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Mendeleev Commun., 2009, **19**, 326–328

Mendeleev Communications

Multichannel reaction of 1-(3′-hydroxy-3′-methylbutynyl)-9,10-anthraquinone with guanidine

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DOI: 10.1016/j.mencom.2009.11.011

The interaction of guanidine with 1-(3′-hydroxy-3′-methylbutynyl)-9,10-anthraquinone in refluxing butan-1-ol leads to the formation of the cascade transformations products: addition/elimination/cyclization/dehydrocyclization – anthra[9,1-*de*][1,3]diazocine-2,9-dione, chromeno[4,5,6-*cde*]benzo[*h*]quinoline-1,6-dione and 12-(9,10-anthraquinon-1-yl)-2*H*-phenanthro[2,1,10-*def*]chromene-1,6-dione systems.

Acetylene compounds are convenient building blocks in organic and medicinal chemistry and materials science.[1,2]

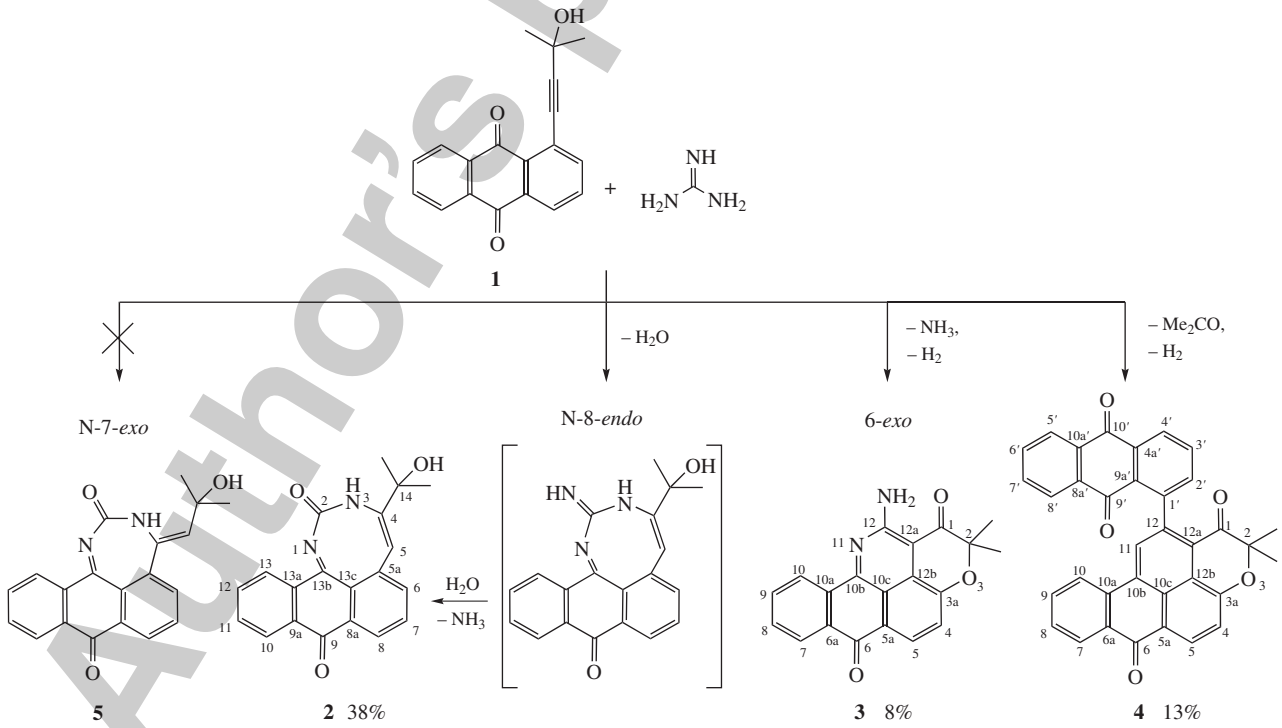
The cyclizations of *vic*-substituted aryl and hetaryl acetylenes become an efficient approach towards the preparation of condensed heterocyclic systems.[3] An important problem is *exo*/*endo* selectivity.

The search of new types of heterocyclization with participation of reactive triple bond is our actual task. Recently,[4] we investigated a new reaction of *peri*-substituted arylacetylenyl-9,10-anthraquinones with guanidine. Our assumption that a combination of two electrophilic centres (the α- and β-carbon atoms in the triple bond) and three nucleophilic centres (‘imine’ and two ‘amine’ nitrogen atoms) in the guanidine moiety can lead to a multichannel character of the reaction was confirmed. We observed unusual results of such transformations: the formation of 1-aryl-7*H*-dibenzo[*de*,*h*]isoquinoline-3,7-dione, aryl-7*H*-dibenzo[*de*,*h*]quinolin-7-one and 2-amino-3-aroyl-7*H*-dibenzo[*de*,*h*]quinolin-7-one systems, which prompted us to study the behaviour of *peri*-substituted alkylacetylenyl-9,10-anthraquinones to test generality or limitations of this interaction.

We report here the new synthesis of condensed 9,10-anthraquinones based on interaction of 1-(3′-hydroxy-3′-methylbutynyl)-9,10-anthraquinone with guanidine.

Under standard Sonogashira conditions,[5] condensation of 1-iodo-9,10-anthraquinone with 3-hydroxy-3-methylbut-1-yne (60 °C, 1.5 h) provides disubstituted acetylene **1** in 80% yield.

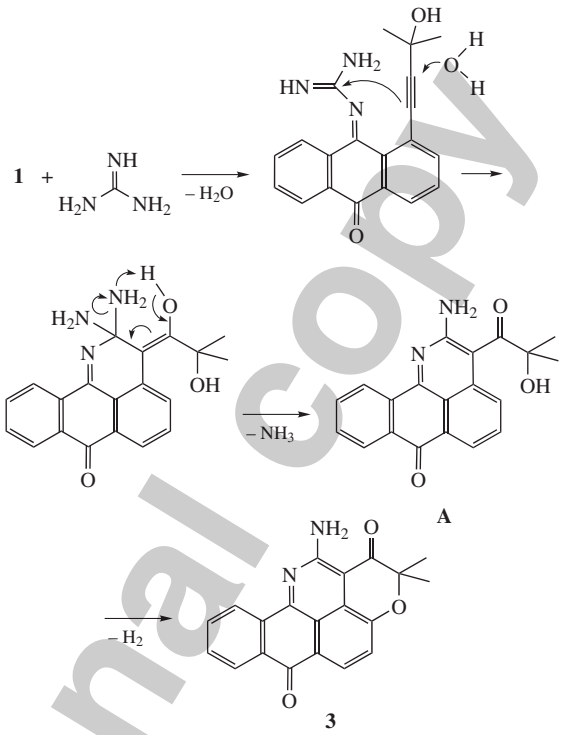
Indeed, the reaction of acetylene **1**† with guanidine‡ in refluxing butanol leads to the formation of three products:§ 3*H*-4-(2-hydroxypropan-2-yl)anthra[9,1-*de*][1,3]diazocine-2,9-dione **2**, 12-amino-2,2-dimethyl-2*H*-chromeno[4,5,6-*cde*]benzo[*h*]quinoline-1,6-dione **3** and 12-(9,10-anthraquinon-1-yl)-2,2-dimethyl-2*H*-phenanthro[2,1,10-*def*]chromene-1,6-dione **4** (Scheme 1).



Scheme 1

The formation of condensed 8-membered cycle **2** can be represented as a series of consecutive reactions of the addition of the guanidine molecule to the anthraquinone carbonyl group with following elimination of water, the addition of the second amine fragment to β-carbon atom of triple bond (N-8-*endo*-dig-attack), and hydrolysis of the imine group at the final stage.

The choice of the structure of the reaction product between **2** and **5** is based on the analysis of NMR spectra (2D COSY, 2D HXCO, 2D COLOC). The position of the double C^4–C^5 bond has been established from the correlation at distant constants of the spin–spin interaction between the Me protons and C^{14} and C^4 atoms, whereas the H^5 proton correlates with the C^{14}, C^6, C^{13c} atoms.



Scheme 2

We suppose that the formation of product **3** can be represented as a series of consecutive or synchronous addition–elimination reactions (Scheme 2). The first stage involves the addition of one of the guanidine amino groups to carbonyl group with the elimination of a water molecule. The latter attacks a positively polarized β-carbon atom of the triple bond (6-*exo*-dig-attack) with the synchronous attack of a polarized carbon atom of the guanidine fragment by the α-carbon atom of the triple bond and elimination of the proton from the water molecule. Probably, the proton is eliminated from the hydroxyl group by strong base guanidine (comparable with KOH)[6] with simultaneous shift of a pair of electrons and elimination of ammonia. Supposed mechanism is correlated with our data,[4] where structures of 2-amino-3-aroyl-7*H*-dibenzo[*de*,*h*]quinolin-7-ones (relative to intermediate **A**) were established. The presence of OH group leads to intramolecular nucleophilic substitution of hydride anion in the 4-position by internal alkoxide anion (from hydroxy group). Note that nucleophilic substitution of hydride anion is a typical reaction of π-electron deficient molecules.

Such dehydrocyclization is possible due to both the conformation, which assures the spatial vicinity of corresponding carbon and oxygen atoms, and facility of the 6-membered cycle formation.

It is interesting that compound **4** has no nitrogen atoms and, according to the HRMS data, corresponds to the empirical formula $C_{35}H_{20}O_5$. For confirming such an unexpected structure we used 2D ^{1}H–^{1}H correlation with double quantum filter (COSYDQF), inverse ^{13}C–^{1}H correlation using direct (HSQC) and remote (HMBC) ^{13}C–^{1}H coupling constants, as well as X-ray diffraction (Figure 1).¶

Thus, cyclocondensation of *peri*-substituted acetylenyl-9,10-anthraquinones with guanidine is shown to offer a novel and relatively simple approach to the poorly known anthra[9,1-*de*]-[1,3]diazocine-2,9-dione, chromeno[4,5,6-*cde*]benzo[*h*]quinoline-

† The IR spectra of new compounds were recorded on a Bruker Vector 22 spectrometer in KBr pellets. The NMR spectra were recorded on a Bruker AV 400 spectrometer (400.13 MHz) in $CDCl_3$ and Bruker-BioSpin AVANCE 600 spectrometer (600 MHz) in [$^2H_6$]DMSO. The mass spectra were obtained on a DFS (Thermo Electron Corporation) mass spectrometer by the direct injection method (the temperature of the ionization chamber was 220–270 °C and the ionization voltage was 70 eV). Merck 60 (0.063–0.2 mm) silica gel was used for column chromatography; TLC monitoring was carried out on Silufol 60 F254 (Merck, 0.2 mm) plates.

1-(3′-Hydroxy-3′-methylbutynyl)anthraquinone **1**. A mixture of 2-methylbut-3-yn-2-ol (0.8 g, 9 mmol), 1-iodoanthra-9,10-quinone (3 g, 9 mmol), $PdCl_2(PPh_3)_2$ (20 mg, 0.028 mmol), CuI (10 mg, 0.052 mmol) and Et_3N (7 ml, 38.6 mmol) in 60 ml of toluene was stirred in argon for 1.5 h at 60 °C. The reaction mixture was cooled and filtered through silica gel (25×15 mm), eluting with toluene. The solvents were evaporated at a reduced pressure, and the residue was recrystallized from toluene to give 2.1 g (80%) of 1-(3′-hydroxy-3′-methylbutynyl)anthraquinone, mp 157–158 °C (lit.,[7] mp 157.5–158.5 °C).

‡ *1 M solution of guanidine in methanol.* Small pieces of sodium (2.3 g, 0.1 mol) were slowly added to MeOH (100 ml) with stirring. When sodium was dissolved completely, guanidine hydrochloride (9.55 g, 0.1 mol) was added. The resulting mixture was stirred at room temperature for 1 h, and the white precipitate was filtered off.

§ *Reaction of* **1** *with guanidine*. A mixture of compound **1** (870 mg, 3 mmol) and guanidine (15 mmol, 15 ml of 1 M solution in methanol) in 60 ml of butan-1-ol was boiled for 4 h. The solvent was evaporated at a reduced pressure. The mixture was purified by column chromatography on silica gel (d = 25 mm, h = 210 mm, elution with benzene and then ethyl acetate). Subsequent recrystallization gave pure compounds **2**–**4**.

For **2**: yield 380 mg (38%), mp 290–290.4 °C (1,4-dioxane). IR (ν/cm^{-1}): 1662, 1688 (C=O); 3399 (OH). ^{1}H NMR ([$^2H_6$]DMSO, 600 MHz) δ: 9.17 (m, 1H, H^6), 8.18 (m, 1H, H^{13}), 8.12 (m, 1H, H^{10}), 7.91 (m, 1H, H^8), 7.89 (m, 1H, H^{12}), 7.85 (m, 1H, H^{11}), 7.68 (m, 1H, H^7), 7.63 (br. s, 2H, NH, OH), 6.96 (s, 1H, H^5), 1.54 (s, 6H, Me). ^{13}C NMR ([$^2H_6$]DMSO, 100 MHz) δ: 184.41 (C^{13b}), 183.19 (C^9), 166.92 (C^4), 166.46 (C^2), 141.49 (C^{5a}), 135.51 (C^6), 134.91 (C^{13a}), 134.40 (C^{12}), 134.30 (C^{8a}), 133.42 (C^{11}), 132.20 (C^7), 131.99 (C^{9a}), 126.90 (C^{13}), 125.87 (C^{10}), 125.62 (C^{13c}), 122.77 (C^8), 94.74 (C^5), 88.78 (C^{14}), 27.34 (2Me). HRMS, *m*/*z*: 332.1158 [M]$^+$ ($C_{20}H_{16}N_2O_3$).

For **3**: yield 80 mg (8%), mp 259.6–260 °C (benzene–ethyl acetate). IR (ν/cm^{-1}): 1629, 1643 (C=O), 3304, 3417 (NH_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.73 (d, 1H, H^{10}, J 8 Hz), 8.38 (d, 1H, H^7, J 8.64 Hz), 8.24 (d, 1H, H^5, J 8 Hz), 7.67–7.76 (m, 2H, H^9, H^8), 7.19 (d, 1H, H^4, J 8 Hz), 5.88 (s, 2H, NH_2), 1.63 (s, 6H, 2-Me). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 195.52 (C^1), 182.15 (C^6), 155.47 (C^{12}), 155.37 (C^{3a}), 153.95 (C^{10b}), 134.97 (C^{5a}), 133.86 (C^{10a}), 133.41 (C^9), 132.16 (C^8), 128.19 (C^7), 127.79 (C^5), 126.16 (C^{6a}), 126.02 (C^{10}), 122.73 (C^{12b}), 117.29 (C^{10c}), 117.13 (C^4), 94.56 (C^{12a}), 84.46 (C^2), 25.61 (2Me). HRMS, *m*/*z*: 330.1000 [M]$^+$ ($C_{20}H_{14}N_2O_3$).

For **4**: yield 100 mg (13%), mp 334–334.5 °C (1,4-dioxane). IR (ν/cm^{-1}): 1645, 1675, 1697 (C=O). ^{1}H NMR ([$^2H_6$]DMSO, 600 MHz) δ: 8.70 (d, 1H, H^5, J 8 Hz), 8.69 (s, 1H, H^{11}), 8.59–8.62 (m, 1H, H^{10}), 8.40–8.44 (m, 2H, H^4, H^7), 8.25–8.27 (m, 1H, $H^{5'}$), 8.00 (t, 1H, $H^{3'}$, J 7.54 Hz), 8.89–8.93 (m, 2H, $H^{8'}$, $H^{6'}$), 7.81–7.85 (m, 1H, $H^{7'}$), 7.77–7.81 (m, 1H, H^9), 7.70–7.74 (m, 1H, H^8, $H^{2'}$), 7.52 (d, 1H, H^4, J 8 Hz), 1.54 (s, 3H, Me), 1.49 (s, 3H, Me). ^{13}C NMR ([$^2H_6$]DMSO, 100 MHz) δ: 194.06 (C^1), 182.32 ($C^{9'}$), 182.21 ($C^{10'}$), 180.66 (C^6), 155.90 (C^{3a}), 142.05 ($C^{1'}$), 141.27 (C^{12}), 135.67 ($C^{2'}$), 134.09 ($C^{7'}$), 133.85 (C^{10a}), 133.80 ($C^{6'}$), 133.51 ($C^{4a'}$), 133.21 ($C^{8a'}$), 133.13 ($C^{3'}$), 132.90 (C^9), 132.16 ($C^{10a'}$), 131.41 (C^5), 131.04 (C^{6a}), 130.99 (C^{10b}), 130.47 ($C^{9a'}$), 129.57 (C^8), 127.11 (C^{11}), 126.87 (C^7), 126.60 (C^{10c}), 126.23 ($C^{8'}$), 126.19 ($C^{4'}$), 125.99 ($C^{5'}$), 124.38 (C^{10}), 121.16 (C^{5a}), 120.70 (C^{12b}), 119.70 (C^{12a}), 114.38 (C^4), 83.23 (C^2), 23.82 (Me), 23.67 (Me). HRMS, *m*/*z*: 520.1308 [M]$^+$ ($C_{35}H_{20}O_5$).

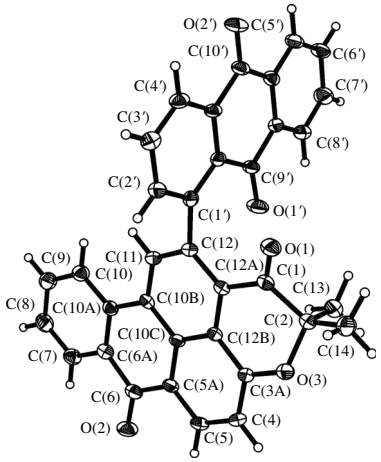


Figure 1 Molecular structure of compound **4** (only one molecule is shown from two crystallographically independent in the unit cell).

¶ *X-ray crystallographic data for compound* **4** *anisole-solvate*. $2(C_{35}H_{20}O_5) + C_7H_8O$, $M = 1149.15$, triclinicic, $P\bar{1}$, $a = 9.3307(4)$, $b = 15.1661(7)$ and $c = 20.3125(9)$ Å, $\alpha = 86.490(3)°$, $\beta = 81.537(3)°$, $\gamma = 74.426(2)°$, $V = 2738.0(2)$ Å^3, $Z = 2$, $d_{calc} = 1.394$ g cm^{-3}, $\mu(MoK\alpha) = 0.093$ mm^{-1}, $T = 173$ K, $wR_2 = 0.1447$, $S = 1.016$ for all 9569 *hkl* [$R = 0.0536$ for observed $4581I > 2\sigma(I)$].

The data were measured on a Bruker Kappa Apex II diffractometer with graphite monochromated MoKα radiation (0.71073 Å) using φ, ω scans ($2\theta < 50°$). A correction for absorption was made by an empirical method using the SADABS program (transmission of 0.84–0.93). The structure was solved by direct methods using the SHELXS-97 program and refined in the full-matrix anisotropic (isotropic for H atoms) approximation using the SHELXL-97 program. The H atom positions were located geometrically.

CCDC 752299 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2009.

1,6-dione and 12-(9,10-anthraquinon-1-yl)-2*H*-phenanthro-[2,1,10-*def*]chromene-1,6-dione systems.

This work was supported by the Russian Foundation for Basic Research (grant no. 07-03-00048-a), the Siberian Branch of the Russian Academy of Sciences [grant no. 93 (2009–2011)], the Russian Academy of Sciences [grant no. 5.9.3. (2009–2011)] and the Chemical Service Centre of the Siberian Branch of the Russian Academy of Sciences.

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Received: 2nd July 2009; Com. 09/3359