Studies on Quinones. XII. Cycloketalization of Michael Adducts from Hydroxyquinones [1]

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The reaction of 2-hydroxy-3-(1-phenyl-3-oxobutyl)-1,4-naphthoquinone (**1**) with either acidic methanol or a mixture of trimethyl orthoformate, methanol and ammonium chloride resulted in the formation of the *p*-quinonic cycloketals: *trans*- and *cis*-4-phenyl-2-methyl-2-methoxy-3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (**2a,2b**). Cyclization of the Michael adducts **6, 10** and **11**, which are structurally related to **1**, with trimethyl orthoformate-methanol-ammonium chloride gave the corresponding *p*-quinonic cycloketals **7, 12** and **13**. The structures of the regioisomers **2a** and **2b** are proposed based on the spectral properties of compound **7** and by analysis of its proton nmr spectra.

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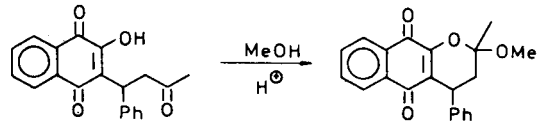
Introduction.

The synthesis of dihydronaphthopyrandiones have attracted interest because of the antimicrobial and antitumoral properties of these compounds [2]. Recently, the Michael adducts obtained from 2-hydroxy-1,4-naphthoquinones and α,β-unsaturated carbonyl compounds have become useful as intermediates in the synthesis of carbotricyclic quinones [3] and dihydronaphthopyrandiones [4]. In order to extend the applicability of the above Michael adducts in synthesis, we studied the intramolecular ketalization of these compounds toward the preparation of naphthopyranoquinones.

Apparently, the only previous study of cycloketalization of Michael adducts of hydroxynaphthoquinones is the preparation of ketal **2** by reaction of 2-hydroxy-3-(1-phenyl-3-oxobutyl)-1,4-naphthoquinone (**1**) with 6% methanolic hydrogen chloride reported by Zaugg [5].

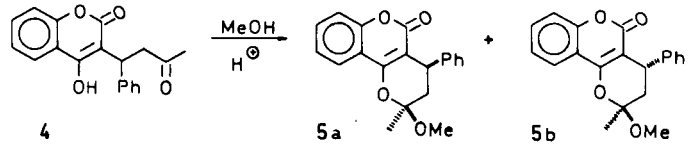
It is noteworthy that cycloketalization of **1** has stereochemical implications. In fact if we consider the known tautomerism 2-hydroxy-1,4-naphthoquinone ⇌ 4-hydroxy-1,2-naphthoquinone [6], the hydroxyquinone **1a** may exist in solution in equilibrium with structure **1b**. This implies that ketalization of **1** must lead to a mixture of diastereomers **2a, 2b** and/or **3a, 3b** (Scheme 1).



1 2

Figure 1

Furthermore, Trager *et al.* [7] have demonstrated that treatment of Warfarin [4], which is structurally related to Michael adduct **1**, with methanolic hydrogen chloride afforded the diastereomeric ketals **5a** and **5b**.



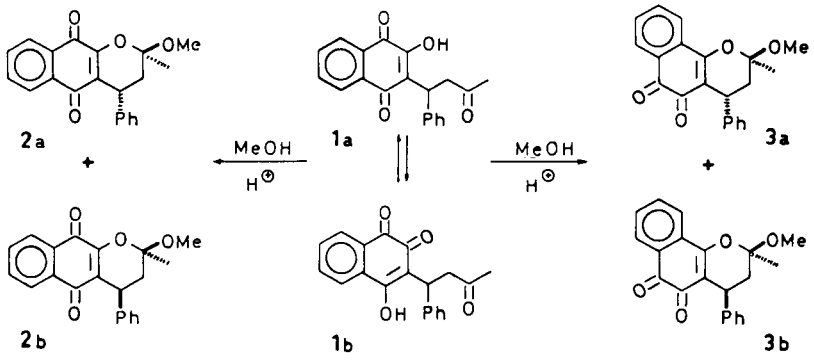
4 5a 5b

Figure 2

Accordingly, in this paper we investigate the course of stereochemical aspects of the ketalization of adduct **1**, in addition to the cycloketalization of related Michael adducts.

Results and Discussion.

Ketalization of the hydroxyquinone **1** with acidic meth-



2a 1a 3a 2b 1b 3b

Scheme 1

Table 1

Spectral Data of Cyclic Ketals **2a**, **2b**, **7**, **12**, **13**

Compound	UV λ max (log ε) (nm)	IR ν C=O (cm^{-1}) [a]	^{1}H-NMR δ (ppm)
2a	245 sh (4.28), 250 (4.32), 280 (4.12), 332 (3.48)	1675 1650	8.10 (m, 1H), 7.88 (m, 1H), 7.64 (m, 2H), 7.21 (s, 5H), 4.18 (dd, 1H, J ~ 12, 7 Hz), 3.35 (s, 3H), 2.41 (dd, 1H, J ~ 14 Hz), 1.92 (dd, 1H, J ~ 12, 14 Hz), 1.67 (s, 3H)
2b	245 sh (4.28), 250 (4.32), 280 (4.12), 332 (3.48)	1675 1650	8.13 (m, 1H), 7.95 (m, 1H), 7.68 (m, 2H), 7.22 (s, 5H), 4.25 (dd, 1H, J ~ 3, 8 Hz), 3.25 (s, 3H), 2.40 (dd, 1H, J ~ 3, 14 Hz), 2.24 (dd, 1H, J ~ 8, 14 Hz), 1.65 (s, 3H)
7	245 sh (4.30), 250 (4.38), 280 (4.15), 332 (3.45)	1675 1650	8.07 (m, 2H), 7.68 (m, 2H), 3.37 (s, 3H), 2.7-2.5 (m, 2H), 2.4-1.7 (m, 2H), 1.70 (s, 3H)
12	260 sh (4.29), 266 (4.39), 295 (4.19), 333 (3.65), 390 (3.13)	1660 1640	8.08 (d, 1H, J ~ 9 Hz), 7.56 (d, 1H, J ~ 3 Hz), 7.17 (dd, 1H, J ~ 9, 3 Hz), 3.97 (s, 3H), 3.38 (s, 3H), 2.8-2.5 (m, 2H), 2.4-1.7 (m, 2H), 1.69 (s, 3H)
13	255 (3.90), 278 (3.88), 368 (2.85)	1695 1640	9.00 (dd, 1H, J ~ 2, 5 Hz), 8.42 (dd, 1H, J ~ 2, 8 Hz), 7.66 (dd, 1H, J ~ 5, 8 Hz), 3.88 (s, 3H), 2.67 (m, 2H), 2.8-1.8 (m, 2H), 1.73 (s, 3H)

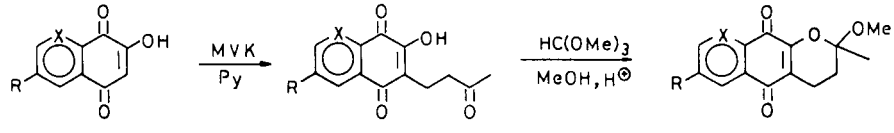
[a] Obtained in methylene chloride solutions (**2a**, **2b**) and potassium bromide (**7**, **12**, **13**).

anol (12 hours under reflux) or with a mixture of methanol, trimethyl orthoformate and ammonium chloride (5 hours under reflux) gave a 71% and 76% yield respectively of a crystalline material, mp 142-144° [8]. The ^{1}H-nmr spectrum showed four singlets at δ 1.65, 1.67, 3.25 and 3.35 ppm corresponding to the methyl and methoxy groups, respectively. This observation is consistent with the sample being a mixture of diastereoisomers. Subsequently, detailed examination of the mixture by thin layer chromatography (tlc), revealed the presence of two components. In view of this result the ^{1}H-nmr spectrum of the mixture was reexamined and it was found that the intensities of the methoxy proton signals were in the ratio of 70/30. Consequently, it was deduced that the material resulting from the ketalization of compound **1** was a 70/30 mixture of cycloketals, separable by preparative tlc. These ketals were shown, by ir and uv spectral data, to possess *p*-quinonic structures [9]. The major diastereomer, the least polar product, showed a simplified ABX pattern for the methine and methylene protons with true vicinals coupling constants of J_{AX} = 12.1 Hz and J_{BX} = 6.9 Hz. On the other hand, the minor diastereomer, more polar product, showed a complex ABX pattern with true vicinal coupling constants of J_{AX} = 8.1 Hz and J_{BX} = 2.9 Hz.

After an inspection of Drieding models of both half-chair conformers which could correspond in configuration to dihydropyran structures **2a** and **2b**, we tentatively assigned the *trans* configuration to the major isomer **2a** and the *cis* configuration to the minor isomer **2b** [10]. Interestingly, the less stable and minor isomer **2a**, was predominantly obtained when the hydroxyquinone **1** was treated with acidic methanol at room temperature for three days (5% of **2a** and 95% of **2b**).

Although we have proposed paraquinonic structures for **2a** and **2b**, the aromatic ^{1}H-nmr signal pattern of these compounds is different from the characteristic A_2B_2 type signal [11] (Table 1). In fact, we observed an unusual upfield chemical shift for the H-6 proton in **2a** and **2b**, (δ 7.88 and 7.95 ppm respectively). An inspection of Drieding models reveals that the proton on C-6 is under the shielding cone of the aromatic moiety (on C-4) when the latter is in a pseudoequatorial position.

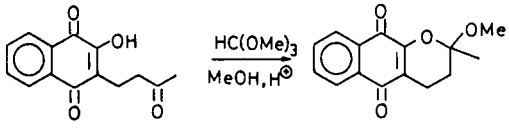
Further evidence in support of the paraquinonic structure assigned to **2a** and **2b** was obtained by preparing the ketal **7**, unsubstituted on C-4 position.



8,9 10,11 12,13

	X	R
8,10,12	C	OMe
9,11,13	N	H

Scheme 2



6 7

Figure 3

Cycloketalization of 2-hydroxy-3-(3-oxobutyl)-1,4-naphthoquinone (**6**) [3] with a mixture of methanol, trimethyl orthoformate and ammonium chloride afforded the heterocyclic quinone **7** in 80% yield. The ^{1}H-nmr spectrum exhibited two singlets at δ 1.70 and 3.37 ppm for the methyl and methoxy groups respectively and a A_2B_2 type signal at δ 7.68 and 8.07 ppm due to four aromatic protons. Furthermore, compound **8** showed uv absorptions at λ max 250 sh, 280 and 332 nm in good agreement to that of α-lapachone a well known natural naphthopyran-*p*-quinone [9]. The above data confirm the paraquinonic structure of cycloketal **7**. The uv spectrum of a mixture of **2a** and **2b** is almost identical to that of **7** (Table 1), confirming that compounds **2a** and **2b** are *p*-quinonic isomers.

The above findings demonstrate that the cycloketalization of **1** gave two compounds, the *trans* isomer **2a** (thermodynamic product) and the *cis* isomer **2b** (kinetic product).

In the present study, the cycloketalization of the Michael adducts **10** and **11** have also been examined. Treatment of the hydroxyquinone **8** and **9**, with methyl vinyl ketone gave compound **10** and **11** respectively. The reactions of Michael adducts **10** and **11** with trimethyl orthoformate-methanol-ammonium chloride afforded the corresponding *p*-pyranoquinone **12** and **13** in good yield (Scheme 2). No *o*-quinonic isomers were detected (tlc) in the cycloketalization of the above Michael adducts.

In conclusion, this study demonstrates that the cycloketalization of Michael adducts obtained from hydroxyquinones is applicable only to the synthesis of *p*-pyranoquinones.

EXPERIMENTAL

Melting points are uncorrected and were determined on a Kofler hot stage microscope. Unless otherwise stated, ir spectra were recorded in nujol mulls on a Perkin-Elmer 567 spectrometer. The uv-visible spectra were taken in ethanol solution and recorded on a Pye-Unicam SP-1800 spectrophotometer. The ^{1}H-nmr were measured in deuteriochloroform solution on a Varian spectrometer using TMS as internal standard. Elemental analyses were performed by Instituto de Química Orgánica General (CSIC) Madrid.

Thin-layer chromatography was run on precoated silica gel GF 254 plates (0.25 mm thickness, Merck). Preparative tlc was performed on precoated silica gel PF-254 plates (1.0 mm thickness, Merck).

Ketalization of 2-Hydroxy-3-(1-phenyl-3-oxobutyl)-1,4-naphthoquinone (**1**) [5].

a) A solution of **1** (70 mg, 0.23 mmole), in methanol (15 ml) containing one drop of hydrochloric acid was heated under reflux for 12 hours. The reaction mixture was evaporated to dryness and the residue was dissolved in chloroform and successively washed with water, ammonium hydroxide and water. After being dried over magnesium sulphate the solvent was removed under vacuum and the yellow solid recrystallized from methanol to give 58 mg (0.17 mmole, 74%) of a mixture of **2a** (*trans*-isomer) and **2b** (*cis*-isomer) in a 70:30 ratio as determined by signals at δ 3.25 and 3.35 ppm in the ^{1}H-nmr; mp 142-144° (lit [6] mp 142-144°); ms: m/e 334 (M^+) (obtained on a Varian MAT-111 spectrometer).

b) In a comparative experiment adduct **1** was treated with methanol containing hydrochloric acid at room temperature for 3 days. Under this condition a mixture (mp 122-125°) of **2a** and **2b** in a 5:95 ratio (^{1}H-nmr) was obtained.

c) A solution of **1** (125 mg, 0.41 mmole), methanol (15 ml), trimethyl orthoformate (5 ml) and a catalytic amount of ammonium chloride was heated under reflux for 5 hours. The resulting mixture was evaporated to dryness and the residue extracted with chloroform. The chloroform extract was successively washed with water, ammonium hydroxide, water and dried over magnesium sulphate. The solvent was evaporated and the solid residue crystallized from methanol to afford 105 mg (0.31 mmole, 76%) of a mixture of **2a** and **2b** in a ratio of 70:30, mp 142-144°.

Eighty mg of this mixture was separated by preparative tlc with benzene as the eluent. Extraction of the lower chromatographic band with chloroform afforded 17 mg of **2b**, mp 191-192° (from methanol).

From the upper band 53 mg of **2a** was isolated, mp 158-159° (from methanol).

2-Methoxy-2-methyl-3,4-dihydro-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (**7**).

A mixture of **6** [3] (50 mg, 0.20 mmole), methanol (10 ml), trimethyl orthoformate (1 ml) and a catalytic amount of ammonium chloride was refluxed for 3 hours. The solution was evaporated and worked up as mentioned in the cycloketalization of **1**. Recrystallization of the residue from cyclohexane gave 42 mg (0.16 mmole, 80%) of **7** as yellow crystals, mp 131-131.5°.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.54; H, 5.19.

2-Hydroxy-3-(3-oxobutyl)-6-methoxy-1,4-naphthoquinone (**10**).

A solution of 2-hydroxy-6-methoxy-1,4-naphthoquinone **8** [12] (1 g, 4.9 mmoles) in pyridine (50 ml) containing methyl vinyl ketone (3 ml) was heated under reflux for 5.5 hours. The reaction mixture was diluted with cold water, acidified with 5% hydrochloric acid, the solid was collected by filtration and recrystallized from cyclohexane-benzene to give 760 mg (2.77 mmoles, 57%) of compound **10**, mp 157-160°; ir (potassium bromide): 3280 (O-H), 1710 (C=O), 1650 and 1640 (C=O quinone) cm^{-1}; ^{1}H-nmr: δ 8.06 (d, 1H, J ~ 9 Hz), 7.60 (d, 1H, J ~ 3 Hz), 7.15 (dd, 1H, J ~ 3 and 9 Hz), 4.00 (s, 3H), 2.78 (m, 4H), 2.21 (s, 3H).

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.69; H, 5.15. Found: C, 65.55; H, 5.46.

7-Hydroxy-6-(3-oxobutyl)quinoline-5,8-dione (**11**).

A mixture of 7-hydroxyquinoline-5,8-dione (**9**) [13] (250 mg, 1.02 mmoles) dry pyridine (20 ml) and freshly distilled methyl vinyl ketone (1 ml) was refluxed for 3 hours. The reaction mixture was evaporated under reduced pressure and the oily residue was chromatographed on silica gel with chloroform as the eluent. Evaporation of the solvent gave 170 mg of **11** (0.65 mmole, 64%) which was recrystallized from chloroform-light petroleum ether (40-60°), mp 162-163°; ir: 3380 (O-H), 1700 (C=O), 1670 and 1635 (C=O quinone); ^{1}H-nmr: δ 8.95 (dd, 1H, J ~ 2 and 5 Hz), 8.42 (dd, 1H, J ~ 2 and 8 Hz), 7.66 (dd, 1H, J ~ 5 and 8 Hz), 2.82 (m, 4H), 2.22 (s, 3H).

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.57; H, 4.52; N, 5.71. Found: C, 63.66; H, 4.75; N, 5.67.

2,7-Dimethoxy-2-methyl-2,4-dihydro-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (**12**).

A mixture of the adduct **10** (300 mg, 1.09 mmoles), methanol (35 ml), trimethyl orthoformate (10 ml) and a catalytic amount of ammonium chloride was heated under reflux for 2 hours. The solution was evaporated under vacuum and worked up as mentioned in the cycloketalization of **1** (method c). Recrystallization of the crude product from methanol

gave 283 mg (0.98 mmole, 90%) of **12** as bright brown crystals, mp 158-159°; ir: (potassium bromide): 1660 and 1640 (C=O quinone) cm^{-1}; ^{1}H-nmr: δ 8.08 (d, 1H, J ~ 9 Hz), 7.56 (d, 1H, J ~ 3 Hz), 7.17 (dd, 1H, J ~ 3 and 9 Hz), 3.97 (s, 3H), 3.38 (s, 3H), 2.8-2.5 (m, 2H), 2.4-1.7 (m, 2H), 1.69 (s, 3H).

Anal. Calcd. for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.59; H, 5.34.

2-Methoxy-2-methyl-3,4-dihydro-2*H*-quinolin[3,2-*g*]pyran-5,10-dione (**13**).

A mixture of Michael adduct **11** (50 mg, 0.18 mmole) methanol (10 ml), trimethyl orthoformate (1 ml) and ammonium chloride was heated under reflux for 3 hours. The resulting solution was evaporated and the residue extracted with hot cyclohexane which on cooling gave 41.5 mg (0.15 mmole, 83%) of ketal **13**, mp 139-140°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.83; H, 5.06. Found: C, 64.35; H, 5.24.

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