A FACILE SYNTHESIS OF THE PYRANONAPHTHAZARIN SYSTEM

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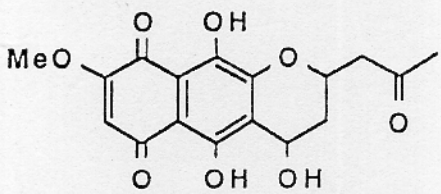
ABSTRACT :The synthesis of pyranoquinone **9** starting from hydroxyquinone **4** through Michael adduct **5** is described.

The synthesis of pyranonaphthoquinones have received increasing attention because of the interesting biological properties of these heterocyclic quinones either from natural or synthetic origin[1]. The research in this area has been focused mainly on the synthesis of pyranoquinones derived from 1,4-naphthoquinone or 5-hydroxy-1,4-naphthoquinone[2], but those derived from 5,8-dihydroxy-1,4-naphthoquinone (naphthazarin) such as erythrostominone **1**[3] and the pyranonaphthazarin **2**[4] have been unexplored.



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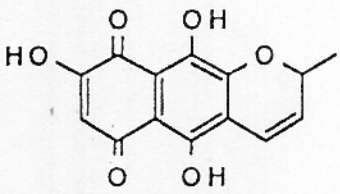

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In our continued effort to find a synthetic route to obtain highly oxygenated pyranoquinones, we developed an efficient method to synthesize pyranonaphthoquinones using Michael adducts of hydroxyquinones[5]. In this study we want to extend this approach to the synthesis of pyranonaphthazarin **9**.

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The Michael adduct approach to pyranoquinones requires an hydroxyquinone, and in order explore this route to obtain pyranonaphthazarins we chose the known hydroxyquinone 4[6] as starting material.

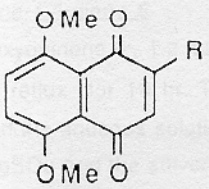
Acid-catalyzed addition of water to 5,8-dimethoxy-1,4-naphthoquinone 3[7] gave hydroxyquinone 4 in 90% yield. Reaction of 4 with methyl vinyl ketone (MVK) in pyridine-t-butanol mixture afforded Michael adduct 5 in 70% yield. The IR spectrum of 5 showed two carbonyl absorptions at 1660 and 1640 cm^{-1} and a singlet at δ 2.17 ppm was observed by ^{1}Hnmr confirming its structure.

Attemps to convert adduct 5 into the corresponding alcohol 6, by reduction with sodium borohydride, indicated that 6 underwent a ready cyclization to *o*-pyranoquinone 7 during the isolation procedure. Since compound 7 could provide a pyranonaphthazarin by acid-catalyzed rearrangement[8], we decided to induce the cyclization of alcohol 6 leaving it overnigth in the chloroform extract, under aerobial condition. This procedure afforded quinone 7 in 92% isolated yield.

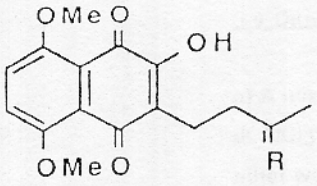
The conversion of *o*-pyranonaphthoquinones to *p*-pyranonaphthoquinones was studied in detail by Ettlinger[8], and in our case the isomerization of the heterocyclic quinone 7 was achieved by heating in 20% sulfuric acid for 30 minutes to afford *p*-pyranoquinone 8 in 95% yield.

Demethylation of 8 by treatment with aluminum chloride at room temperature yielded pyranonaphthazarin 9 or 10 in good yield (71%). The product displayed the signals of two coupled protons (J = 9.5 Hz) at δ 7.16 and 7.26 ppm for the naphthazarin system. Considering this fact and, the well known study reported by Moore and Scheuer[9] on the influence of a variety of substituents on the tautomerism of naphthazarins, it is highly probable that the naphthazarin released from 8 has the pyran ring fused to the quinonic nucleus, as in structure 9. Interestingly, quinone 9 can be obtained in one step from 7 by heating the latter in 20% sulfuric acid for 2 hr in 77% yield.

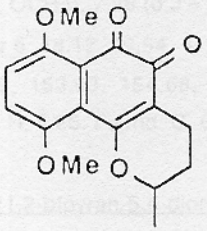
In conclusion, we have shown that our method is useful to obtain highly oxygenated pyranoquinones. We are currently dying the synthesis of erythrostominone derivatives using this approach.



3 R = H
4 R = OH



5 R = O
6 R = H,OH



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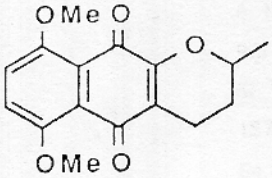

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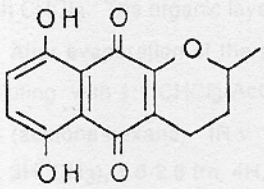

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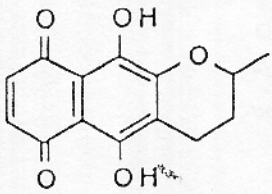

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EXPERIMENTAL

Melting points were determined with a Kofler modified apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer Model 1310 Spectrometer. 1H and 13C nmr spectra were recorded on Varian XL-100 and Varian XL-300 spectrometers, respectively, using tetramethylsilane as internal reference. Column chromatography was performed on Silica-gel 60 (Merck). Elemental analyses were performed at the Instituto de Química Orgánica General, Madrid, Spain.

5,8-dimethoxy-2-hydroxynaphthalene-1,4-dione 4.

Obtained in 90% yield from 5,8-dimethoxynaphthalene-1,4-dione 3[7] using Fariña et al.[6] procedure.

5,8-Dimethoxy-2-hydroxy-3-(3-oxobutyl)naphthalene-1,4-dione 5.

A mixture of 500 mg (2.14 mmol) of hydroxyquinone 4 , 1.2 mL of MVK and 50 mL of pyridine-t-butanol (1:5) was heated under reflux for 14 hr. The residue after removal of solvent was acidified with 5% HCl, and the aqueous solution was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and the solvent removed under vacuum. The crude product was chromatographed on silica gel using 1:1 chloroform-ethyl acetate as eluent to give 460 mg (71%) of quinone 5, mp 141-143 °C (acetone-hexane). IR ν max : 3240 (OH), 1660 and 1640 (C=O) cm $^{-1}$. ^{1}H-nmr δ: 2.17 (s, 3H, CH_3), 2.6-2.9 (m, 4H, CH_2CH_2), 3.97 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.26 (d,*J* = 9.5 Hz, 1H), 7.41 (d,*J* = 9.5 Hz, 1H), 7.60 (s ,1H, OH) ppm. ^{13}C-nmr δ: 18.12, 29.54, 41.73 56.74, 57.12, 118.92, 121.83, 122.98, 123.02, 123.04, 152.05, 153.93, 154.68, 179.99, 184.38, 207.89 ppm. Anal. Calcd. for $C_{16}H_{16}O_6$: C, 63.16; H, 5.26. Found: C, 63.03; H, 5.24.

3,4-Dihydro-7,10-dimethoxy-2-methyl-*2H*-naphtho[1,2-b]pyran-5,6-dione 7.

To an ice-cold solution containing 320 mg (1.05 mmol) of quinone 5 in 35 mL of 10:1 THF /MeOH was added in portions 111 mg (3.15 mmol) of $NaBH_4$ with stirring. The mixture was stirred for 50 min in an ice bath, then quenched with 50 mL of water . The solution was acidified with 5% HCl and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and then allowed to stand overnigth. After evaporation of the solvent, the residue was purified by column chromatography eluting with 1:1 $CHCl_3$/AcOEt to yield 280 mg (97%) of pyranoquinone 7, mp 174-176 °C (acetone-hexane). IR ν max : 1670 and 1620 (C=O) cm $^{-1}$. ^{1}H-nmr δ: 1.50 (d, *J* = 6 Hz, 3H, CH_3), 1.6-2.8 (m, 4H, CH_2CH_2), 3.82 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.2-4.4 (m, 1H, CH), 7.08 (d,*J* = 9.5 Hz, 1H), 7.28 (d,*J* = 9.5 Hz, 1H) ppm. ^{13}C-nmr δ: 18.49, 20.56, 27.44, 56.66, 58.62, 75.09, 112.90, 116.91, 119.11, 121.99, 125.45, 151.69, 156.75, 165.53, 179.45, 180.60 ppm. Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.67; H, 5.56. Found: C, 66.38; H, 5.40.

3,4-Dihydro-6,9-dimethoxy-2-methyl-*2H*-naphtho[2,3-b]pyran-5,10-dione 8.

A solution of 40 mg (0.14 mmol) of quinone 7 in 50 mL of 20% H_2SO_4 was heated at 50 °C for 30 min with stirring. The solution was extracted with ether and the extract was dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel using 1:1 $CHCl_3$/AcOEt as eluent to give 38 mg (95%) of pyranoquinone 8, mp 160-162 °C (acetone-hexane). IR ν max : 1650 and 1620 (C=O) cm $^{-1}$. ^{1}H-nmr δ: 1.46 (d, *J* = 6 Hz, 3H, CH_3), 1.6-2.7 (m, 4H, CH_2CH_2), 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 4.1-4.4 (m, 1H, CH), 7.20(d,*J* = 9.5 Hz, 1H), 7.30 (d,*J* = 9.5 Hz, 1H) ppm. Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.67; H, 5.56. Found: C, 66.40; H, 5.81.

3,4-Dihydro-6,9-dihydroxy-2-methyl-*2H*-naphtho[2,3-b]pyran-5,10-dione 9.

a) A mixture of 28 mg (0.1 mmol) of quinone 8, 5 mL of CH_2Cl_2 and 100 mg (0.76 mmol) of $AlCl_3$ was stirred at room temperature for 6 hr. After cooling in an ice bath, water and ether were added and the layers separated. The aqueous layer was extracted with ether and the combined organic layers were dried over $MgSO_4$. The solvents were evaporated in vacuo and the residue was chromatographed on silica gel using $CHCl_3$ as eluent to give 18 mg (71%) of pyranoquinone 9, mp 128-130 °C. IR ν max : 1600 (C=O) cm^{-1}. ^{1}H-nmr δ: 1.52 (d, *J* = 6 Hz, 3H, CH_3), 1.2-4.0 (m, 4H, CH_2CH_2), 4.2-4.6 (m, 1H, CH), 7.16 (d,*J* = 9.5 Hz, 1H), 7.26 (d,*J* = 9.5 Hz, 1H), 12.20 (s, 1H, OH), 12.70 (s, 1H, OH) ppm. ^{13}C-nmr δ: 17.95, 20.36, 27.04, 74.75, 110.56, 111.25, 121.86, 127.96, 130.14, 155.86, 157.89, 182.39, 187.64 ppm. Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.61; H, 4.61. Found: C, 64.50; H, 4.27.

b) A mixture of 100 mg (0.35 mmol) of quinone 7 in 25 mL of 20% H_2SO_4 was heated to reflux for 2 hr. The aqueous mixture was extracted with ether and the extract was washed with brine , dried, and evaporated in vacuo. The residue was chromatographed on silica gel using $CHCl_3$ as eluent to give 54 mg of pyranoquinone 9. Further elution with the same solvent afforded 22 mg of the starting quinone 7. Based on recovered 7 the yield of 9 is 77%.

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