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Cyclization of Adducts of 1-Amino-2-ethynylanthraquinone and Secondary Amines

Alexandr V. Piskunov and Mark S. Shvartsberg*

Institute of Chemical Kinetics and Combustion, Siberian Branch of the Russian Academy of Sciences, 630090 Novosibirsk, Russian Federation. Fax: +7 383 235 2350; e-mail: shvarts@kinetics.nsk.su

Adducts of 1-amino-2-ethynylanthraquinone and secondary amines are cyclized to 2-dialkylamino-2,3-dihydronaphtho[2,3-*g*]-indole-6,11-diones and subsequently, depending on the reaction conditions, are either deaminated to naphtho[2,3-*g*]indole-6,11-dione or dehydrogenated to its 2-dialkylamino derivatives.

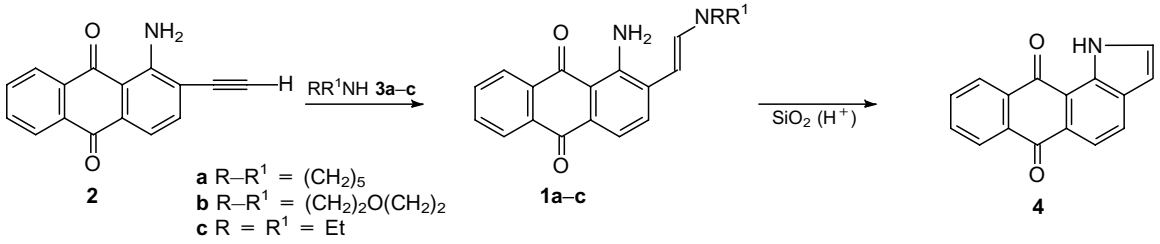
The indole nucleus is a structural fragment of many natural and synthetic drugs.[1] One of the approaches to its synthesis is based on the cyclization reaction of *ortho*-acetylenic aromatic amines. These compounds are cyclized in the presence of copper(I) and other metal salts, sometimes of bases or acids, to form a pyrrole ring.[2–6] *vic*-Alkynylaminoanthraquinones can be also transformed into naphthoindole-6,11-diones by a special method *via* adducts of these acetylenes and piperidine.[3,7] The cyclization of similar adducts of 1-amino-2-ethynylanthraquinone and secondary amines **1** is considered here in more detail.

1-Amino-2-ethynylanthraquinone **2** readily adds amines **3a**–**c** to the triple bond. The resulting compounds **1a**–**c** like the analogous adducts of 1- or 2-ethynylanthraquinone[8] are the corresponding 2-(dialkylamino)vinyl derivatives of *trans*-configuration.† These blue or violet substances are very labile and change quickly even upon weak heating in solution. On a silica gel surface or under the action of dilute HCl they give naphtho[2,3-*g*]indole-6,11-dione **4**[3] (Scheme 1).

On silica gel, **1a**–**c** almost immediately turn into red intermediates that then transform comparatively slowly to yellow coloured **4**. We have found that the same red compounds – intermediates in the cyclization on the silica gel surface can be prepared from **1a,b** in refluxing benzene within 2–3 min in 70–80% yields. It follows from analytical and

† The ^{1}H NMR spectra of **1a**–**c** contain doublets for two ethylenic protons at δ 5.0–5.6 and 6.9–7.2 ppm, *J* 13.3–13.8 Hz, as well as signals for the other protons in accordance with the structure ascribed.

‡ All compounds synthesized gave satisfactory analytical and spect-



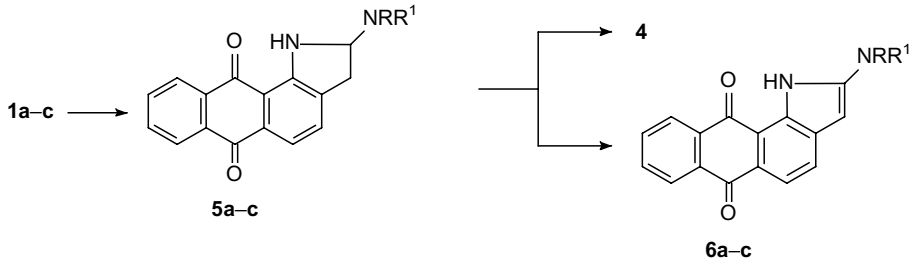
Scheme 1

spectroscopic data that they are 2-piperidino- **5a** and 2-morpholino-2,3-dihydronaphtho[2,3-*g*]indole-6,11-dione **5b**, respectively.‡ It should be noted that ethynylanthraquinones and other compounds with an activated triple bond usually add only one amine molecule.[8,9] The inclination of **1** to intramolecular addition of the amino group is probably explained by sterically closed and favourable positions of the interacting groups.

The cycloadducts **5a,b** react with dilute HCl and on silica gel to give **4**. Vinylamine **1c** cyclizes in boiling benzene much more slowly than **1a,b**, apparently due to steric hindrance. Under these conditions there is no accumulation of **5c** in the solution and it rapidly undergoes deamination to **4** (Scheme 2).

(KOH, pyridine, air, 20 °C; yields ~ 60%). Compound **6c** was obtained under the same conditions from **1c** in 22% yield side by side with **4** as the main product.

Thus, at least one (if not the only possible) route for the cyclization **2** → **4** *via* the adducts **1** includes intramolecular addition of the amino group to the double bond of **1** to yield **5** and the elimination of the secondary amine either as a direct result of the tertiary amino group protonation or by hydrolysis of **5** and subsequent dehydration. Intermediates **5** can then be aromatized in an oxidative medium without loss of the dialkylamino group to afford 2-amino-substituted naphtho[2,3-*g*]indole-6,11-diones **6**.



Scheme 2

Obviously, a motivating force for the final stage of the process under consideration is an aspiration of polycyclic system to be aromatic. However, in parallel with the deamination to **4** there is another way for aromatization of **5** – dehydrogenation affording **6**. We have succeeded in achieving this reaction of **5a,b** and in the synthesis of **6a,b**§

roscopic data. **5a**: decomp. > 140 °C (from benzene–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40–1.44 (m, 2H, γ-CH_2), 1.52–1.58 (m, 4H, β-CH_2), 2.42–2.46, 2.49–2.55 (m, 4H, CH_2NCH_2), 3.08 (dd, 1H, $J_{3a,2}$ 18.5 Hz, $J_{3a,3b}$ 3.2 Hz, H^{3a}), 3.22 (ddd, 1H, $J_{2,3a}$ 18.5 Hz, $J_{2,3b}$ 9.1 Hz, $J_{2,1}$ 1.3 Hz, H^2), 5.03 (dd, 1H, $J_{3b,2}$ 9.1 Hz, $J_{3b,3a}$ 3.2 Hz, H^{3b}), 7.29 (d, 1H, *J* 7.3 Hz, $H^{4(5)}$), 7.54 (d, 1H, *J* 7.3 Hz, $H^{5(4)}$), 7.69–7.76 (m, 2H, $H^{8,9}$), 8.09 (br.s, 1H, NH), 8.24–8.27 (m, 2H, $H^{7,10}$).

5b: decomp. > 120 °C (from benzene–hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50–2.60 (m, 4H, CH_2NCH_2), 3.06 (dd, 1H, $J_{3a,2}$ 18.5 Hz, $J_{3a,3b}$ 3.4 Hz, H^{3a}), 3.23 (ddd, 1H, $J_{2,3a}$ 18.5 Hz, $J_{2,3b}$ 9.0 Hz, $J_{2,1}$ 1.5 Hz, H^2), 3.65–3.70 (m, 4H, CH_2OCH_2), 5.01 (dd, 1H, $J_{3b,2}$ 9.0 Hz, $J_{3b,3a}$ 3.4 Hz, H^{3b}), 7.31 (d, 1H, *J* 7.3 Hz, $H^{4(5)}$), 7.57 (d, 1H, *J* 7.3 Hz, $H^{5(4)}$), 7.70–7.80 (m, 2H, $H^{8,9}$), 8.06 (br.s, 1H, NH), 8.23–8.27 (m, 2H, $H^{7,10}$).

§ **6a**: m.p. 219.5–221 °C (from benzene–hexane); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.75 (br.s, 6H, β-, β′- and γ-CH_2), 3.35 (br.s, 4H, CH_2NCH_2), 5.53 (d, 1H, *J* 2.0 Hz, H^3), 7.48 (d, 1H, *J* 7.8 Hz, $H^{4(5)}$), 7.60–7.80 (m, 2H, $H^{8,9}$), 7.92 (d, *J* 7.8 Hz, $H^{5(4)}$), 8.10–8.35 (m, 2H, $H^{7,10}$), 10.15 (br.s, 1H, NH).

6b: m.p. 264–266 °C (from benzene); ^{1}H NMR (90 MHz, $CDCl_3$) δ 3.15–3.40 (m, 4H, CH_2NCH_2), 3.75–4.00 (m, 4H, CH_2OCH_2), 5.60 (d, 1H, *J* 2.0 Hz, H^3), 7.57 (d, 1H, *J* 7.5 Hz, $H^{4(5)}$), 7.65–7.80 (m, 2H, $H^{8,9}$), 7.98 (d, 1H, *J* 7.5 Hz, $H^{5(4)}$), 8.10–8.35 (m, 2H, $H^{7,10}$), 10.22 (br. s, 1H, NH).

6c: m.p. 155.5–157 °C (from benzene–hexane); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.32 (t, 6H, *J* 6.8 Hz, Me), 3.47 (q, 4H, *J* 6.8 Hz, CH_2), 5.45 (d, 1H, *J* 2.0 Hz, H^3), 7.43 (d, 1H, *J* 7.8 Hz, $H^{4(5)}$), 7.60–7.80 (m, 2H, $H^{8,9}$), 7.93 (d, 1H, *J* 7.8 Hz, $H^{5(4)}$), 8.10–8.35 (m, 2H, $H^{7,10}$), 10.15 (br.s, 1H, NH).

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