. Selected physicochemical properties and spectroscopic characteristics of substituted benz[*g*]indole-6,9-diones **5a—c** and benzo[*h*]quinoline-7,10-diones **12a—c** and **13a,b**

Compound	M.p./°C (toluene—hexane)	Found / Calculated (%)			Molecular formula	^{1}H NMR, δ (*J*/Hz)	IR, ν/cm^{-1}	UV, λ/nm (ε)
		C	H	N				
5a	136—137	76.51 76.72	5.69 5.85	7.95 8.13	$C_{22}H_{20}N_2O_2$	1.31 (t, 6 H, 2 Me, *J* = 7.0); 3.58 (q, 4 H, 2 NCH_2, *J* = 7.0); 5.82 (s, 1 H, H(7)); 6.84 (d, 1 H, H(3), *J* = 2.3); 7.30—7.60 (m, 3 H, *m*-H arom., *p*-H arom.); 7.70—7.95 (m, 4 H, *o*-H arom., H(4), H(5)); 10.5 (br.s, 1 H, NH)	1620, 1670, (C=O); 3460 (NH)	285 (2.31), 406 (1.12)
5b	93—94	71.55 71.62	5.87 6.01	10.62 10.44	$C_{16}H_{16}N_2O_2$	1.29 (t, 6 H, 2 Me, *J* = 7.0); 3.57 (q, 4 H, 2 NCH_2, *J* = 7.0); 5.82 (s, 1 H, H(7)); 6.59 (m, 1 H, H(3), $J_{H(3),H(2)}$ = 3.1, $J_{H(3),H(1)}$ = 1.8); 7.41 (m, 1 H, H(2), $J_{H(2),H(3)}$ = 3.1, $J_{H(2),H(1)}$ = 2.2); 7.81 (d, 1 H, H(4) (H(5)), *J* = 8.1); 7.88 (d, 1 H, H(5) (H(4)), *J* = 8.1); 10.25 (br.s, 1 H, NH)	1620, 1670 (C=O); 3470 (NH)	277 (1.53), 394 (0.84)
5c	108—109	74.06 74.00	6.41 6.54	8.83 9.08	$C_{19}H_{20}N_2O_2$	1.29 (t, 6 H, 2 NCMe, *J* = 7.0); 2.15 (s, 3 H, C=CMe); 3.56 (q, 4 H, 2 NCH_2, *J* = 7.0); 5.23, 5.54 (both s, 1 H each, 2 =CH); 5.81 (s, 1 H, H(7)); 6.54 (d, 1 H, H(3), *J* = 2.0); 7.72—7.81 (m, 2 H, H(4), H(5)); 10.27 (br.s, 1 H, NH)	1620, 1660 (C=O); 3470 (NH)	278 (2.23), 402 (1.11)
12a	107.5—108	76.32 76.51	6.52 6.65	9.31 9.56	$C_{28}H_{29}N_3O_2$	1.36 (t, 6 H, 2 Me, *J* = 7.0); 1.80—2.00 (m, 6 H, CH_2—CH_2—CH_2); 3.10—3.50 (m, 4 H, CH_2—N—CH_2); 3.56 (q, 4 H, 2 NCH_2, *J* = 7.0); 5.76, 7.39 (both s, 1 H each, H(8), H(3)); 7.30—7.60 (m, 3 H, *m*-H arom., *p*-H arom.); 8.08 (d, 1 H, H(5) (H(6)), *J* = 8.6); 8.20—8.45 (m, 3 H, *o*-H arom., H(6) (H(5)))	1620, 1690 (C=O)	276 (1.85), 401 (0.42)
12b	133—134	73.37 73.45	6.22 6.16	9.28 9.52	$C_{27}H_{27}N_3O_3$	1.37 (t, 6 H, 2 Me, *J* = 7.0); 3.27 (br.t, 4 H, CH_2—N—CH_2, *J* = 4.4); 3.57 (q, 4 H, 2 NCH_2, *J* = 7.0); 4.02 (br.t, 4 H, CH_2—O—CH_2, *J* = 4.4); 5.74, 7.40 (both s, 1 H each, H(8), H(3)); 7.45—7.60 (m, 3 H, *m*-H arom., *p*-H arom.); 8.11 (d, 1 H, H(5) (H(6)), *J* = 8.6); 8.25 (d, 1 H, H(6) (H(5)), *J* = 8.6); 8.15—8.30 (m, 2 H, *o*-H arom.)	1630, 1690 (C=O)	277 (2.65), 390 (0.61)
12c	83—84	75.60 75.85	6.75 6.84	9.71 9.83	$C_{27}H_{29}N_3O_2$	1.18, 1.37 (both t, 6 H each, 2 C(3)NCMe, 2 C(9)NCMe, *J* = 7.0); 3.42, 3.57 (both q, 4 H each, 2 C(3)NCH_2, 2 C(9)NCH_2, *J* = 7.0); 5.76, 7.40 (both s, 1 H each, H(8), H(3)); 7.40—7.60 (m, 3 H, *m*-H arom., *p*-H arom.); 8.06 (d, 1 H, H(5) (H(6)), *J* = 8.6); 8.10—8.35 (m, 3 H, H(6) (H(5)), *o*-H arom.)	1620, 1680 (C=O)	278 (3.22), 405 (0.74)
13a	92—93	73.78 74.04	7.71 7.71	10.21 10.36	$C_{25}H_{31}N_3O_2$	1.20—1.45 (m, 12 H, 2 NCMe, CMe_2); 2.95—3.25 (m, 5 H, CH=, CH_2NCH_2); 1.70—1.95 (m, 6 H, CH_2—CH_2—CH_2); 3.53 (q, 4 H, 2 NCH_2, *J* = 7.0); 5.71, 6.78 (both s, 1 H each, H(8), H(3)); 8.01 (d, 1 H, H(5) (H(6)), *J* = 8.6); 8.17 (d, 1 H, H(6) (H(5)), *J* = 8.6)	1620, 1680 (C=O)	285 (3.70), 391 (1.16)
13b	110—111	70.58 70.74	7.09 7.17	10.52 10.31	$C_{24}H_{29}N_3O_3$	1.34 (t, 6 H, 2 NCMe, *J* = 7.1); 1.36 (d, 6 H, CMe_2, *J* = 6.9); 2.95—3.30 (m, 5 H, CH=, CH_2—N—CH_2); 3.53 (q, 4 H, 2 NCH_2, *J* = 4.5); 3.98 (br.t, 4 H, CH_2—O—CH_2, *J* = 4.5); 5.72, 6.81 (both s, 1 H each, H(8), H(3)); 8.05 (d, 1 H, H(5) (H(6)), *J* = 8.6); 8.17 (d, 1 H, H(6) (H(5)), *J* = 8.6)	1620, 1680 (C=O)	289 (1.81), 384 (0.55)

5-Amino-3-diethylamino-6-(3-hydroxy-3-methylbutynyl)-1,4-naphthoquinone (4b). The reaction of iodide **2** (2.20 g, 6.0 mmol) with 3-methylbut-1-yn-3-ol (**3b**) (0.90 g, 0.7 mL, 10.7 mmol) was carried out analogously to the synthesis of compound **4a**. The reaction time was 7 min. The reaction mixture was diluted with water and extracted with $CHCl_3$. The chloroform solution was filtered through an Al_2O_3 layer (30×50 mm). The yield of acetylenic alcohol **4b** was 1.70 g (87.0%) (see Table 1).

5-Amino-3-diethylamino-6-(3-hydroxy-3-phenylpropynyl)-1,4-naphthoquinone (4c). Compound **4c** was prepared analogously to alcohol **4b** from iodide **2** (0.39 g, 1.0 mmol) and 3-phenylprop-1-yn-3-ol (**3c**) (0.22 g, 0.22 mL, 1.7 mmol). The reaction time was 20 min. The yield of compound **4c** was 0.37 g (94.9%) (see Table 1).

5-Amino-3-diethylamino-6-(3-hydroxy-4-methylpentynyl)-1,4-naphthoquinone (4d). Compound **4d** was prepared analogously to alcohols **4b,c** from iodide **2** (0.54 g, 1.5 mmol) and 4-methylpent-1-yn-3-ol (**3d**) (0.33 g, 3.4 mmol). The condensation time was 10 min. The yield of alcohol **4d** was 0.36 g (79.5%) (see Table 1).

5-Amino-3-diethylamino-6-ethynyl-1,4-naphthoquinone (4e). A calcined KOH powder (1.00 g, 17.8 mmol) was added with stirring to a solution of compound **4b** (2.00 g, 6.1 mmol) in toluene (210 mL) at 70 °C. The reaction mixture was heated to 110 °C, stirred for 20 min, cooled, and filtered through a small Al_2O_3 layer. The solvent was removed *in vacuo*. Ethynylnaphthoquinone **4e** was isolated in a yield of 1.60 g (95%) (see Table 1).

8-Diethylamino-2-phenylbenz[*g*]indole-6,9-dione (5a). A mixture of compound **4a** (0.35 g, 1.0 mmol) in DMF (20 mL) was heated in the presence of cuprous phenylacetylide (0.08 g, 0.5 mmol) and CuCl (0.05 g, 0.5 mmol) under argon at 155 °C for 4.5 h, poured into water (400 mL), and extracted with toluene. The solvent was removed *in vacuo*. The yield of benzindoledione **5a** was 0.29 g (82.2%) (see Table 2).

8-Diethylaminobenz[*g*]indole-6,9-dione (5b). A mixture of compound **4e** (0.10 g, 0.4 mmol) and piperidine (4 mL) was heated at 70 °C for 3.5 h. Excess piperidine was distilled off *in vacuo*. The residue was dissolved in $CHCl_3$, applied onto SiO_2 (45×140 mm), and allowed to stand for 2 days. Benzindoledione **5b** was washed with $CHCl_3$ and a $CHCl_3$—EtOH mixture. The yield was 0.08 g (80%) (see Table 2).

8-Diethylamino-2-isopropenylbenz[*g*]indole-6,9-dione (5c). A mixture of acetylenic alcohol **4b** (0.60 g, 1.8 mmol) was subjected to cyclization in the presence of cuprous phenylacetylide (0.15 g, 0.9 mmol) and CuCl (0.09 g, 0.9 mmol) in DMF (35 mL) analogously to heterocyclization of compound **4a** in indole **5a**. The reaction time was 5 h. Chromatography on SiO_2 (toluene and a toluene—acetone mixture as the eluents) afforded isopropenylbenzindole **5c** in a yield of 0.31 g (55.4%) (see Table 2).

5-Amino-6-benzoylethynyl-3-diethylamino-1,4-naphthoquinone (7). ***A.*** The Collins reagent[24] (1.90 g, 7.3 mmol) was added portionwise with stirring to a cold solution of compound **4c** (0.54 g, 1.4 mmol) in dry freshly distilled CH_2Cl_2 (75 mL) for 10 min, so that the temperature of the reaction mixture was maintained no higher than 10 °C. The reaction mixture was stirred at 20 °C for 1 h, diluted with $CHCl_3$ (100 mL), and poured into a solution of $NaHCO_3$ (3.00 g, 35.7 mmol) in water (70 mL). The organic layer was separated, washed with water (3×100 mL), and dried with $MgSO_4$. The solvent was removed *in vacuo*. Ketone **7** was obtained in a yield of 0.50 g (94.3%) (see Table 1).

B. A mixture of iodide **2** (1.10 g, 2.8 mmol) and cuprous benzoylacetylide (0.80 g, 4.3 mmol) in DMF (30 mL) was stirred at 140 °C under argon for 1 h, cooled, diluted with benzene (200 mL), and repeatedly washed with water. After removal of the solvent *in vacuo*, the residue was chromatographed on SiO_2 (benzene and $CHCl_3$ as the eluents). Ketone **7** was crystallized from hexane. The yield of 0.70 g (66%).

C. A mixture of benzoyl chloride (0.52 g, 0.42 mL, 4.0 mmol) and Et_3N (0.60 g, 0.84 mL, 6.0 mmol) in benzene (8 mL) was stirred under argon (2—3 min). Then a solution of ethynylnaphthoquinone **4e** (0.54 g, 2.0 mmol) in benzene (10 mL) was added, the reaction mixture was warmed to 60 °C, and $Pd(PPh_3)_2Cl_2$ (30 mg) was added. Then the mixture was heated to 80 °C and stirred for 5 min. Chromatography on Al_2O_3 (30×80 mm) in benzene afforded ketone **7** (0.30 g, 42%).

5-Amino-3-diethylamino-6-(4-methyl-3-oxopentynyl)-1,4-naphthoquinone (8). Alcohol **4d** (0.80 g, 2.3 mmol) was oxidized with the Collins reagent (7.50 g, 29.0 mmol) in CH_2Cl_2 (150 mL) under the conditions of the synthesis of ketone **7**. The yield of ketone **8** was 0.60 g (78%) (see Table 1).

5-Amino-6-benzoylethynyl-3-hydroxy-1,4-naphthoquinone (9). A solution of ketone **7** (0.30 g, 0.8 mmol) and $HgSO_4$ (60 mg) in dioxane (20 mL) acidified with 45% H_2SO_4 (0.3 mL) was stirred at 85 °C for 4 h. Then the reaction mixture was cooled, poured into water (300 mL), and extracted with $CHCl_3$. The organic layer was washed with water to neutral pH and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue was triturated with hexane. Hydroxynaphthoquinone **9** was obtained in a yield of 0.23 g (76.7%) (see Table 1).

9-Diethylamino-4-piperidino-2-phenylbenzo[*h*]quinoline-7,10-dione (12a). A solution of ketone **7** (0.30 g, 0.8 mmol) in piperidine (12 mL) was stirred at 20 °C for 45 min. After completion of the reaction, the mixture was poured into water (300 mL) and extracted with benzene 100 mL. The product was isolated from the benzene extract with 12% HCl (2×45 mL). A hydrochloric acid solution was gradually alkalized with a 20% aqueous KOH solution (260 mL) and extracted with benzene (100 mL) as the mixture became neutral. After separation, the aqueous alkaline layer was additionally extracted with benzene (3×50 mL). The combined benzene extracts were washed with water to neutral pH and dried with $MgSO_4$. The solvent was removed *in vacuo*. Compound **12a** was obtained in a yield of 0.24 g (68.6%) (see Table 2).

9-Diethylamino-4-morpholino-2-phenylbenzo[*h*]quinoline-7,10-dione (12b). Compound **12b** was prepared analogously from ketone **7** (0.48 g, 1.3 mmol) and morpholine (13 mL) at 20 °C (2 h) in a yield of 0.52 g (91%) (see Table 2).

4,9-Bis(diethylamino)-2-phenylbenzo[*h*]quinoline-7,10-dione (12c). Compound **12c** was prepared analogously from ketone **7** (0.49 g, 1.3 mmol) and Et_2NH (27 mL) at 20 °C (1 h) in a yield of 0.30 g (55.6%) (see Table 2).

9-Diethylamino-2-isopropyl-4-piperidinobenzo[*h*]quinoline-7,10-dione (13a). Compound **13a** was prepared analogously from acetylenic ketone **8** (0.28 g, 0.8 mmol) and piperidine 18 mL at 20 °C (70 min). The yield of benzoquinolinedione **13a** was 0.17 g (51.3%) (see Table 2).

9-Diethylamino-2-isopropyl-4-morpholinobenzo[*h*]quinoline-7,10-dione (13b). Compound **13b** was prepared analogously from ketone **8** (0.30 g, 0.9 mmol) and morpholine (9 mL) at 20 °C

(105 min). The yield of benzoquinolinedione **13b** was 0.18 g (50%) (see Table 2).

References

1. A. P. Krapcho, M. E. Petry, and M. P. Hacker, *J. Med. Chem.*, 1990, **33**, 2651.
2. B. Kesteleyn and N. De Kimpe, *Tetrahedron Lett.*, 2000, **41**, 755.
3. I. M. Gomez-Monterrey, P. Campiglia, O. Mazzoni, E. Novellino, and M. V. Diurno, *Tetrahedron Lett.*, 2001, **42**, 5755.
4. M. S. Shvartsberg, I. D. Ivanchikova, and S. F. Vasilevsky, *Tetrahedron Lett.*, 1994, **35**, 2077.
5. M. S. Shvartsberg, I. D. Ivanchikova, and L. G. Fedenok, *Izv. Akad. Nauk, Ser. Khim.*, 1996, 1803 [*Russ. Chem. Bull.*, 1996, **45**, 1714 (Engl. Transl.)].
6. M. A. Mzhel´skaya, I. D. Ivanchikova, N. E. Polyakov, A. A. Moroz, and M. S. Shvartsberg, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 2686 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 2798].
7. I. D. Ivanchikova, N. I. Lebedeva, and M. S. Shvartsberg, *Synthesis,* 2004, 2131.
8. I. D. Ivanchikova and M. S. Shvartsberg, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 2205 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 2303].
9. V. S. Romanov, A. A. Moroz, and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1985, 1090 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1985, **34**, 994 (Engl. Transl.)].
10. M. S. Shvartsberg, I. D. Ivanchikova, and N. I. Lebedeva, *Tetrahedron Lett.*, 2000, **41**, 5757.
11. I. I. Barabanov, I. D. Ivanchikova, and M. S. Shvartsberg, *Mendeleev Commun.*, 2000, 188.
12. M. S. Shvartsberg and I. D. Ivanchikova, *Tetrahedron Lett.*, 2000, **41**, 771.
13. I. D. Ivanchikova, R. N. Myasnikova, and M. S. Shvartsberg, *Izv. Akad. Nauk, Ser. Khim.*, 2001, 1590 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1668].
14. M. S. Shvartsberg, A. A. Moroz, N. V. Ivashkina, and S. B. Cherepanov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 2485 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 2273 (Engl. Transl.)].
15. A. V. Piskunov, A. A. Moroz, and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 828 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 755 (Engl. Transl.)].
16. M. S. Shvartsberg, A. A. Moroz, A. V. Piskunov, and I. A. Budzinskaya, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1987, 2517 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1987, **36**, 2338 (Engl. Transl.)].
17. A. V. Piskunov and M. S. Shvartsberg, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 1444 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 1306 (Engl. Transl.)].
18. M. S. Shvartsberg, A. V. Piskunov, M. A. Mzhel´skaya, and A. A. Moroz, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1423 [*Russ. Chem. Bull.*, 1993, **42**, 1357 (Engl. Transl.)].
19. M. S. Shvartsberg, A. N. Kozhevnikova, and I. L. Kotlyarevskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1967, 466 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1967, **16** (Engl. Transl.)].
20. A. S. Zanina, S. I. Shergina, I. E. Sokolov, and I. L. Kotlyarevskii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1981, 1158 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1981, **30** (Engl. Transl.)].
21. V. V. Davydov, M. G. Sarabia, A. I. Ezhov, G. V. Sheban, S. L. Kuznetsov, M. A. Mzhel´skaya, A. V. Piskunov, M. S. Shvartsberg, and B. E. Zaitsev, *Koord. Khim.*, 1994, **20**, 144 [*Sov. J. Coord. Chem.*, 1994, **20** (Engl. Transl.)].
22. B. E. Zaitsev, V. V. Davydov, M. G. Sarabia, M. S. Shvartsberg, M. A. Mzhel´skaya, and G. V. Sheban, *Zh. Obshch. Khim.*, 1993, **63**, 389 [*Russ. J. Gen. Chem.*, 1993, **63** (Engl. Transl.)].
23. S. I. Dikalov, G. V. Rumyantseva, A. V. Piskunov, and L. M. Weiner, *Biochemistry*, 1992, **31**, 8947.
24. J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 1968, **30**, 3363.

Received July 16, 2004