SYNTHESIS OF FURANONAPHTHAZARIN DERIVATIVES

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Abstract - A three-step synthesis of the 5,8-dihydroxy-2-(1-methylethyl)naphth[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)naphth[2,3-b]furan-4,9-dione (10).

The biological activity of naturally occurring or synthetic naphthofuran-4,9-diones has stimulated 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 berghei. 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.

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 steps from 5,8-dimethoxynaphthalene-1,4-dione in 19% yield, is the only approach to a furanonaphthazarin derivative described in the literature.\textsuperscript{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.\textsuperscript{5} The hydroxyquinone (4) was subjected to a modified Hooker reaction\textsuperscript{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.\textsuperscript{7-9} The reaction of 5b with DDQ at room temperature gave a mixture of pyranonaphthoquinones,\textsuperscript{7} while isopentenylnaphthoquinones (5c)\textsuperscript{8} and (5d)\textsuperscript{9} afforded mixtures of pyranonaphthoquinones and furanonaphthoquinones, the latter being the minor components. A mechanism for this process has been proposed.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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
at C-2, the oxidation of quinone (9) with selenium dioxide was then examined.\textsuperscript{12} The reaction of furanonaphthazarin (9) with selenium dioxide was carried out in the presence of pyridine N-oxide as co-oxidant\textsuperscript{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 Å 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 chromatography (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) $\lambda_{\text{max}}$ nm (log $\varepsilon$): 285 (4.13), 445 (3.84). $^1$H-NMR (CDCl$_3$) $\delta$: 1.10 (d, 6H, $J = 6.9$ Hz, CH$_3$), 2.40-2.60 (m, 1H, CH$[\text{CH}_3]_2$), 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$_3$) $\delta$: 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 chromatographed 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) $\lambda_{\text{max}}$ nm (log $\varepsilon$): 268 (4.05), 282 (3.96), 494 (3.89). $^1$H-NMR (C$_2$D$_6$CO) $\delta$: 1.41 (d, 6H, $J = 6.9$ Hz, CH$_3$), 3.15 (br septuplet, 1H, $J = 6.9$ Hz,
CH(CH₃)₂, 3.97 (s, 3H, OCH₃), 3.98 (s, 3H, OCH₃), 6.59 (d, 1H, J = 0.9 Hz, H-3'), 7.56 (s, 2H, H-6,7). ¹³C-NMR (C₂D₆CO) 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 C₁₇H₁₆O₅: 300.0999. Found: 300.0997.

The second fraction (Rf = 0.23, dichloromethane-ethyl acetate, 19:1) yielded 6,9-dimethoxy-2,2-dimethyl-2H-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 (GO) cm⁻¹. UV (EtOH) λmax nm (log ε): 287 (4.03), 449 (3.70). ¹H-NMR δ: 1.51 (s, 6H, 2xCH₃), 3.94 (s, 6H, 2xOCH₃), 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). ¹³C-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 C₁₇H₁₆O₅: 300.0999. Found: 300.0998.

The third fraction (Rf = 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) λmax nm (log ε): 235 (4.98), 265 (4.76), 387 (3.99), 492 (4.13). ¹H-NMR (CDCl₃) δ: 1.32 (d, 6H, J = 6.9 Hz, CH₃), 3.05 (br septuplet, 1H, J = 6.9 Hz, CH[CH₃]₂), 3.91 (s, 3H, OCH₃), 3.93 (s, 3H, OCH₃), 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'). ¹³C-NMR (CDCl₃) 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 C₁₇H₁₆O₅: 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).

2-Isopropyl-5,8-dihydroxynaphtho[2,3-b]furan-4,9-dione (9).

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 (MgSO₄) 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) λmax nm (log ε): 268 (4.00), 282 (3.92), 494 (3.84), 532 (3.71). ¹H-NMR
(CDCl₃) δ: 1.38 (d, 6H, J = 6.9 Hz, CH₃), 3.15 (br septuplet, 1H, J = 6.9 Hz, CH[CH₃]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). ¹³C-NMR (CDCl₃) 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 C₁₅H₁₂O₅: 272.0686. Found: 272.0685.

2-(1-Hydroxy-1-methylethyl)-5,8-dihydroxynaphtho[2,3-b]furan-4,9-dione (10).

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 % NaHCO₃ and brine (15 mL) and extracted with dichloromethane (3x 30 mL). The organic extract was dried (MgSO₄), 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) λmax nm (log ε): 268 (4.00), 282 (3.92), 494 (3.84), 532 (3.71). ¹H-NMR (CD₂Cl₂) δ: 1.72 (s, 6 H, 2xCH₃), 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 C₁₅H₁₂O₆: 288.0635. Found: 288.0634.

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REFERENCES

11. PM3 calculation of differential heat of formation between an assumed commun transition structure, in which the distance between the hydroxyl group and the C-2' carbon atom was constrained to 1.5 Å, and the substrate, lead to the following values: compound (5a) = 52.1 Kcal/mol, compound (5c) = 49.7 Kcal/mol, and compound (5b) = 49 Kcal/mol. This indicate that the reactivity is favoured with the presence of methoxy groups. The PM3 calculations were carried out with Spartan version 5.0. Wavefunction Inc., Von Karman Ave 370, Irvine, CA 1997.

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