SYNTHESIS OF FURANONAPHTHAZARIN DERIVATIVES

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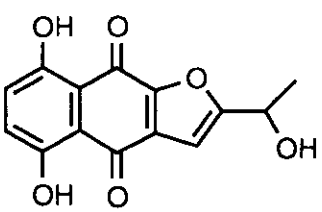
Abstract - A three-step synthesis of the 5,8-dihydroxy-2-(1-methylethyl)naphtho[2,3-*b*]furan-4,9-dione (**9**) starting from 2-hydroxy-5,8-dimethoxy-1,4-naphthoquinone (**4**), is described. Further treatment of (**9**) with selenium dioxide in the presence of pyridine *N*-oxide as co-oxidant gave 2-(1-hydroxy-1-methylethyl)naphtho[2,3-*b*]furan-4,9-dione (**10**).

The biological activity of naturally occurring or synthetic naphthofuran-4,9-diones has stimuled the attention of synthetic chemist and several methods have been described.[1] It has been recently reported that the chloroform extract of *Tabebuia ochracea* ssp. *neochrysanta*, has shown cytotoxicity against melanoma B16 cells, and antimalarial activity *in vitro* against strains of *Plasmodium bergei*. The new naphthofuran-4,9-diones (**1**) and (**2**) along with four known derivatives were isolated from this extract.[2] The heterocyclic quinone (**1**) is the first example of a natural product in which the furan nucleus is fused to a 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) system.



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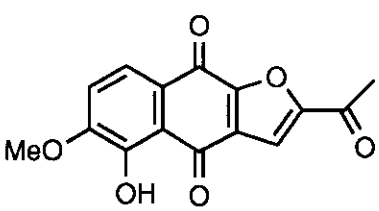

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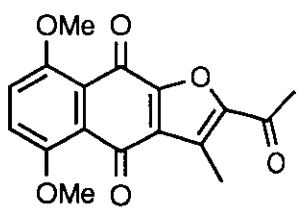

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Following our studies on the synthesis of heterocyclic quinones with potential biological activity,[3] we report here the synthesis of furanonaphthazarins (**7**-**10**).

To the best of our knowledge, the synthesis of the acetyl derivative (**3**) in three step from 5,8-dimethoxynaphthalene-1,4-dione in 19 % yield, is the only approach to a furanonaphthazarin derivative described in the literature.[4]

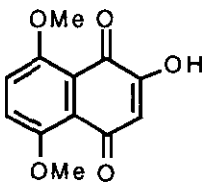
In order to obtain a furanonaphthazarin system employing a different approach, we decided to take advantage of our experience on the use of hydroxynaphthoquinones in the synthesis of pyranonaphthoquinones and use of hydroxynaphthoquinone (**4**) as a starting material.[5] The hydroxyquinone (**4**) was subjected to a modified Hooker reaction[6] with 3-methylbutanal and triethylamine in acetonitrile to produce the isopentenylnaphthoquinone (**5a**) in 43 % yield after column chromatography. Oxidative cyclization of **5a** was then attempted using DDQ.

The oxidative cyclization of naphthoquinones related to **5a** has been reported. [7-9] The reaction of **5b** with DDQ at room temperature gave a mixture of pyranonaphthoquinones,[7] while isopentenylnaphthoquinones (**5c**)[8] and (**5d**)[9] afforded mixtures of pyranonaphthoquinones and furanonaphthoquinones, the later being the minor components. A mechanism for this process has been proposed.[7]

The oxidative cyclization of **5a** with DDQ in methylene chloride at room temperature gave a mixture of pyranonaphthoquinone (**6**) and furanonaphthoquinones (**7**) and (**8**) in yields of 11 %, 28 % and 18 % respectively. The yield of the furanonaphthoquinone (**7**) can be increased to 41 % by isomerizing the *ortho*-quinone (**8**) in acid media.[8,10] The predominant formation of furanonaphthoquinones in the oxidation of **5a** might be attributed to a nucleophilicity increase of the hydroxyl group due to the directing effect of the methoxy groups on the aromatic ring.[11]

^{1}H, ^{13}C, and MS data clearly showed that **7** and **8** were isomers. The specific assignment of structures was based on their IR and UV spectra. The IR spectra of *para*-quinone (**7**) showed absorption bands at 1660 and 1670 cm^{-1} for carbonyl groups, while in *ortho*-quinone (**8**) the interaction of the two carbonyl groups shift the absorptions to higher wavenumber, 1660 and 1685 cm^{-1}. Furthermore, in the UV spectra the dark purple *ortho*-quinone (**8**) showed a more intense absorption band at longer wavelength than the yellow *para*-quinone (**7**). Demethylation of furanonaphthoquinone (**7**) with 20 % sulfuric acid under reflux for 3 h gave furanonaphthazarin (**9**) in 55 %.

Considering that a number of furanonaphthoquinones have an hydroxyl group on the side chain



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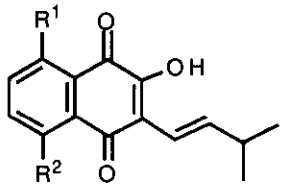
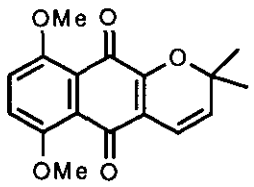


5 a $R^1 = R^2 = OMe$
5 b $R^1 = R^2 = H$
5 c $R^1 = OMe$, $R^2 = H$
5 d $R^1 = OH$, $R^2 = H$



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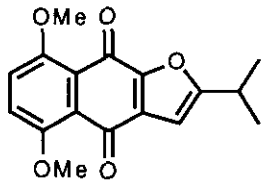

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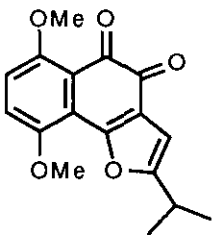

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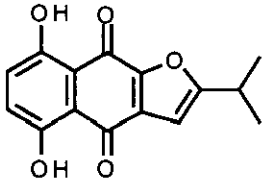

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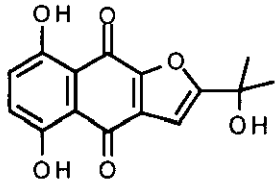

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at C-2, the oxidation of quinone (**9**) with selenium dioxide was then examined.[12] The reaction of furanonaphthazarin (**9**) with selenium dioxide was carried out in the presence of pyridine *N*-oxide as co-oxidant[13] in dioxane under reflux for 3 day and gave furanonaphthazarin (**10**) in 80 % yield. This is a simple and convenient method for the hydroxylation of 2-alkyl substituted furanonaphthoquinones.

The furanonaphthazarins synthesized in this study are currently under evaluation for their biological activity.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are not corrected. IR spectra were recorded on a Bruker Model Vector 22 spectrophotometer. UV spectra were taken

on a Milton Roy Spectronic 3000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-200 spectrometer, using tetramethylsilane as internal reference. Column chromatography was performed on silica gel Merck 60 (70-230 mesh). Elemental analysis was carried out on a Hereaus CHN analyzer. Accurate MS measurements were determined at the SERC Mass Spectrometry Centre, Leicester University.

2-Hydroxy-3-(3-methyl-1-butenyl)-5,8-dimethoxynaphthalene-1,4-dione (**5a**).

A stirred mixture of **4** (300 mg, 0.78 mmol), 3-methylbutanal (0.25 mL, 2.34 mmol), triethylamine (1.5 mL) and 4 A° molecular sieves (2.0 g) in acetonitrile (15 mL) was heated under reflux for 16 h. After cooling, the mixture was filtered and then evaporated. The residue was acidified with 5 % HCl and extracted with dichloromethane (4x50 mL). The extract was dried ($MgSO_4$) and evaporated. The residue was purified by column chromathography (dichloromethane-ethyl acetate, 4:1) to give isopentenylquinone (**5a**) (165 mg, 43 %); mp 149-151 °C (ethyl acetate-hexane). IR (KBr): 3240 (OH), 1655 and 1640 (C=O), 1620 (C=C) cm^{-1}. UV (EtOH) λ_{max} nm (log ε): 285 (4.13), 445 (3.84). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (d, 6H, J = 6.9 Hz, CH_3), 2.40-2.60 (m, 1H, C<u>H</u>[CH_3]$_2$), 3.96 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.54 (dd, 1H, J = 1.3 and 16.4 Hz, H-1'), 7.01 (dd, 1H, J = 7.0 and 16.4 Hz, H-2'), 7.24 (d, 1H, J = 9.5 Hz, H-6 or H-7), 7.37 (d, 1H, J = 9.5 Hz, H-7 or H-6), 7.93 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$) δ: 22.2, 33.3, 56.7, 57.2, 116.1, 117.9, 118.4, 118.6, 121.6, 123.0, 149.4, 150.1, 153.8, 154.3, 180.3, 184.3. Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C, 67.45; H, 6.32.

Reaction of isopentenylquinone (**5a**) with DDQ.

DDQ (180 mg, 0.79 mmol) was added to a solution of **5a** (150 mg, 0.52 mmol) in dichloromethane (30 mL). After stirring the reaction mixture for 12 h at rt, 5 % sodium bicarbonate (50 mL) solution was added. The aqueous layer was extracted with dichloromethane (2x25 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was chromathographed on silica gel (dichloromethane-ethyl acetate, 19:1) to give 41 mg (28 %) of 5,8-dimethoxynaphtho[2,3-*b*]furan-4,9-dione (**7**) (R_f = 0.27, dichloromethane-ethyl acetate, 19:1) as a yellow solid; mp 134-135 °C (ethyl acetate-hexane). IR (KBr): 1660 and 1670 (C=O) cm^{-1}. UV (EtOH) λ_{max} nm (log ε): 268 (4.05), 282 (3.96), 494 (3.89). ^{1}H-NMR (C_2D_6CO) δ: 1.41 (d, 6H, J = 6.9 Hz, CH_3), 3.15 (br septuplet, 1H, J = 6.9 Hz,

C<u>H</u>[CH3]$_2$), 3.97 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.59 (d, 1H, J = 0.9 Hz, H-3'), 7.56 (s, 2H, H-6,7). ^{13}C-NMR (C_2D_6CO) δ: 21.4, 29.3, 57.3, 57.7, 102.6, 122.0, 123.0, 123.1, 131.7, 152.0, 156.0, 156.3, 169.4, 173.4, 180.7. HRMS calcd for $C_{17}H_{16}O_5$: 300.0999. Found: 300.0997.

The second fraction (R_f = 0.23, dichloromethane-ethyl acetate, 19:1) yielded 6,9-dimethoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (**6**) (17 mg, 11 %) as an orange solid; mp 140 °C (decomp) (ethyl acetate-hexane). IR (KBr): 1670 and 1645 (C=O) cm^{-1}. UV (EtOH) λ_{max} nm (log ε): 287 (4.03), 449 (3.70). ^{1}H-NMR δ: 1.51 (s, 6H, 2xCH_3), 3.94 (s, 6H, 2xOCH_3), 5.66 (d, 1H, J = 10.0 Hz, H-4), 6.64 (d, 1H, J = 10.0 Hz, H-3), 7.26 (s, 2H, ArH). ^{13}C-NMR δ: 28.1, 57.0, 57.1, 79.9, 115.6, 117.5, 118.4, 120.0, 120.8, 121.1, 130.3, 151.8, 153.6, 154.0, 179.3, 181.5. HRMS calcd for $C_{17}H_{16}O_5$: 300.0999. Found: 300.0998

The third fraction (R_f = 0.17, dichloromethane-ethyl acetate, 19:1) gave **8** (27 mg, 18 %) as a dark purple solid, mp 168-169 °C (ethyl acetate-hexane). IR (KBr): 1685 and 1660 (C=O) cm^{-1}. UV (EtOH) λ_{max} nm (log ε): 235 (4.98), 265 (4.76), 387 (3.99), 492 (4.13). ^{1}H-NMR ($CDCl_3$) δ: 1.32 (d, 6H, J = 6.9 Hz, CH_3), 3.05 (br septuplet, 1H, J = 6.9 Hz, C<u>H</u>[CH3]$_2$), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.41 (d, 1H, J = 1.1 Hz, H-3'), 6.98 (d, 1H, J = 9.4 Hz, H-7'), 7.20 (d, 1H, J = 9.4 Hz, H-8'). ^{13}C-NMR ($CDCl_3$) δ: 20.6, 27.9, 57.3, 101.1, 115.8, 117.2, 118.4, 122.4, 149.5, 157.8, 158.5, 165.0, 174.8, 180.7. HRMS calcd for $C_{17}H_{16}O_5$: 300.0999. Found: 300.0997.

Isomerization of *ortho*-quinone (**8**) (10 mg, 0.033 mmol) in ethanol (5 mL) and 36%hydrochloric acid (0.5 mL) heated under reflux for 30 min gave *para*-quinone (**7**) (7.5 mg, 75 %) after purification by column chromatography (dichloromethane-ethyl acetate, 9:1).

<u>2-Isopropyl-5,8-dihydroxynaphtho[2,3-*b*]furan-4,9-dione (**9**)</u>.

A mixture of the quinone (**7**) (40 mg, 0.13 mmol) and 20 % sulfuric acid (15 mL) was heated under reflux for 3 h. After cooling, the solution was diluted with water (15 mL) and extracted with dichloromethane (3x30 mL). The extract was washed with water (30 mL), dried ($MgSO_4$) and evaporated. The residue was purified by column chromathography (dichloromethane) to give quinone (**9**) (20 mg, 55 %); mp158-160 °C (ethyl acetate-hexane). IR (KBr): 3444 (OH), 1614 (C=O) cm^{-1}. UV (EtOH) λ_{max} nm (log ε): 268 (4.00), 282 (3.92), 494 (3.84), 532 (3.71). ^{1}H-NMR

($CDCl_3$) δ: 1.38 (d, 6H, J = 6.9 Hz, CH_3), 3.15 (br septuplet, 1H, J = 6.9 Hz, C<u>H</u>[CH_3]$_2$), 6.63 (d, 1H, J = 0.9 Hz, H-3'), 7.23 (s, 2H, Ar-H), 12.60 (s, 1H, OH), 12.72 (s, 1H, OH). ^{13}C-NMR ($CDCl_3$) δ: 20.7, 28.5, 102.3, 112.0, 112.4, 129.8, 130.0, 132.2, 151.0, 158.4, 158.7, 170.6, 176.4, 184.7. HRMS calcd for $C_{15}H_{12}O_5$: 272.0686. Found: 272.0685 .

<u>2-(1-Hydroxy-1-methyethyl)-5,8-dihydroxynaphtho[2,3-*b*]furan-4,9-dione (**10**)</u>.

Selenium dioxide (12 mg, 0.11 mmol) and pyridine *N*-oxide (32 mg, 0.34 mmol) were added to a solution of the quinone (**9**) (10 mg, 0.037 mmol) in dioxane (5 mL) under nitrogen. The mixture was heated under reflux for 3 day, and after cooling was diluted with ethyl acetate (20 mL). The solution was washed with 10 % HCl water (15 mL), 5 % $NaHCO_3$ and brine (15 mL) and extracted with dichloromethane (3x 30 mL). The organic extract was dried ($MgSO_4$), evaporated and the product was purified by column chromathography (dichloromethane-ethyl acetate, 9:1). Evaporation of the solvent gave quinone (**10**) (8.5 mg, 80 %); mp 204-205 °C (ethyl acetate-hexane). IR (KBr): 3350 (OH), 1620 (C=O) cm^{-1}. UV (EtOH) λ_{max} nm (log ε): 268 (4.00), 282 (3.92), 494 (3.84), 532 (3.71). ^{1}H-NMR (C_2D_6CO) δ: 1.72 (s, 6 H, 2xCH_3), 5.70 (s, 1H, OH), 7.00 (s, 1H, H-3), 7.43 (s, 2H, H-6 and H-7), 12.50 (s, 1H, OH), 12.72 (s, 1H, OH). HRMS calcd for $C_{15}H_{12}O_6$: 288.0635. Found: 288.0634.

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