Reaction of guanidine with *peri*-substituted (R-ethynyl)-9,10-anthraquinones bearing electron-donating substituents

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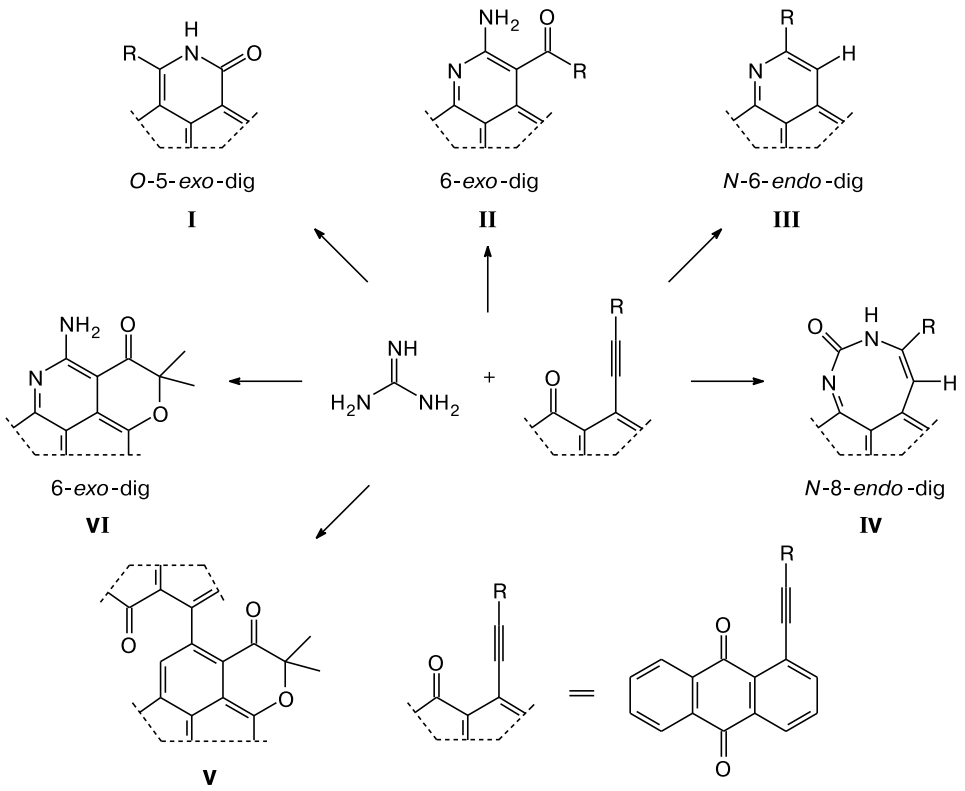
2-Amino-3-aroyl-7*H*-dibenzo[*de*,*h*]quinolin-7-ones were synthesized by the reaction of guanidine with *peri*-(R-ethynyl)-9,10-anthraquinones in boiling *n*-butanol.

Key words: alkynes, cross-coupling, heterocyclization, guanidine, 7*H*-dibenzo[*de*,*h*]-quinolin-7-ones.

Recently,[1,2] we have reported on the new heterocyclizations and unusual rearrangements accompanying reactions of guanidine with 1-aryl- and 1-alkylethynyl-9,10-anthraquinones. These transformations are of interest from the point of view of *exo*/*endo*-selective ring formations (the Baldwin's rules).[3] For instance, it was shown[1,2] that the reaction of *peri*-(R-ethynyl)-9,10-anthraquinones with guanidine leads to 1-aryl-7*H*-dibenzo[*de*,*h*]isoquinoline-3,7-dione (**I**), 2-amino-3-aroyl-7*H*-dibenzo-[*de*,*h*]quinolin-7-one (**II**), 2-aryl-7*H*-dibenzo[*de*,*h*]-quinolin-7-one (**III**), 3*H*-4-(2-hydroxyprop-2-yl)anthra-[9,1-*de*][1,3]diazocine-2,9-dione (**IV**), 12-(9,10-dioxo-anthracen-1-yl)-2,2-dimethyl-2*H*-phenanthro[2,1,10-*def*]-chromen-1,6-dione (**V**), and 12-amino-2,2-dimethyl-2*H*-chromeno[4,5,6-*cde*]benzo[*h*]quinoline-1,6-dione (**VI**) systems (Scheme 1), with the ratio and type of the reaction

Scheme 1



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products being dependent on the structure of acetylene substituent.

The compounds obtained can be of significant interest for medicinal chemistry, since the 7*H*-dibenzo[*de*,*h*]-quinolin-7-one skeleton relates them to the natural alkaloids of the isoaporphine family (*Isoaporphines*) exhibiting anticancer activity[4,5] and enhanced effect of acetylcholinesterase suppression.[6]

In this connection, we continued our systematic study on the reaction of guanidine with 1-(R-ethynyl)-9,10-anthraquinones. In the present work, the substrates bearing electron-donating substituents on the acetylene fragment have been studied.

Results and Discussion

The heterocyclization of 1-(het)arylethynyl-9,10-anthraquinones **1a—c** with guanidine was carried out in boiling *n*-butanol (Scheme 2).

Note that in these transformation, the choice of solvent and temperature is crucial: anthraquinones **1** are poorly soluble in methanol, ethanol, propan-2-ol, pyridine, and no reaction takes place in these solvents at temperatures about 40—50 °C. Reflux of compounds **1** in aliphatic alcohols, pyridine, DMF, and DMSO is accompanied by deep resinification. Out of all solvents, *n*-butanol proved the most appropriate: it completely dissolves starting anthraquinones on reflux with the lowest degree of resinification.

The optimum reaction time is 28 h with incomplete conversion of the starting acetylenes. Attempts to reach higher conversion using longer reaction time led to significant resinification, which complicated isolation of final products. Components of the reaction mixture were separated by chromatography on Alumina.

In all the cases, quinolin-7-ones **2a—c** are formed in 25, 64, and 33% yield, respectively, *i.e.*, products of the 6-*exo*-dig-cyclization. For compound **1a**, a partial *O*-5-*exo*-dig-cyclization was observed leading to the formation of isoquinoline-3,7-dione system **3** (19%). It should be noted that for the substrates containing electron-withdrawing substituents, if the corresponding amino ketones **2** were formed, then only as minor products.[1] The data obtained agree with the results reported earlier,[1] according to which the reaction of guanidine with 1-[(4-methoxyphenyl)ethynyl]-9,10-anthraquinone mainly gives amino ketone of the type **2**.

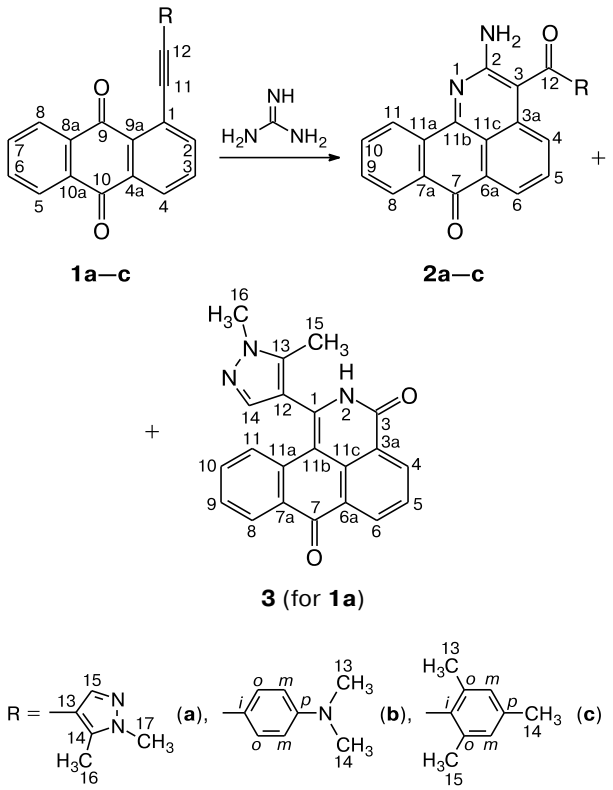
The structures of compounds synthesized were confirmed by analytical and spectral data (Tables 1 and 2).

The IR spectra of amino ketones **2a—c** contain band of the stretching vibrations of the NH_2 group (3303—3471 cm^{-1}) and two C=O groups (1611—1660 cm^{-1}). A combination of spectral and analytical data allows us to assign to compounds **2a—c** the structure of 2-amino-3-aroyl-7*H*-dibenzo[*de*,*h*]quinolin-7-ones.

The IR spectrum of isoquinoline-3,7-dione **3** exhibits bands of the stretching vibrations of the NH group (3059 cm^{-1}) and two C=O groups (1650, 1681 cm^{-1}). The ^1H and ^{13}C NMR spectra, as well as HRMS, allows us to unambiguously establish the structure of 1-(1,5-dimethylpyrazol-4-yl)-7*H*-dibenzo[*de*,*h*]isoquinoline-3,7-dione (**3**). In addition, the determining the structure of this compound was facilitated by a possibility of comparison with the spectra of its analogs, the structure of which has been established by us earlier,[1] including by X-ray diffraction analysis.

The starting compounds were obtained from 1-iodo-9,10-anthraquinone (**4**) and terminal acetylenes **5a—c** under standard conditions of the Sonogashira reaction[7] in the system $PdCl_2(PPh_3)_2$—CuI—Et_3N (Scheme 3). The

Scheme 2



Scheme 3

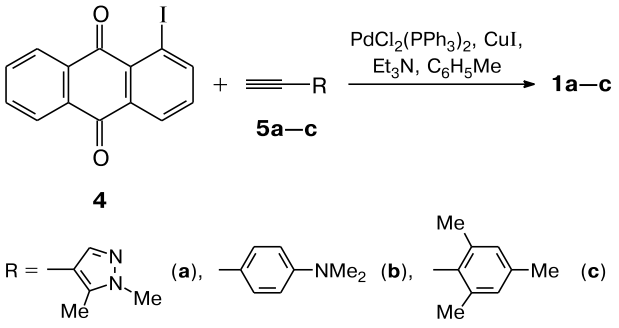


Table 1. ^{1}H and ^{13}C NMR (in $CDCl_3$) and IR spectra of alkynes **1a—c**

Compound	NMR, δ (*J*/Hz)		IR, ν/cm^{-1}
	^{1}H	^{13}C	
1a	2.59 (s, 3 H, C(14)Me); 3.82 (s, 3 H, NMe); 7.65—7.68 (m, 2 H, H(3), H(15)); 7.73—7.77 (m, 2 H, H(6), H(7)); 7.75 (dd, 1 H, H(2), *J* = 7.8, *J* = 1.2); 8.24—8.26 (m, 2 H, H(5), H(8)); 8.30—8.33 (m, 1 H, H(4))	10.44 (C(17)); 36.81 (C(16)); 89.16 (C(11)); 91.91 (C(12)); 102.63 (C(13)); 124.58 (C(1)); 126.76 (C(8)); 126.99 (C(5)); 127.58 (C(4)); 132.60 (C(10a)); 132.87 (C(7)); 132.93 (C(9a)); 133.79 (C(6)); 134.36 (C(3)); 134.41 (C(8a)); 134.58 (C(4a)); 139.79 (C(2)); 141.14 (C(15)); 143.27 (C(14)); 182.01 (C(10)); 183.07 (C(9))	1671 (C=O), 2205 (C≡C)
1b	3.01 (s, 6 H, Me); 6.69 (d, 2 H, H_m, *J* = 8.9); 7.60 (d, 2 H, H_o, *J* = 8.9); 7.67 (t, 1 H, H(3), *J* = 7.7); 7.74—7.79 (m, 2 H, H(6), H(7)); 7.91 (dd, 1 H, H(2), *J* = 7.8, *J* = 1.2); 8.22—8.27 (m, 2 H, H(5), H(8)); 8.35 (dd, 1 H, H(4), *J* = 7.7, *J* = 1.2)	39.95 (C(13), C(14)); 88.05 (C(11)); 92.21 (C(12)); 109.69 (C_i); 111.64 (C_m); 124.76 (C(1)); 126.20 (C(8)); 126.64 (C(5)); 127.36 (C(4)); 132.35 (C(10a)); 132.47 (C(7)); 132.70 (C(9a)); 133.38 (C(6)); 134.09 (C(3)); 134.23 (C(8a)); 134.34 (C(4a)); 150.48 (C_p); 139.75 (C(2)); 133.46 (C_o); 181.78 (C(10)); 182.92 (C(9))	1671 (C=O), 2185 (C≡C)
1c	2.30 (s, 3 H, C_pMe); 2.64 (s, 6 H, C_oMe); 6.92 (s, 2 H, H_m); 7.71 (t, 1 H, H(3), *J* = 7.8); 7.75—7.79 (m, 2 H, H(6), H(7)); 7.97 (dd, 1 H, H(2), *J* = 7.8, *J* = 1.4); 8.26—8.36 (m, 3 H, H(4), H(5), H(8))	20.98 (C(13), C(15)); 21.33 (C(14)); 94.61 (C(11)); 96.61 (C(12)); 119.78 (C_i); 124.37 (C(1)); 126.65 (C(8)); 126.69 (C(5)); 126.79 (C(4)); 127.41 (C_m); 132.46 (C(10a)); 132.54 (C(7)); 132.66 (C(9a)); 133.48 (C(6)); 134.14 (C(3)); 134.16 (C(8a)); 134.38 (C(4a)); 138.59 (C_p); 140.18 (C(2)); 141.19 (C_o), 181.85 (C(10)); 182.85 (C(9))	1672 (C=O), 2195 (C≡C)

Table 2. ^{1}H and ^{13}C NMR (in $CDCl_3$) and IR spectra of 7*H*-dibenzo[*de*,*h*]quinolin-7-ones **2a—c** and 7*H*-dibenzo[*de*,*h*]isoquinoline-3,7-dione **3**

Compound	NMR, δ (*J*/Hz)		IR, ν/cm^{-1}
	^{1}H	^{13}C	
2a	2.58 (s, 3 H, Me); 3.82 (s, 3 H, NMe); 5.57 (br.s, 2 H, NH_2); 7.34 (s, 1 H, H(15)); 7.55—7.65 (m, 2 H, H(9), H(10)); 7.75 (t, 1 H, H(5), *J* = 7.6); 7.86 (d, 1 H, H(4), *J* = 7.6); 8.27 (d, 1 H, H(6), *J* = 7.6); 8.35 (d, 1 H, H(8), *J* = 7.8); 8.76 (d, 1 H, H(11), *J* = 7.8)	11.02 (C(16)); 36.09 (C(17)); 109.09 (C(3)); 117.75 (C(3b)); 121.83 (C(14)); 125.50 (C(11)); 125.67 (C(6)); 127.37 (C(8)); 129.02 (C(3a)); 130.08 (C(5)); 130.53 (C(4)); 130.79 (C(9)); 132.45 (C(7a)); 133.71 (C(10)); 135.47 (C(11a)); 135.76 (C(6a)); 142.02 (C(15)); 143.53 (C(13)); 149.81 (C(11b)); 153.40 (C(2)); 183.33 (C(7)); 190.09 (C(12))	1611, 1651 (C=O); 3347, 3463 (NH_2)
2b	2.93 (s, 6 H, NMe); 5.21 (br.s, 2 H, NH_2); 6.48 (d, 2 H, H_m, *J* = 9.1); 7.43 (t, 1 H, H(9), *J* = 7.3); 7.52 (t, 1 H, H(10), *J* = 7.3); 7.59—7.67 (m, 4 H, H_o, H(5), H(4)); 8.17 (d, 1 H, H(6), *J* = 7.1); 8.26 (dd, 1 H, H(8), *J* = 7.8, *J* = 0.9); 8.68 (d, 1 H, H(11), *J* = 7.8)	39.87 (C(13), C(14)); 109.44 (C(3)); 110.7 (C_m); 117.46 (C(11c)); 125.36 (C(11)); 125.57 (C(6)); 125.86 (C_p); 127.31 (C(8)); 128.96 (C(3a)); 130.22 (C(5)); 130.43 (C(4)); 130.64 (C(9)); 132.39 (C_o), 132.44 (C(7a)); 133.63 (C(10)); 135.92 (C(11a)); 136.15 (C(6a)); 149.02 (C_i); 153.37 (C(11b)); 153.84 (C(2)); 183.52 (C(7)); 194.31 (C(12))	1615, 1658 (C=O); 3343, 3471 (NH_2)
2c	2.06 (s, 6 H, C_oMe); 2.34 (s, 3 H, C_pMe); 6.90 (s, 2 H, H_m); 7.38—7.42 (m, 1 H, H(5)); 7.54—7.56 (m, 1 H, H(4)); 7.69 (m, 1 H, H(9)); 7.78—7.80 (m, 1 H, H(10)); 8.20—8.22 (m, 1 H, H(6)); 8.37 (dd, 1 H, H(8), *J* = 9.1, *J* = 1.2); 8.85 (dd, 1 H, H(11), *J* = 9.1, *J* = 1.2)	19.46 (C(13), C(15)); 21.07 (C(14)); 105.13 (C(3)); 117.97 (C(11c)); 124.93 (C(11)); 126.02 (C(6)); 127.27 (C(8)); 128.65 (C(5)); 129.29 (C_m); 131.39 (C(4)); 131.48 (C(9)); 132.61 (C_p); 133.71 (C(3a)); 133.73 (C(10)); 135.21 (C(7a)); 136.65 (C(11a)); 139.04 (C_o); 140.72 (C(6a)); 148.31 (C_i); 153.11 (C(11b)); 157.45 (C(2)); 183.44 (C(7)); 199.60 (C(12))	1611, 1660 (C=O); 3303, 3442 (NH_2)
3 *	2.00 (s, 3 H, Me); 3.84 (s, 3 H, NMe); 7.41—7.43 (m, 3 H, H(9), H(10), H(11)); 7.64 (s, 1 H, H(14)); 7.85 (t, 1 H, H(5), *J* = 7.7); 8.26—8.29 (m, 1 H, H(8)); 8.63—8.70 (m, 2 H, H(4), H(6)), 11.80 (s, 1 H, NH)	10.10 (C(14)); 36.82 (C(16)); 105.19 (C(11b)); 114.82 (C(13)); 124.90 (C(3a)); 125.78 (C(11)); 126.69 (C(9)); 127.09 (C(5)); 127.29 (C(8)); 127.73 (C(6a)); 130.14 (C(7a)); 132.62 (C(10)); 132.76 (C(4)); 133.08 (C(6)); 134.84 (C(11c)); 136.01 (C(11a)); 137.88 (C(14)); 138.45 (C(12)); 138.65 (C(1)); 161.51 (C(3)); 182.00 (C(7))	1650, 1681 (C=O); 3059 (NH)

* The spectrum was recorded in DMSO-d_6.

reaction time was 2—4 h, the product **1a—c** yields were 82—96%.

In conclusion, it was shown that cyclocondensation of guanidine with *peri*-substituted (R-ethynyl)-9,10-anthraquinones containing R-electron-donating substituent follows the 6-*exo*-dig-cyclization pathway, leading to a predominant or exclusive formation of amino ketones.

Experimental

IR spectra were recorded on a Bruker Vector 22 spectrometer in KBr pellets. NMR spectra were recorded on a Bruker AV 400 spectrometer (400.13 MHz) in $CDCl_3$ and DMSO-d_6. Mass spectra were obtained on a DFS mass spectrometer (Thermo Electron Corporation) with direct injection (70 eV, the temperature of ionization chamber was 220—270 °C). Column chromatography was performed on Alumins (50—150 μm, TU 6-09-3916-75), TLC monitoring was carried out on Silufol 60 F254 plates.

1-(R-Ethynyl)-9,10-anthraquinones 1a—c (general procedure). A mixture of 1-iodo-9,10-anthraquinone (**4**) (4.5 mmol), terminal acetylene **5a—c** (4.5 mmol), $PdCl_2(PPh_3)_2$ (0.013 mmol), CuI (0.027 mmol) and Et_3N (12.7 mmol) in toluene (50 mL) was stirred for 2—4 h under argon at 60 °C (TLC monitoring with toluene as an eluent). The reaction mixture was cooled, filtered through the Al_2O_3 layer (d = 25 mm, h = 30 mm), and eluted with toluene. The solvent was evaporated *in vacuo*. Crystallization from toluene gives compounds **1a—c**.

1-[(1,5-Dimethylpyrazol-4-yl)ethynyl]-9,10-anthraquinone (1a). The yield was 82%, m.p. 177—178 °C (toluene). HRMS, found: m/z 325.0971 $[M - H]^+$. $C_{21}H_{14}N_2O_2$. Calculated: M = 326.1055.

1-(4-Dimethylaminophenylethynyl)-9,10-anthraquinone (1b). The yield was 96%, m.p. 223—224 °C (toluene). HRMS, found: m/z 351.1249 $[M]^+$. $C_{24}H_{17}NO_2$. Calculated: M = 351.1254.

1-(2,4,6-Trimethylphenylethynyl)-9,10-anthraquinone (1c). The yield was 95%, m.p. 188—189 °C (toluene). HRMS, found: m/z 350.1306 $[M]^+$. $C_{25}H_{18}O_2$. Calculated: M = 350.1307.

Preparation of 1 *M* solution of guanidine in methanol. Sodium metal (2.3 g, 0.1 mol) was dissolved in small portions in MeOH (50 mL), the solution obtained was mixed with guanidine hydrochloride (9.55 g, 0.1 mol) in MeOH (50 mL). A precipitate of NaCl formed was filtered off.

Reaction of 1-(R-ethynyl)-9,10-anthraquinones 1a—c with guanidine (general procedure). A mixture of compound **1a—c** (3.25 mmol) and guanidine (27 mmol, 27 mL of 1 *M* solution in methanol) in *n*-butanol (60 mL) was refluxed for 28 h (TLC monitoring with chloroform as an eluent). The solvent was evaporated *in vacuo*. The mixture was separated by column chromatography on Al_2O_3 (d = 25 mm, h = 170 mm) with benzene and ethyl acetate as subsequent eluents. Pure compounds **2a—c** and **3** were obtained by crystallization.

2-Amino-3-(1,5-dimethylpyrazol-4-ylcarbonyl)-7*H*-dibenzo-[*de*,*h*]quinolin-7-one (2a). The yield was 25%, m.p. 220—221.5 °C (benzene). HRMS, found: m/z 368.1261 $[M]^+$. $C_{22}H_{16}N_4O_2$. Calculated: M = 368.1268.

1-(1,5-Dimethylpyrazol-4-yl)-7*H*-dibenzo[*de*,*h*]isoquinoline-3,7-dione (3). The yield was 19%, m.p. >360 °C (ethanol). HRMS, found: m/z 341.1154 $[M]^+$. $C_{21}H_{15}N_3O_2$. Calculated: M = 341.1159.

2-Amino-3-(4-dimethylaminobenzoyl)-7*H*-dibenzo[*de*,*h*]-quinolin-7-one (2b). The yield was 64%, m.p. 215.5—216.5 °C (benzene). HRMS, found: m/z 392.1398 $[M - H]^+$. $C_{25}H_{19}N_3O_2$. Calculated: M = 393.1477.

2-Amino-3-(2,4,6-trimethylbenzoyl)-7*H*-dibenzo[*de*,*h*]-quinolin-7-one (2c). The yield was 33%, m.p. 201—202 °C (benzene). HRMS, found: m/z 392.1523 $[M]^+$. $C_{26}H_{20}N_2O_2$. Calculated: M = 392.1519.

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