STUDIES ON QUINONES. XX[1]. A CONVENIENT APPROACH TO THE SYNTHESIS OF 2-ACETONYLPYRANONAPHTHOQUINONES.

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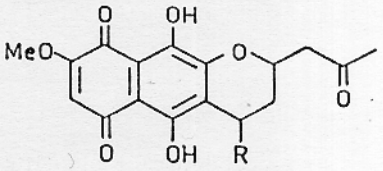
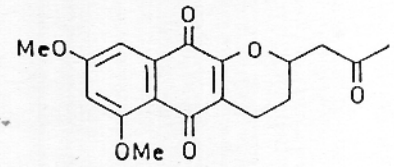
ABSTRACT: A short and efficient synthesis of 2-acetonylpyranonaphthoquinones (**13** and **14**) starting from Michael adduct **5** is described.

The synthesis of pyranonaphthoquinones have recently received significant interest because an increasing number of natural products having this structure exhibit various biological activities.[2] In connection with our studies on the synthesis of carbocyclic and heterocyclic quinones,[3] a group of antibacterial pigments; erythrostominone (**1**) and deoxyerithrostominone (**2**) isolated from deep cultures of *Gnomonia Erythrostoma*[4] have attracted our attention. The effort on the synthesis of these pigments has been restricted to the preparation of the analogue **3** to elucidate the structure of **1** and **2**, and the method[5] besides involving too many steps gave low yields.



1 R= OH
2 R= H



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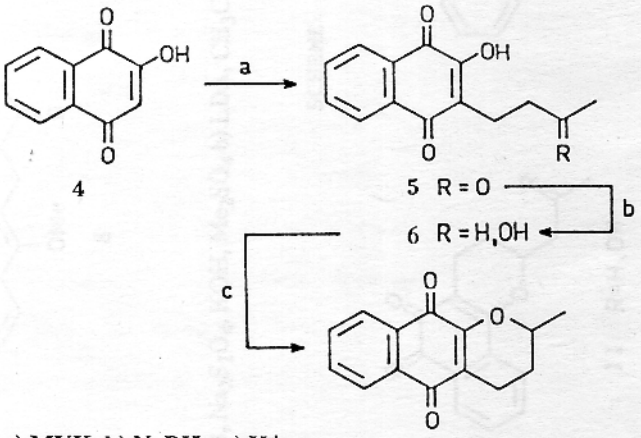
We report here an efficient procedure to synthesize pyrano-naphthoquinones having the substitution pattern identical to that of deoxyerythrostominone (2) on the pyran ring, starting from the easily available Michael adduct **5**.

In a previous work, we have described an alternative and convenient method[6] to obtain pyranonaphthoquinone **7**, through Michael adduct **5**, prepared by reaction of 2-hydroxy-1,4-naphthoquinone (**4**) with methyl vinyl ketone (MVK) in refluxing pyridine, followed by reduction and cyclization (Scheme 1). Furthermore, improved yield of Michael adduct **5** has been obtained in pyridine-t-butanol (1:10 v/v), instead of pyridine alone as solvent. The successful preparation of diheterocyclic quinones by using this synthetic approach, starting from heterocyclic hydroxyquinones was recently described.[7]



SCHEME 1

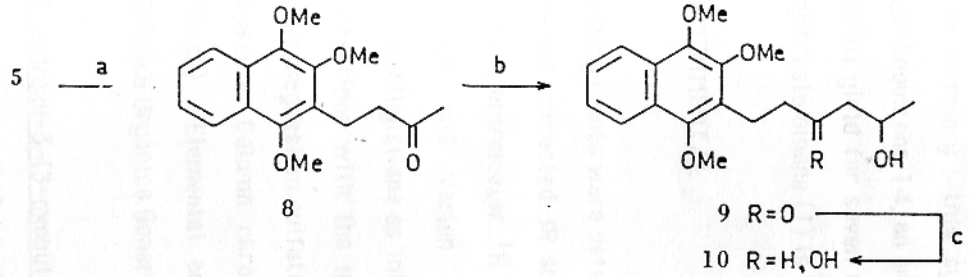
Taking in account that Michael adduct **5** has a terminal activated methyl group suitable to extend the side chain, we consider this

compound as a potential synthon for the elaboration of the carbon framework of erythrostominones (Scheme 2).

First, we studied protection of the quinone moeity in compound **5** by reductive methylation. The best result was obtained using the method [8] described by Kraus and On Man. By this procedure, reduction of quinone **5** with sodium dithionite in the presence of tetrabutylammonium bromide (TBAB), to improve solubility of the reduced quinone anion , followed by the addition of potassium hydroxide and dimethyl sulfate, gave ketone **8** in 65% yield . Then, generation of the enolate of ketone **8** with lithium diisopropylamide (LDA) at -78°C, followed by the addition of freshly distilled acetaldehyde gave ketoalcohol **9** in 95% yield. Its ^{1}H nmr spectrum that exhibited, a doublet at δ 1.20 ppm (J=6 Hz) and a multiplet at δ 4.1-4.4 ppm, assigned to the CH_3CH- group, and the disappearance of the singlet at δ 2.20 ppm for the CH_3CO- group of substrate **8**, are consistent with the structure of compound **9**. Reduction of ketoalcohol **9** with sodium borohydride [9] in MeOH/THF (1:10 v/v) at room temperature, furnished the corresponding diol **10** in excellent yield (98%), as a mixture of diastereoisomers that were not separated.

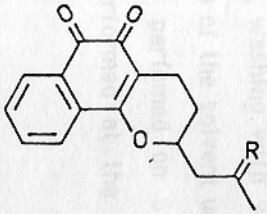
Oxidative demethylation of diol **10** with cerium (IV) ammonium nitrate (CAN)[10] gave a mixture of two heterocyclic compounds that were separated by column chromatography. The less polar compound isolated in 75% yield, was o-piranoquinone **11** on the basis of its analytical and spectroscopic data.

The minor by-product (9%) , which was isolated as an unstable



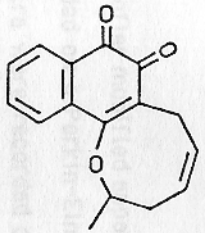
a) TBAB, $Na_2S_2O_4$, KOH, Me_2SO_4 b) LDA, CH_3CHO, c) $NaBH_4$

SCHEME 2



11 R=H,OH

13 R=O



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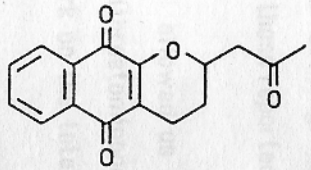

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orange oil, was assigned the structure **12** from its spectral properties. This compound exhibited quinonic carbonyl absorptions at 1700 and 1645 cm^{-1}. The ^1H nmr spectrum display a typical ABCD pattern (δ 7.5-8.3 ppm) for bencenoid protons of a 1,2-naphthoquinone system. The analysis of the remaining signals along with decoupling experiments indicated the presence of two vicinal vinylic protons at δ 5.16 ppm, two pairs of allylic protons at δ 1.1-2.4 ppm assigned to CH_2-CH=CH-CH_2 group, and the protons of a methyl group at δ 1.15 ppm coupled with a methinic proton at δ 3.7-4.0 ppm.

The formation of the *o*-quinones **11** and **12** on the oxidative demethylation of **10** probably occurs by cyclization of the corresponding cations after the quinone nucleus was released. Nevertheless, taking into account the mechanisms evidences[11] on oxidative demethylation, the possibility that heterocyclization take place during the deprotection reaction by attack of the hydroxylic group of the carbon-chain of **10** on the hydration-oxidation step, cannot be disregarded.

Before studing isomerization of the angular quinone toward the linear pyranonaphthoquinone system[12], the oxidation of the secondary alcohol moiety was attempted. This transformation was readily accomplished with pyridinium chlorochromate[13] (PCC) in dichloromethane at room temperature, to give the ketone **13** in 90% yield. Isomerization of the *o*-pyranonaphthoquinone **13** was carried out in aqueous sulphuric acid to give *p*-quinone **14** in 90 % yield. The structure of the later was mainly supported by its ^1H-nmr spectrum,

which display a characteristic A_2B_2 pattern for the aromatic protons,[14] and the proton signals for the acetonyl substituent at C-2 position are in good agreement with those reported by Cross and Zamitt[5] for compound **3**.

In summary , this synthetic approach allowed us to obtain the naphthoquinone **14**, an analogue of deoxyerithrostominone (**2**) , in 40% overall yield for seven steps. Further work on the total synthesis of erythrostominone (**1**) is in progress.

EXPERIMENTAL

Melting points were determinated with a Kofler modified apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer Model 1310 Spectrometer. ^1H and ^{13}C nmr spectra were recorded on Varian XL-100 and Varian XL-300 spectrometers respectively, using tetramethylsilane as internal reference. The workup conditions involve extractions with the indicated solvent, washing with water, drying with magnesium sulfate and evaporation of the solvent under reduced pressure. Column chromatography was perfomed on Silica-gel 60 (Merck) . Elemental analyses were performed at the Instituto de Química Orgánica General, Madrid, Spain.

2-Hydroxy-3-(3-oxobutyl)naphthalene-1,4-dione (**5**).

The quinone **4** (5.1 g, 29.2 mmol) was dissolved in a dry pyridine/ t-butanol mixture (1:10, v/v, 110 ml), and after the addition of freshly distilled MVK (5 ml), the solution was heated under reflux for 12 h. The

reaction mixture was cooled, acidified with 1:1 hydrochloric acid and eyaporated under reduce pressure. The solid residue was washed with water and dried to yield 7 g (28.7 mmol,98%) of **5**. Recrystallization from ethanol gave yellow needles, m.p.149-149.5 °C (lit.[15] 149-149.5 °C).

3-(3-Oxobutyl)-1,2,4-trimethoxy naphthalene (**8**).

The hydroxyquinone **5** (2.10 g, 8.6 mmol) was dissolved in THF (30 ml) and tetrabutyl ammonium bromide (0.33 g), water (12 ml) and aqueous sodium dithionite (10.07 g, 57.9 mmol in 25 ml of water) were added : The reaction vessel was flushed with nitrogen , the mixture stirred 15 min at ambient temperature and aqueous potassium hydroxide (11.05 g, 197 mmol in 12.5 ml of water) was added . After 5 min, 17 ml of dimethyl sulfate was added and the mixture was stirred for 16 h. The reaction mixture was diluted with water and worked up with dichloromethane. The crude product was purified by silica gel chromatography (eluant dichloromethane) to give compound **8** (1.60 g, 65%) m.p. 70-72 °C (white needles from pentane); IR (KBr) 1700 cm^{-1}; ^1H nmr ($CDCl_3$) δ : 2.18 (s,3H, $COCH_3$), 2.6-3.2 (m, 4H,m,CH_2CH_2), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.4-7.6 (m, 2H, ArH), 7.9-8.2 (m, 2H, ArH) ppm. Anal. calcd. for $C_{17}H_{20}O_4$: C, 70.83; H, 6.94. Found: C, 70.70; H, 6.84.

3-(3-Oxo-5-hydroxyhexyl)-1,2,4-trimethoxy-naphthalene (**9**)

To a solution of LDA formed from diisopropylamine (0.33 ml.,2.4 mmol)

and n-butyl lithium (1.7 ml , 2.4 mmol) in dry THF (7.5 ml) at -78°C was added a solution of ketone **11** (0.61 g ,2.1 mmol) in THF (6 ml). After being stirred for 0.5 h at -78°C, precooled acetaldehyde (0.2 ml, 3.5 mmol) was added to the mixture, and the stirring was continued for a further 0.5 h at -78°C . The reaction mixture was quenched by the addition of 3 ml of 1:1 hydrochloric acid and worked up with diethyl ether. The residue was recrystallized from cyclohexane to give the product **9** (0.69g, 98.5 %) as white needles, mp 80.5-81.5°C; IR (KBr) 3450,1740 cm^{-1}; ^1H nmr ($CDCl_3$) δ :1.20 (d, 3H, J=6Hz, CH_3), 2.5-3.2 (m, 7H, OH and 3xCH_2), 3.92 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.1-4.4 (m,1H, CH), 7.4-7.6 (m, 2H, ArH), 7.90-8.24 (m, 2H ,ArH) ppm; ^{13}C nmr ($CDCl_3$) δ: 19.0, 22.4, 43.9, 50.5, 60.9, 62.3, 64.0, 121.6, 122.0, 125.0, 125.4, 125.8, 128.5, 143.6, 148.0, 150.2, 211.4 ppm. Anal. calcd. for $C_{19}H_{24}O_5$: C, 68.69; H, 7.22 %. Found : C, 68.70; H, 7.38.

3-(3,5-dihydroxy hexyl)-1,2,4-trimethoxy-naphthalene (**10**).

The ketoalcohol **9** (0.35 g ,1.05 mmol) dissolved in methanol-tetrahydrofuran (1:10, v/v; 11ml) was cooled to 0 °C (ice bath) . Sodium borohydride (0.046 g , 1.2 mmol) was added in three portions, and the mixture stirred for 15 min at 0°C . The reaction was then quenched by the addition of an ice-cold and after the work up with diethyl ether, the mixture of diastereoisomers **10** was obtained as an oil (0.34 g, 97%); IR (KBr) 3380 cm^{-1}; ^1H nmr ($CDCl_3$) δ : 1.14 and 1.20 (two d, 3H, J=6Hz, 58% and 42% respectively, CH_3), 1.24-1.96 (4H, m,

2xCH_2), 2.96 (2H, t, J=7Hz, ArCH_2), 3.6-4.3 (2H, m, 2xCH) , 3.96 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 3.70 and 4,10 (two br s, 2xOH, exchangeable with D_2O) 7.4-7.6 (2H, m,ArH), 7.9-8.2 (2H,m,ArH). Anal. calcd. for $C_{19}H_{26}O_5$: C, 68.28; H, 7.78. Found: C, 68.30; H, 7.86.

2-(2-hydroxypropyl)-3,4-dihydro-2H-naphto[1,2-b]pyran-5,6-dione(**11**)

A solution of CAN (0.98 g, 1.80 mmol) in water (3 ml) was added in one portion to a stirred solution of diol **10** (200 mg, 0.60 mmol) in acetonitrile (3 ml) at 0°C . After stirring for 30 min, at 0°C, the reaction mixture was diluted with water, and worked up with chloroform. The residue was column chromatographed (eluant chloroform) to afford the quinone **11**(120 mg, 75 %) as orange crystals from benzene, m.p.122-3 °C; IR(KBr) 3440,1680 and 1630 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.37 (d, 3H, J=6 Hz, CH_3), 1.6-2.9 (m, 7H, OH and 3xCH_2), 4.1-4.7 (m, 2H, two CH), 7.4-7.9 (m, 3H, ArH), 8.0-8.2 (m,1H, ArH). Anal. calcd. for $C_{16}H_{16}O_4$: C, 70.61; H, 5.88. Found : C, 70.40; H, 5.73.

A less polar compound (**12**) was also obtained in fair yield (13.7 mg, 9%). IR (neat) 1700 and 1645 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.15 (d, 3H, J=6Hz, CH_3), 1.1-2.4 (m, 4H, $\mathbf{CH_2}$-CH=CH-$\mathbf{CH_2}$), 3.7-4.0 (m,1H, CH), 5.16 (br s, 2H, -CH=CH-), 7.5-8.3 (m, 4H, ArH).

2-(2-oxopropyl)-3,4-dihydro-2H-naphto[1,2-b]pyran-5,6-dione (**13**)

Pyridinium chlorochromate (0.11 g, 0.5 mmol) was suspended in anhydrous dichloromethane (10 ml). The quinone **11** (90 mg, 0.33 mmol)

dissolved in 5 ml of dichloromethane was then added in one portion to the magnetically stirred suspension. After 8 h, dry diethyl ether (15 ml) was added and the supernatant liquid was decanted from a black gum. The insoluble residue was washed with diethyl ether (3 x10 ml). The combined organic solutions was passed through a short silica gel column (chloroform) and the solvent evaporated. The ketone **13** was recrystallized from benzene (80 mg, 90 %), m.p. 162-164°C as orange needles ; IR (KBr) 1715, 1690 and 1640 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.32 (s, 3H, CH_3CO), 1.6-2.7 (m, 4H, CH_2CH_2), 2.7-3.3 (eight lines, 2H, AB portion of an ABX system, $CH\mathbf{CH_2}CO$), 4.6-5.0 (m, 1H, CH), 7.4-7.9 (m, 3H, ArH), 8.0-8.2 (m,1H, ArH); ^{13}C nmr ($CDCl_3$) δ:17.7, 25.8, 30.8, 48.1, 74.4, 113.8, 123.9, 128.7, 130.0, 130.8, 131.9, 134.9, 162.3, 178.6, 179.4, 204.6. Anal. calcd. for $C_{16}H_{14}O_4$: C, 71.13; H, 5.18. Found : C, 70.90; H, 5.24.

2-(2-oxopropyl)-3,4-dihydro-2H-naphto [2,3-b] pyran-5,10-dione (**14**)

A solution of quinone **13** (40 mg, 0.15 mMol) in aqueous sulphuric acid (20%, 25 ml) was smoothly heated (at 50ºC) for 30 min. The yellow solution was diluted with water and worked up with diethyl ether. The residue was passed through a short silica gel column (eluant chloroform) to afford the naphtopyranquinone **6** (38 mg, 95%) as yellow needles , (mp. 117-119°C) from cyclohexane ; IR (KB r) 1710, 1680, 1635 cm^{-1} ; ^1H nmr ($CDCl_3$) δ: 1.4-2.8 (m, 4H, CH_2CH_2), 2.28 (s, 3H, CH_3CO), 2.88 (eight lines, 2H, AB portion of an ABX system, $CH\mathbf{CH_2}CO$),

4.4-4.8 (1H,m, CH), 7.6-7.8 (2H, m,ArH), 8.0-8.2 (2H, m,ArH); ^{13}C nmr ($CDCl_3$) δ: 18.4, 25.6, 31.0, 48.0, 73.8, 121.5, 126.1, 126.3, 131.0, 132.0, 133.1, 134.0, 155.1, 179.4, 184.2, 205.1. Anal. calcd. for $C_{16}H_{14}O_4$: C, 71.13; H, 5.18. Found : C, 70.95; H, 5.17.

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