Reactions of 2-hydroxynaphthazarins with cyclohexane-1,2-dione as a new method for the synthesis of pyranonaphthazarin systems

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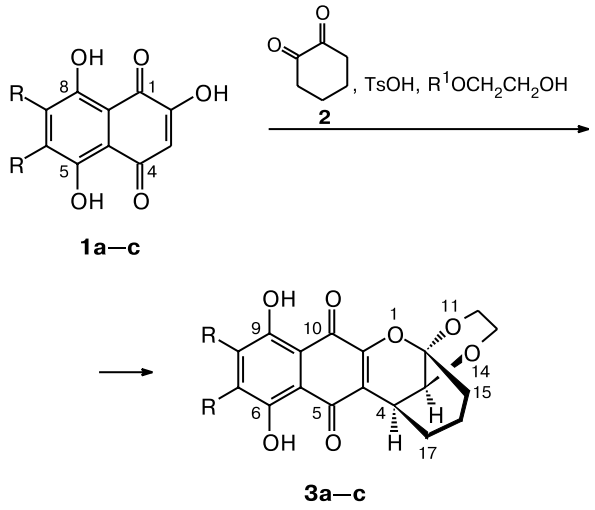
3,4-Dihydro-2*H*-naphtho[2,3-*b*]pyran-5,10-diones are produced by many micro- and macroorganisms in the living nature.[1,2] Most often, they are derivatives of parent 1,4-naphthoquinone or 5-hydroxy-1,4-naphthoquinone (juglone) and more rarely, of 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin). Only a few examples of natural pyranonaphthazarins are known.[1,2] Approaches to their synthesis[3,4] are scanty and the first of them[3] is of low utility due to complexity and a large number of steps involved.

We found that reactions of 2-hydroxynaphthazarins (**1**) with cyclohexane-1,2-dione (**2**) open up a facile and a rather efficient route to pyranonaphthazarin systems.

Scheme 1



1, 3: R = Cl (**a**), Me (**b**), H (**c**)
2: R^1 = H, Me, $(CH_2)_2OMe$

The reactions of compounds **1a—c** with dione **2** under conditions of acid catalysis take place only in an alcohol solution; the best choice is heating in a solution in ethylene glycol or its monoethers. Irrespective of the group R^1 in $R^1OCH_2CH_2OH$, the reaction gives pentacyclic pyranonaphthazarins **3a—c** in 40—85% yields (Scheme 1). The structure of these products was established using various 1D (DEPT-135) and 2D (COSY-45, HMBC, HMQC) ^1H and ^{13}C NMR techniques. The relative stereochemistry of stereogenic centers, C(2), C(3), and C(4), in compounds **3a—c** was established by NOE experiments for **3a**, in particular, irradiation of the α-axial proton at C(3) induces NOE effects for the signals of the α-axial protons at C(15) (~7%), C(17) (~7%), and C(13) (~5%) and the α-equatorial proton at C(4) (~16%), while irradiation of the α-equatorial proton at C(4) entails NOE effects for the signals of α-axial protons at C(3) (~9%) and C(15) (~4%). Study of the mechanism of this reaction is the subject of further research.

^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX-300 spectrometer (300.13 MHz for ^1H and 75.47 MHz for ^{13}C) in $CDCl_3$ (Me_4Si as the internal standard). IR spectra were measured on a Bruker Vector 22 FT spectrometer in $CHCl_3$. Mass spectra (EI, 70 eV) were run on an LKB-9000S instrument. The reactions were monitored and the purity of the obtained compounds was checked by TLC on Merck 60 F-254 plates in a hexane—Me_2CO system (2 : 1). The individual compounds were isolated by preparative TLC (PTLC) on 20×20 cm plates with an unbound silica gel layer (5—40 μm, pretreated with oxalic acid) in a 2 : 1 hexane—Me_2CO system. Melting points were determined on a Boetius hot stage and not corrected. Compounds **1b,c** were prepared by analogy[5] with the synthesis of **1a**. Commercial cyclohexane-1,2-dione (Aldrich) was used in the reactions.

Synthesis of pyranonaphthazarins 3a—c (general procedure). A solution of the required 2-hydroxynaphthazarin **1** (1.0 mmol), 1,2-diketone **2** (5.0 mmol), and anhydrous TsOH (0.05 mmol) in 5 mL of anhydrous 2-methoxyethanol was refluxed for 10—12 h. The reaction mixture was cooled, diluted with water (20 mL), and extracted with EtOAc (4×10 mL). The combined extracts were washed with saturated brine (3×20 mL) and dried with Na_2SO_4 and the solvent was evaporated. The products were isolated by PTLC.

(2*S*,3*R*,4*R*)-7,8-Dichloro-2,3-ethylenedioxy-6,9-dihydroxy-2,4-trimethylene-3,4-dihydronaphtho[2,3-*b*]pyran-5,10(2*H*)-dione (3a). Yield 79%, R_f 0.54, m.p. 233—235 °C. Found (%): C, 52.58; H, 3.45; Cl, 17.51. $C_{18}H_{14}Cl_2O_7$. Calculated (%): C, 52.32; H, 3.42; Cl, 17.16. IR, ν/cm^{-1}: 3500—2100 (OH); 1611 (C=O, C=C); 1592 (C=C); 1560 (C=C); 1451; 1408; 1397; 1290; 1125. ^1H NMR, δ: 1.39—1.97 (m, 5 H, C(16)H_{ax}, C(16)H_{eq}, C(15)H_{ax}, C(17)H_{ax}, C(17)H_{eq}); 2.18 (ddt, 1 H,

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C(15)H_{eq}, J = 1.3 Hz, J = 1.3 Hz, J = 5.3 Hz, J = 13.7 Hz); 3.54 (q, 1 H, C(4)H, J = 3.4 Hz); 3.66 (dd, 1 H, C(12)H_{eq}, J = 2.7 Hz, J = 12.0 Hz); 3.77 (dd, 1 H, C(13)H_{eq}, J = 3.2 Hz, J = 12.0 Hz); 3.78 (d, 1 H, C(3)H, J = 3.4 Hz); 3.91 (ddd, 1 H, C(13)H_{ax}, J = 2.7 Hz, J = 12.0 Hz, J = 12.0 Hz); 4.21 (ddd, 1 H, C(12)H_{ax}, J = 3.2 Hz, J = 12.0 Hz, J = 12.0 Hz); 12.84 (s, 1 H, C(9)OH); 13.37 (s, 1 H, C(6)OH). ^{13}C NMR, δ: 18.4 (C(16)); 29.2 (C(17)); 33.5 (C(4)); 36.1 (C(15)); 61.6 (C(12)); 66.4 (C(13)); 72.9 (C(3)); 101.2 (C(2)); 108.8 (C(5a)); 110.1 (C(9a)); 121.2 (C(4a)); 132.7 (C(8)); 135.0 (C(7)); 156.2 (C(10a)); 156.3 (C(6)); 157.3 (C(9)); 177.2 (C(5)); 183.2 (C(10)). MS, m/z (I_{rel} (%)): 417 $[M + 1]^+$ (4.2), 416 $[M]^+$ (17.3), 415 $[M - 1]^+$ (19.5), 414 $[M]^+$ (87.2), 413 $[M - 1]^+$ (28.7), 412 $[M]^+$ (98.6), 411 $[M - 1]^+$ (28.4), 330 $[M - C_4H_6O_2]^+$ (6.5), 328 $[M - C_4H_6O_2]^+$ (23.6), 326 $[M - C_4H_6O_2]^+$ (33.9), 278 $[M - C_4H_6O_2 - C_4H_4]^+$ (8.3), 276 $[M - C_4H_6O_2 - C_4H_4]^+$ (9.4), 274 $[M - C_4H_6O_2 - C_4H_4]^+$ (13.8), 69 (100).

(2*S*,3*R*,4*R*)-2,3-Ethylenedioxy-6,9-dihydroxy-7,8-dimethyl-2,4-trimethylene-3,4-dihydronaphtho[2,3-*b*]pyran-5,10(2*H*)-dione (3b). Yield 63%, R_f 0.53, m.p. 211—215 °C. Found (%): C, 64.30; H, 5.48. $C_{20}H_{20}O_7$. Calculated (%): C, 64.51; H, 5.42. IR, ν/cm^{-1}: 3450—2120 (OH); 1602 (C=O, C=C); 1580 (C=C); 1456; 1423; 1394; 1295; 1252; 1130. ^{1}H NMR, δ: 1.40—1.96 (m, 5 H, C(16)H_{ax}, C(16)H_{eq}, C(15)H_{ax}, C(17)H_{ax}, C(17)H_{eq}); 2.18 (ddt, 1 H, C(15)H_{eq}, J = 1.3 Hz, J = 1.3 Hz, J = 5.2 Hz, J = 13.8 Hz); 2.26 (s, 6 H, C(7)Me, C(8)Me); 3.53 (q, 1 H, C(4)H, J = 3.3 Hz); 3.63 (dd, 1 H, C(12)H_{eq}, J = 2.7 Hz, J = 12.0 Hz); 3.75 (d, 1 H, C(3)H, J = 3.3 Hz); 3.76 (dd, 1 H, C(13)H_{eq}, J = 3.1 Hz, J = 12.0 Hz); 3.90 (ddd, 1 H, C(13)H_{ax}, J = 2.7 Hz, J = 12.0 Hz, J = 12.0 Hz); 4.24 (ddd, 1 H, C(12)H_{ax}, J = 3.1 Hz, J = 12.0 Hz, J = 12.0 Hz); 13.06 (s, 1 H, C(9)OH); 13.42 (s, 1 H, C(6)OH). ^{13}C NMR, δ: 12.3 (C(18)); 12.6 (C(19)); 18.5 (C(16)); 29.4 (C(17)); 33.5 (C(4)); 36.3 (C(15)); 61.5 (C(12)); 66.4 (C(13)); 73.3 (C(3)); 100.3 (C(2)); 107.7 (C(5a)); 109.4 (C(9a)); 120.5 (C(4a)); 137.7 (C(8)); 140.4 (C(7)); 155.8 (C(10a)); 161.0 (C(6)); 162.4 (C(9)); 175.9 (C(5)); 182.2 (C(10)). MS, m/z (I_{rel} (%)): 373 $[M + 1]^+$ (23.2), 372 $[M]^+$ (100), 371 $[M - 1]^+$ (44.3), 286 $[M - C_4H_6O_2]^+$ (9.6), 234 $[M - C_4H_6O_2 - C_4H_4]^+$ (13.8)).

(2*S*,3*R*,4*R*)-2,3-Ethylenedioxy-6,9-dihydroxy-2,4-trimethylene-3,4-dihydronaphtho[2,3-*b*]pyran-5,10(2*H*)-dione (3c). Yield 44%, R_f 0.53, m.p. 203—205 °C. Found (%): C, 62.90; H, 4.59. $C_{18}H_{16}O_7$. Calculated (%): C, 62.79; H, 4.68. IR, ν/cm^{-1}: 3460—2190 (OH); 1608 (C=O, C=C); 1575 (C=C); 1504; 1457; 1286; 1249; 1147; 1123. ^{1}H NMR, δ: 1.40—1.96 (m, 5 H, C(16)H_{ax}, C(16)H_{eq}, C(15)H_{ax}, C(17)H_{ax}, C(17)H_{eq}); 2.19 (ddt, 1 H, C(15)H_{eq}, J = 1.3 Hz, J = 1.3 Hz, J = 5.2 Hz, J = 13.7 Hz); 3.54 (q, 1 H, C(4)H, J = 3.4 Hz); 3.66 (dd, 1 H, C(12) H_{eq}, J = 2.7 Hz, J = 12.0 Hz); 3.76 (d, 1 H, C(3)H, J = 3.4 Hz); 3.77 (dd, 1 H, C(13)H_{eq}, J = 2.7 Hz, J = 12.0 Hz); 3.91 (ddd, 1 H, C(13)H_{ax}, J = 2.7 Hz, J = 12.0 Hz, J = 12.0 Hz); 4.23 (ddd, 1 H, C(12)H_{ax}, J = 2.7 Hz, J = 12.0 Hz, J = 12.0 Hz); 7.18 (d, 1 H, C(8)H, J = 10.6 Hz); 7.26 (d, 1 H, C(7)H, J = 10.6 Hz); 12.29 (s, 1 H, C(9)OH); 12.72 (s, 1 H, C(6)OH). ^{13}C NMR, δ: 18.5 (C(16)); 29.3 (C(17)); 33.4 (C(4)); 36.2 (C(15)); 61.6 (C(12)); 66.4 (C(13)); 73.1 (C(3)); 100.8 (C(2)); 110.9 (C(5a)); 111.7 (C(9a)); 121.9 (C(4a)); 128.3 (C(8)); 130.5 (C(7)); 156.4 (C(10a)); 157.1 (C(6)); 158.4 (C(9)); 181.1 (C(5)); 186.7 (C(10)). MS, m/z (I_{rel} (%)): 345 $[M + 1]^+$ (3.4), 344 $[M]^+$ (11.5), 258 $[M - C_4H_6O_2]^+$ (5.6), 206 $[M - C_4H_6O_2 - C_4H_4]^+$ (19.8), 59 (100).

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