SYNTHESIS OF NAPHTHO[2,3-*b*]PYRANOQUINONES AND ITS AZA-ANALOGUES FROM A USEFUL BENZOPYRANOQUINONE INTERMEDIATE

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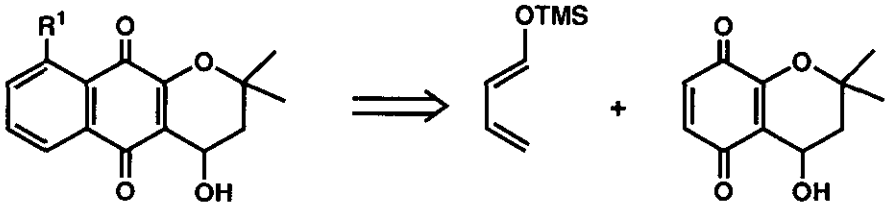
Abstract-The synthesis of racemic pyranonaphthoquinone (**2**), a new cytotoxic agent, and its aza-analogues (**11**) and (**12**) employing Diels-Alder cycloaddition reactions is described.

The interest in the synthesis of tricyclic pyranoquinones arose from the fact that a number of these heterocyclic quinones either from natural or synthetic origin were found to posses antitumor and/or antimicrobial activity.[1] As part of a program on the synthesis of heterocyclic quinones[2,3] we have recently reported a new method to obtain pyranonaphthoquinones by a Diels-Alder reaction of pyranoquinone (**3**) with (*E*)-1-trimethylsilyloxy-1,3-butadiene.[4]



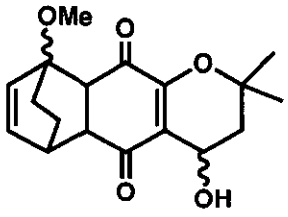
1 R^1 = H
2 R^1 = OMe

3

This study revealed that the cycloaddition afforded a 3:2 mixture of cycloadducts which underwent facile elimination of the trimethylsilyloxy group to give 3,4-dihydro-2,2-dimethyl-4-hydroxy-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (4-hydroxy-α-lapachone, **1**) in 82% yield. In order to find out the utility of the quinone (**3**) for the synthesis of other pyranonaphthoquinones and aza-analogues, we decided to study the reaction of **3** with dienes that give more stable Diels-Alder adducts.

We wanted to explore also the influence of the pyran ring upon the regiochemistry of the cycloaddition of **3** with unsymmetrically substituted electron-rich dienes. In this paper we report the results of the reaction of **3** with 1-methoxy-1,3-cyclohexadiene (**4**), 1-dimethylamino-3-methyl- and 1-dimethylamino-4-methyl-1-aza-1,3-butadiene, (**5**) and (**6**) respectively.

The reaction of the quinone (**3**) with 1-methoxy-1,3-cyclohexadiene (**4**)[5] in methanol at room temperature afforded a 1:4 mixture of adducts (**7**)[6] in 83% yield. This mixture was treated with sodium hydride followed by oxidation with silver(I) oxide to provide **8** as a 1:4 mixture[7] of diastereoisomers in 70% yield. Considering that the ratio is maintained after their enolization, we assume that the mixture of adducts (**7**) are C(4) regioisomers. Aromatization of product (**8**) on heating in xylenes gave the pyranoquinone (**2**) in 79% yield. The product showed proton and carbon spectral properties that agree with those reported for natural (4*S*)-4-hydroxy-9-methoxy-α-lapachone.[8] This result suggests that in the reaction of the quinone (**3**) with 1-methoxy-1,3-cyclohexadiene (**4**), the more nucleophilic terminus of the diene becomes attached to C-6 of the substrate. This regiochemistry can be rationalized from the electron-donating effect of the alkoxy moiety (pyran ring) in the quinone (**3**) and to the expected regioselectivity of the diene (**4**).[5]



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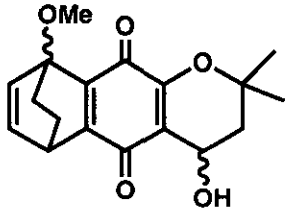

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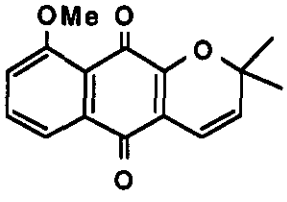

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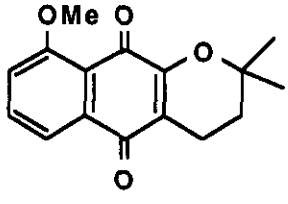

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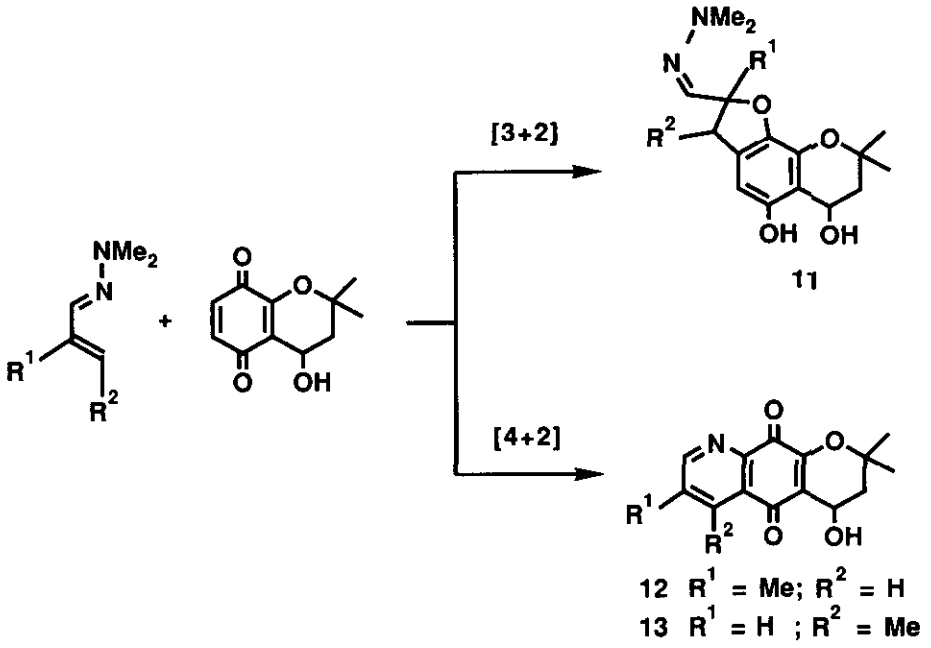
Furthermore, heating of the compound (**8**) in xylene in the presence of *p*-toluenesulfonic acid gave 3,4-dehydro-9-methoxy-α-lapachone (**9**)[5b] in 83% yield. Hydrogenation of the latter yielded another naturally occurring compound, *i. e.*, 9-methoxy-α-lapachone (**10**).[9] These results confirm the assigned regiochemistry of the cycloaddition.

The described regioselectivity of the cycloaddition of **3** with 1-methoxy-1,3-cyclohexadiene (**4**) led us to investigate the behavior of **3** with polarized 1-aza-1,3-butadienes. These dienes which

have been successfully employed to prepare the aza-anthraquinones[10] are easily obtained by condensation of α, β-unsaturated aldehydes with *N,N*-dimethylhydrazine.[11] It has been described that aza-dienes could have also a nucleophilic behavior with a quinone giving dihydrobenzofuran derivatives through a [3+2] process in acid medium. Nevertheless the [4+2] process to build nitrogen six-membered rings is favored in the absence of acid.[12]



The reaction of the quinone (**3**) with 3-methyl-1-dimethylamino-1-aza-1,3-butadiene (**5**) in dichloromethane at room temperature, in the absence of acid, gave an unstable adduct, which was oxidized *in situ* with silver(I) oxide to afford the aza-lapachone (**12**) in 57 % yield, and no bezofuran derivative such as (**11**) was observed. It has been previously proposed that in the reaction of this diene and quinones, the initial 1:1 cycloadduct easily lost dimethylamine by 1,4-elimination affording a tautomeric hydroquinone which is slowly oxidized.[10] Elimination of dimethylamine leads to a nucleophilic addition with the quinone (**3**); in order to avoid this side reaction we used the azadienes in excess. Similarly, reaction of the quinone (**3**) with 4-methyl-1-dimethylamino-1-aza-1,3-butadiene (**6**) gave the aza-lapachone (**13**) in 18 % yield. However, when we used 2,3-dichoro-5,6-dicyano-1,4-benzoquinone (DDQ) as the oxidizing agent instead of silver(I) oxide, the yield of aza-lapachone (**13**) was 50%. For the cycloaddition reaction of the

quinone (**3**) with both azadienes the structural assignment is based on the assumption, that the steric and electronic factors, which determine the observed regiochemistry in the reaction of the quinone (**3**) with 1-methoxy-1,3-cyclohexadiene (**4**), are also valid here.

EXPERIMENTAL

Melting points were determined with a Kofler modified apparatus and are not corrected. Ir spectra were recorded on a Perkin-Elmer Model 1310 spectrophotometer. ^{1}H and ^{13}C nmr spectra were recorded on a Bruker AM-200 spectrometer, using tetramethylsilane as internal reference. Column chromatography was perfomed on silica gel Merck 60 (70-230 mesh). Elemental analyses of all new compounds were performed at the Instituto de Química Orgánica General, Madrid, Spain.

Reaction of the quinone (3) with 1-methoxy-1,3-cyclohexadiene (4).

A mixture of the quinone (**3**) (280 mg, 1.35 mmol), 1-methoxy-1,3-cyclohexadiene (**4**) (156 mg, 1.42 mmol) and methanol (10 ml), was stirred for 1 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography using first dichloromethane and then 5% of ethyl acetate in dichloromethane as eluant (Rf 0.48 in dichloromethane-ethyl acetate 2:1). After evaporation of the solvent, 357 mg (83 %) of a mixture of the adducts (**7**) was obtained. This mixture, was immediately used without further purification because became darker on standing.

6,9-Ethano-3,4,6,9-tetrahydro-4-hydroxy-9-methoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (8).

A solution of the above adducts (279 mg, 0.88 mmol) in tetrahydrofuran (10 ml) was added dropwise to a suspension of 80% sodium hydride (81 mg, 2.71 mmol) in tetrahydrofuran (10 ml) at 0 °C. The mixture was stirred for 30 min at 0 °C, and then quenched by the addition of a saturated aqueous ammonium chloride solution. The phases were separated and the aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, and dried over $MgSO_4$. After evaporation of the solvent, the residue was dissolved in tetrahydrofuran and then Ag_2O (200 mg, 0.86 mmol) and $MgSO_4$ (200 mg) were added. The suspension was stirred for 1.5 h and filtered through Celite, and the solvent was evaporated to

afford 200 mg (70%) of a mixture of diastereoisomers (**8**). Recrystallization from benzene-hexanes (1:2.5) gave 140 mg of a single isomer as yellow needles, mp 131-133 °C; ir ν_{max}: 3400 (OH), 1680 and 1635 (C=O), 1320 and 1120 (C-O) cm^{-1}. ^{1}H-Nmr δ: 1.38-1.79 (m, 4H, CH_2CH_2), 1.41 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 1.99 (eight lines, 2H, CH_2), 3.35 (br s, 1H, OH), 3.61 (s, 3H, OCH_3), 4.27-4.30 (m, 1H, bridgehead H) 4.80 (t, 1H, J = 6.3 Hz, CH), 6.35 (dd , 1H, J = 6.1 and 7.7 Hz), 6.56 (dd, 1 H, J = 1.0 and 7.7 Hz) ppm. ^{13}C-Nmr δ: 25.1, 26.8, 27.0, 31.3, 33.2, 39.6, 55.9, 59.4, 79.7, 84.9, 115.5, 131.2, 135.3, 143.4, 149.0, 151.8, 177.5, 184.2 ppm. Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.37; H, 6.43. A small amount of the minor isomer isolated from the mother liquor after recrystallization gave the following spectral data: ^{1}H-Nmr δ: 1.4-1.8 (m, 4H, CH_2CH_2), 1.38 (s, 3H, CH_3), 1.51 (s, 3H, CH_3), 1.97 (eight lines, 2H, CH_2), 3.38 (br s, 1H, OH), 3.61 (s, 3H, OCH_3), 4.28-4.30 (m, 1H, bridgehead H) 4.82 (t, 1H, J = 6.3 Hz, CH), 6.35 (dd , 1H, J = 6.1 and 7.7 Hz), 6.56 (dd, 1H, J = 1.0 and 7.7 Hz) ppm. ^{13}C-Nmr δ: 25.0, 26.6, 27.1, 31.1, 33.2, 39.7, 55.8, 59.9, 79.7, 84.9, 115.2, 131.2, 135.5, 143.6, 148.9, 151.9, 177.4, 184.6 ppm.

3,4-Dihydro-4-hydroxy-9-methoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (2).

A solution of the diastereoisomers (**8**) (107 mg, 0.34 mmol) in xylene (20 ml) was heated under reflux for 45 min. Removal of the solvent under reduced pressure gave the crude product (**2**) (91 mg, 93 %) that was recrystallized from benzene-hexanes (1:2.5) to give 77 mg (79%) of pyranoquinone (**2**), mp 154-156 °C; ir ν_{max} : 3500 (OH), 1670 (C=O), 1280 and 1180 (C-O) cm^{-1}. ^{1}H-Nmr δ: 1.42 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 2.06 (eight lines, 2H, CH_2), 3.85 (s, 1H, OH), 3.98 (s, 3H, OCH_3), 4.95 (t, 1H, J = 6.5 Hz), 7.25 (dd, 1H, J = 1.5 and 8.0 Hz), 7.65 (dd, 1 H, J = 7.7 and 8.0 Hz), 7.73 (dd, 1 H, J = 1.5 and 7.7 Hz) ppm. ^{13}C-Nmr δ: 26.7, 27.1, 39.6, 56.5, 60.0, 79.7, 117.6, 118.3, 118.7, 119.0, 134.1, 135.3, 154.7, 160.0, 178.5, 185.8 ppm. Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.90; H, 5.68.

9-Methoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (9).

A mixture of the diastereoisomers (**8**) (117 mg, 0.37 mmol), *p*-toluenesulfonic acid (5 mg, 0.03 mmol) in xylene (20 ml) was heated under reflux for 75 min. The cooled mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed

on silica gel using first dichloromethane (100 ml) and then 5 % ethyl acetate in dichloromethane (Rf 0.67 in dichloromethane-ethyl acetate 10:1) to give 83 mg (83 %) of the quinone (**9**), mp 139.5-141.5° C (sublimed) (lit.,[5b] 132-134 °C).

3,4-Dihydro-9-methoxy-2,2-dimethyl-2*H*-naphtho[2,3-*b*]pyran-5,10-dione (10).

The quinone (**9**) (43 mg, 0.17 mmol) in ethanol (20 ml) was hydrogenated over 10% palladium on charcoal (5 mg) at room temperature in a Parr hydrogenator for 1 h. The solution was filtered through kieselgur and the filtrate evaporated to give 43 mg (99%) of the crude product **10**, that was recrystallized from methanol, mp 167.5-169.5 °C (lit.,[9] 168-170 °C).

Reaction of the quinone (3) with the dimethylhydrazone (5) : 3,4-dihydro-4-hydroxy-2,2,7-trimethyl-2*H*-quinolin[3,2-*g*]pyran-5,10-dione (12).

A stirred solution of the quinone (**3**) (116 mg, 0.56 mmol) in dichloromethane (10 ml) was treated with the hydrazone (**5**)[11] (125 mg, 1.12 mmol). The yellow solution was stirred for 3 h. Silica gel and silver(I) oxide were added and the mixture was stirred for 24 h at room temperature. The mixture was filtered and the solid filter was rinsed thoroughly with dichloromethane. The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel using hexane-ethyl acetate 2:1 as eluant. (Rf 0.31 hexane-ethyl acetate 1:2) Evaporation of the solvent gave the quinone (**11**) (87 mg, 57 %), mp 170 °C (decomp.). ir ν_{max} : 3260 (OH), 1680 and 1640 (C=O), 1280 and 1120 (C-O) cm^{-1}. ^{1}H-Nmr δ: 1.49 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.00-2.15 (m, 2H, CH_2), 2.55 (s, 3H, CH_3), 3.66 (br s, 1H, OH), 5.06 (t, 1H, J = 6 Hz), 8.26 (d, 1H, J = 2 Hz), 8.86 (d, 1 H, J = 2 Hz) ppm. ^{13}C-Nmr δ: 19.0, 26.9, 27.0, 39.6, 59.9, 80.3, 120.0, 128.7, 133.8, 139.1, 144.9, 154.7, 154.9, 178.3, 185.2 ppm. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.70, H, 5.80, N, 4.96.

Reaction of the quinone (3) with the dimethylhydrazone (6) : 3,4-dihydro-4-hydroxy-2,2,6-trimethyl-2*H*-quinolin[3,2-*g*]pyran-5,10-dione (13).

A stirred solution of the quinone (**3**) (204 mg, 0.98 mmol) in dichloromethane (15 ml) was treated with the hydrazone (**6**) (220 mg, 2.82 mmol). The solution was stirred for 3 h and after the addition of silica gel the resulting suspension was further stirred for 60 min. Then the

mixture was treated with DDQ (483 mg, mmol) and the reaction mixture was refluxed for 15 min. The mixture was filtered and the filtrate was partitioned between dichloromethane (50 ml) and 5% $NaHCO_3$ (100 ml). The aqueous layer was extracted with dichloromethane (2x25 ml) and the combined organic layers were dried. Isolation of the product under the same conditions as above gave to give 3,4-dihydro-4-hydroxy-2,2,6-trimethyl-2*H*-quinolin[3,2-*g*]pyran-5,10-dione (**12**) (134 mg, 50 %), mp. 200 °C (decomp.); ir ν_{max} : 3420 (OH), 1660 (C=O), 1240 and 1100 (C-O) cm^{-1}. ^{1}H-Nmr δ: 1.47 (s, 3H, CH_3), 1.56 (s, 3H, CH_3), 2.00-2.20 (m, 2H, CH_2), 2.81 (s, 3H, CH_3), 4.86 (br s, 1H, OH), 4.97 (t, 1H, J = 6 Hz, CH), 7.42 (d, 1H, J = 4.8 Hz), 8.79 (d, 1H, J = 4.8 Hz) ppm. ^{13}C-Nmr δ: 22.4, 26.8, 27.0, 39.7, 59.9, 79.8, 121.2, 127.2, 131.4, 148.1, 150.3, 152.7, 153.3, 178.6, 187.5 ppm. Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.82, H, 5.80, N, 5.26.

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7. ^{1}H-Nmr δ: 1.35-1.80 (m, 4H, CH_2CH_2), 1.38 (20%) and 1.40 (80%) (two s, 3H, CH_3), 1.50 (80%) and 1.51 (20%) (two s, 3H, CH_3), 1.99 (eight lines, 2H, CH_2), 3.37 (br s, 1H, OH), 3.61 (s, 3H, OCH_3), 4.25-4.35 (m, 1H, CH), 4.82 (80%) and 4.80 (20%) (two t, 1H, J = 6.3 Hz), 6.35 (dd, 1H, J = 6.1 and 7.7 Hz), 6.56 (dd, 1H, J = 0.9 and 7.7 Hz)
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