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Synthesis of 2-Aryl-1-hydroxy-1*H*-naphtho[2,3-*d*]imidazole-4,9-diones by Reaction of 2-Benzylamino-1,4-naphthoquinones with Nitric Acid

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Abstract—2-Aryl-1-hydroxy-1*H*-naphtho[2,3-*d*]imidazole-4,9-diones were synthesized by treatment of 2-benzylamino-1,4-naphthoquinones with a mixture of nitric and sulfuric acids in acetic acid.

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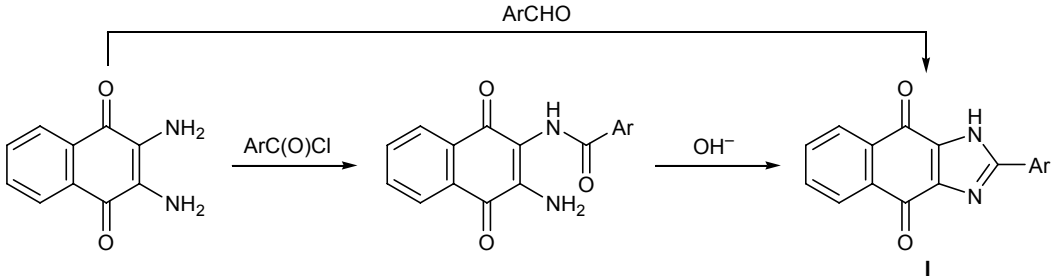
Heterocyclic quinoid compounds containing a fused imidazole ring exhibit various kinds of biological activity. For example, benzimidazoledione derivatives showed anticancer activity [1]. Naphtho[2,3-*d*]imidazole-4,9-diones attract interest as bacteriostatic agents [2]. Nowadays, increased interest is observed in fused *N*-hydroxyimidazoles since they also display diverse biological activity. *N*-Hydroxybenzimidazole derivatives were reported to control the activity of some common microbial species via inhibition of their growth and resistance to antibiotics and oxidants [3].

2-Aryl-1*H*-naphtho[2,3-*d*]imidazole-4,9-diones **I** are generally synthesized by reactions of 2,3-diamino-1,4-naphthoquinone with aromatic aldehydes [1] or acid chlorides [2] (Scheme 1). *N*-Hydroxyimidazole ring is formed in reactions of vicinal nitroso amines with aldehydes [4], as well as in base-catalyzed cyclization of 2-benzylaminonitroarenes [3] (Scheme 2). We have found that treatment of 2-benzylamino-1,4-naphthoquinones **IIa**–**IIc** with a nitrating mixture in acetic acid gives 2-aryl-1-hydroxy-1*H*-naphtho[2,3-*d*]-imidazole-4,9-diones (hydroxyimidazoles) **IIIa**–**IIIc** (Scheme 3).

Presumably, the transformation **II**→**III** involves nitration of initial compounds **IIa**–**IIc** and fast cyclization of intermediate 2-benzylamino-3-nitro-1,4-naphthoquinones **IVa**–**IVc** to *N*-hydroxyimidazoles **IIIa**–**IIIc**, though nitroquinones **IVa**–**IVc** were not detected in the reaction mixture by chromatography. Compounds **IIIa**–**IIIc** are the first representatives of fused quinoid hydroxyimidazoles. Accessibility of these compounds opens a simple route to 2-aryl-1*H*-naphtho[2,3-*d*]imidazole-4,9-diones **I** (Scheme 4).

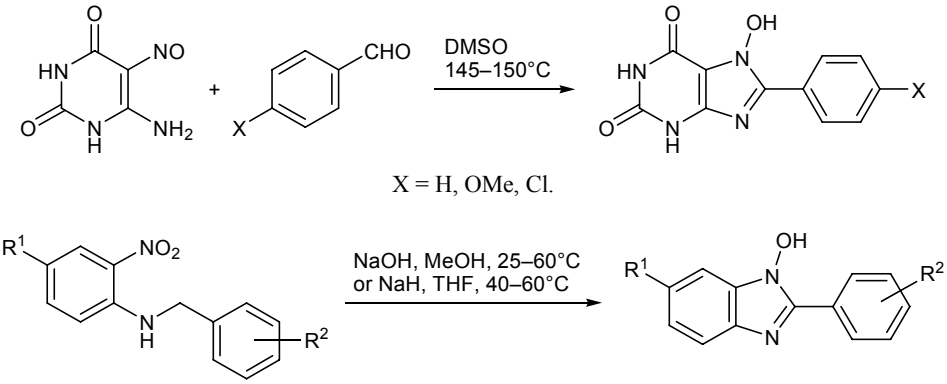
The structure of hydroxyimidazoles **IIIa**–**IIIc** was confirmed by spectral data. The ^{1}H NMR spectra of **IIIa**–**IIIc** were identical to those of 2-aryl-1*H*-naphtho[2,3-*d*]imidazole-4,9-diones **I**; proton in the hydroxy group of **IIIa**–**IIIc** resonated as a broadened singlet at δ 13.10–13.30 ppm. In the IR spectrum of **IIIa**, absorption bands due to stretching vibrations of

Scheme 1.



I

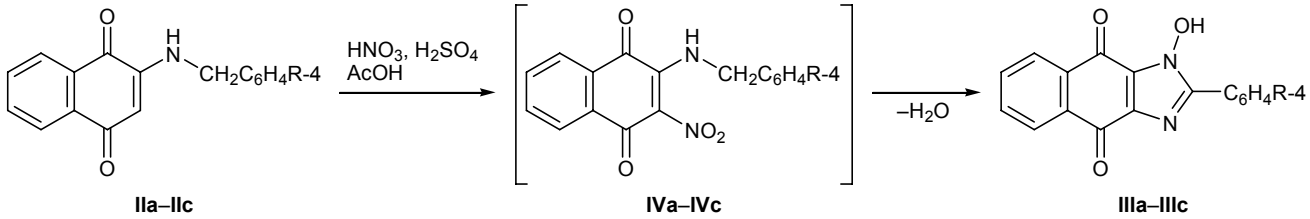
Scheme 2.



X = H, OMe, Cl.

$R^1 = NO_2$, H, F, CN; R^2 = H, 4-Br, 4-OH, 4-OMe, 2-NH_2, 4-NH_2, 3-NH_2, 4-OPh, 4-NMe_2, 3-NMe_2, 2-NHAc, 4-NHAc, 3-NHAc, 4-NHC(O)Ph.

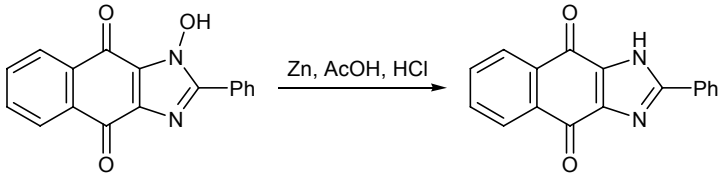
Scheme 3.



IIa–IIc **IVa–IVc** **IIIa–IIIc**

R= H (**a**), Me (**b**), Cl (**c**).

Scheme 4.

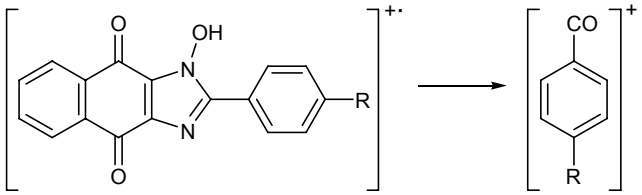


IIIa **Ia**

the carbonyl groups appeared at 1680 and 1662 cm^{-1}. It is known that intramolecular hydrogen bonding in 1-hydroxy- and 1-amino-9,10-anthraquinones leads to low-frequency shift of the carbonyl absorption bands [5]. Presumably, intramolecular hydrogen bonds are also formed in compounds **IIIa**–**IIIc**.

The UV spectra of *N*-hydroxyimidazoles **IIIa**–**IIIc** and naphthoimidazole **Ia** were almost identical. The molecular ion peaks in the mass spectra of **IIIa**–**IIIc** had low intensity; the most abundant fragment ions were acylium ions which are likely to be formed with participation of the hydroxy group (Scheme 5). Unlike compounds **IIIa**–**IIIc**, the molecular ion peak in the mass spectrum of **Ia** was the most intense, while the intensity of the benzoyl cation peak $[PhCO]^+$ was low (8.10%), which indicated a different fragmentation pattern.

Scheme 5.



Thus we have found a convenient synthetic approach to 2-aryl-1-hydroxy-1*H*-naphtho[2,3-*d*]imidazole-4,9-diones **IIIa**–**IIIc**.

EXPERIMENTAL

The ^1H NMR spectra were recorded on a Bruker DRX spectrometer at 500 MHz from solutions in DMSO-d_6, The chemical shifts were measured relative

to tetramethylsilane as internal reference. The mass spectra were obtained on a Finnigan MAT 8200 instrument. The electronic absorption spectra were recorded on an Evolution 300 spectrophotometer from solutions in ethanol (cell path length 1 cm, $c = 2\times10^{-4}$ M). The IR spectra were obtained on a Tensor 27 instrument from samples pelleted with KBr. The progress of reactions and the purity of the isolated compounds were monitored by TLC on Silufol plates using acetone–toluene (1 : 4) as eluent. The melting points were determined on a Boetius micro hot stage. 1,4-Naphthoquinone used in the synthesis of **IIa**–**IIc** was commercial product (from Acros Organics). Compound **IIa** was synthesized as described in [6].

2-[(4-Methylbenzyl)amino]-1,4-dihydronaphthalene-1,4-dione (IIb). 4-Methylbenzylamine, 4.84 g (40.00 mmol), was added to 4.80 g (30.38 mmol) of 1,4-naphthoquinone in 40 ml of isopropyl alcohol, and the mixture was stirred for 3 h at 20°C. The mixture was then kept for 15 h at –10°C, and the orange precipitate was filtered off, washed with aqueous alcohol and water, and recrystallized from alcohol. Yield 4.80 g (53%), mp 168–170°C. UV spectrum: λ_{max} 454 nm (logε 3.55). ^{1}H NMR spectrum, δ, ppm: 2.25 s (3H, Me), 4.40 d (2H, CH_2, J = 7.0 Hz), 5.50 s (1H, 3-H), 7.14 d (2H, 3′-H, 5′-H, J = 8.0 Hz), 7.24 d (2H, 2′-H, 6′-H, J = 8.0 Hz), 7.72 t and 7.81 t (1H each, 6-H, 7-H, J = 7.0 Hz), 7.90 d and 8.99 d (1H each, 5-H, 8-H, J = 7.0 Hz), 8.10 br.s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 277 (39.84) $[M]^+$, 260 (25.93), 105 (100), 89 (10.11), 32 (76.68). Found, %: C 78.00; H 5.22; N 5.14. $C_{18}H_{15}NO_2$. Calculated, %: C 77.98; H 5.41; N 5.05. M 272.32.

2-[(4-Chlorobenzyl)amino]-1,4-dihydronaphthalene-1,4-dione (IIc). A solution of 6.00 ml (49.35 mmol) of 4-chlorobenzylamine in 10 ml of ethanol was added to 4.80 g (30.38 mmol) of 1,4-naphthoquinone in 30 ml of ethanol, and the mixture was stirred for 2 h at 20°C. The mixture was then kept for 12 h at –10°C, and the red–brown precipitate was filtered off and washed with aqueous alcohol and water. Yield 4.40 g (49%), mp 215–217°C. UV spectrum: λ_{max} 452 nm (logε 3.49). ^{1}H NMR spectrum, δ, ppm: 4.44 d (2H, CH_2, J = 6.5 Hz), 5.56 s (1H, 3-H), 7.37– 7.42 m (4H, 2′-H, 3′-H, 5′-H, 6′-H), 7.73 t and 7.81 t (1H each, 6-H, 7-H, J = 7.0 Hz), 7.90 d and 8.00 d (1H each, 5-H, 8-H, J = 7.0 Hz), 8.19 t (1H, NH, J = 6.5 Hz). Mass spectrum, m/z (I_{rel}, %): 297 (34.53) $[M]^+$, 280 (27.53), 125 (100), 89 (38.74), 32 (23.52). Found, %: C 68.60; H 4.02; Cl 11.33; N 4.37. $C_{17}H_{12}ClNO_2$. Calculated, %: C 68.57; H 4.03; Cl 11.93; N 4.71. M 297.74.

1-Hydroxy-2-phenyl-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione (IIIa). A mixture of 1.5 ml of 60% nitric acid and 2.5 ml of 94% sulfuric acid was added dropwise to 1.32 g (5.02 mmol) of compound **IIa** in 30 ml of acetic acid, and the mixture was stirred for 3 h at 20°C. The mixture was then poured onto 250 g of ice. The yellow–orange precipitate was filtered off, washed with water, and dried. A 1.14-g portion of the dry product was heated for 5 min in 20 ml of boiling chloroform, the mixture was cooled, and the yellow precipitate was filtered off. Yield 0.98 g (67%), mp 248–250°C. UV spectrum, λ_{max}, nm (logε): 332 (3.47), 392 (3.19). IR spectrum, ν, cm^{-1}: 3425 br (NOH), 1680–1662 s (C=O). ^{1}H NMR spectrum, δ, ppm: 7.55–7.63 m (3H, 3′-H, 4′-H, 5′-H), 7.86 d and 7.88 t (1H each, 5-H, 8-H, J = 5.5 Hz), 8.12 t (2H, 6-H, 7-H, J = 5.5 Hz), 8.19 d (2H, 2′-H, 6′-H, J = 7.5 Hz), 13.20 br.s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 290 (2.50) $[M]^+$, 114 (19.12), 105 (100), 77 (28.63), 39 (6.71). Found, %: C 70.81; H 3.48; N 9.60. $C_{17}H_{10}N_2O_3$. Calculated, %: C 70.34; H 3.44; N 9.65. M 290.30.

Compounds **IIIb** and **IIIc** were synthesized in a similar way.

1-Hydroxy-2-(4-methylphenyl)-1*H*-naphtho-[2,3-*d*]imidazole-4,9-dione (IIIb) was synthesized from 1.39 g (5.02 mmol) of compound **IIb**. The reaction mixture was stirred for 1.5 h at 20°C, and the product was recrystallized from 2-ethoxyethanol. Yield 0.98 g (64%), mp 268–270°C. UV spectrum, λ_{max}, nm (logε): 335 (3.45), 400 (3.14). ^{1}H NMR spectrum, δ, ppm: 2.36 s (3H, Me), 7.39 d (2H, 3′-H, 5′-H, J = 8.0 Hz), 7.86 d and 7.87 d (1H each, 5-H, 8-H, J = 3.3 Hz), 8.09 d (2H, 2′-H, 6′-H, J = 8.0 Hz), 8.10–8.13 m (2H, 6-H, 7-H), 13.10 br.s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 304 (3.70) $[M]^+$, 288 (7.31), 119 (100), 91 (17.92), 32 (11.01). Found, %: C 70.97; H 3.86; N 9.12. $C_{18}H_{12}N_2O_3$. Calculated, %: C 71.05; H 3.95; N 9.21. M 304.30.

2-(4-Chlorophenyl)-1-hydroxy-1*H*-naphtho-[2,3-*d*]imidazole-4,9-dione (IIIc) was synthesized from 1.50 g (5.04 mmol) of compound **IIc**. The reaction mixture was stirred for 3 h at 20°C. The product was recrystallized from toluene–DMF (1 : 1). Yield 1.19 g (73%), mp 295– 297°C. UV spectrum, λ_{max}, nm (logε): 331 (3.55), 392 (3.15). ^{1}H NMR spectrum, δ, ppm: 7.66 d (2H, 3′-H, 5′-H, J = 8.5 Hz), 7.86 d and

7.88 d (1H each, 5-H, 8-H, J = 3.3 Hz), 8.09–8.14 m (2H, 6-H, 7-H), 8.22 d (2H, 2′-H, 6′-H, J = 8.5 Hz), 13.30 br.s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 324 (4.80) $[M]^+$, 139 (100), 101 (19.82), 76 (24.22), 32 (21.82). Found, %: C 62.85; H 2.69; Cl 10.36; N 8.36. $C_{17}H_9ClN_2O_3$. Calculated, %: C 62.87; H 2.77; Cl 10.94; N 8.63. M 324.72.

2-Phenyl-1*H*-naphtho[2,3-*d*]imidazole-4,9-dione (Ia). A mixture of 0.58 g (2.00 mmol) of compound **IIIa**, 20 ml of acetic acid, and 2 ml of concentrated aqueous HCl was heated for 15 min at 60°C. Zinc dust, 0.65 g (10.00 mmol), was then added gradually, and the mixture was heated for 1.5 h more. When the reaction was complete, the mixture was heated to the boiling point and filtered. After cooling, the yellow precipitate was filtered off and washed with water and alcohol. Yield 0.42 g (77%), mp 339–341°C. UV spectrum, λ_{max}, nm (logε): 339 (3.43), 402 (3.26). ^{1}H NMR spectrum, δ, ppm: 7.51–7.60 m (3H, 3′-H, 4′-H, 5′-H), 7.86 d and 7.87 d (1H each, 5-H, 8-H, J = 3.3 Hz), 8.10–8.14 m (2H, 6-H, 7-H), 8.25 d (2H, 2′-H, 6′-H, J = 7.8 Hz), 14.40 s (1H, NH). Mass spectrum, m/z (I_{rel}, %): 274 (100) $[M]^+$, 171 (39.84), 130 (34.23), 104 (45.75), 76 (37.64), 32 (98.90). M 274.28.

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