

STUDIES ON QUINONES. VI. ACID-CATALYZED REARRANGEMENTS IN SOME
4-ACETYL-2,3-DIHYDROBENZO[*b*]FURANS¹Luis BARRIOS, V. Manuel RUIZ, Ricardo TAPIA, Jaime VALDERRAMA*,
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The reaction of 2-acetyl- and 5-acetyl-2-methoxy-1,4-benzoquinone (1a, 1c) with N-propenylpiperidine gave the corresponding 2,3-dihydrobenzo[*b*]furans, 2b and 2c, containing the acetyl group at C-4. Acid treatment of these dihydrofurans rearranged to 8-methyl- and 2-methoxy-8-methyljuglone (4a, 4b). Juglone (4c) and 2,3-dihydrojuglone (6) were obtained in fair yields from 4-acetyl-2,5-dihydroxy-2,3-dihydrobenzo[*b*]furan (2e).

It is known that 2-acetyl-1,4-benzoquinone (1a) and related compounds such as 2-methoxycarbonyl-1,4-benzoquinone (1b) are very reactive at the C-3 position to various nucleophiles.²⁻⁷ In a recent communication⁸ we have described the reaction of quinones 1a and 1b with enamines giving substituted furans. These are formed by attack of the nucleophile at C-3 followed by cyclization; i.e. the addition of N-(2-methyl-1-propenyl)-piperidine to 1a gives 4-acetyl-5-hydroxy-3,3-dimethyl-2-piperidino-2,3-dihydrobenzo[*b*]furan (2a).

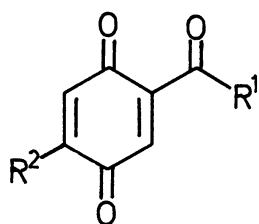
It is interesting to note that the O,N-acetal 2a experiments a ring opening under acidic conditions (ethanol-aqueous HCl) followed by the formation⁸ of the 1(4H)-naphthalenone 3. This reaction occurs due to the presence of a potential C=O group at C-2 and the acetyl group in 2a.

These results prompted us to study the formation of juglones (5-hydroxy-1,4-naphthoquinones) from benzo[*b*]furans capable to experiment the above rearrangement, followed by aromatization of the newly formed carboxylic ring.

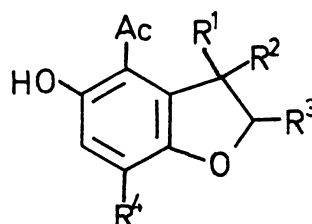
Reaction of 1a and N-propenylpiperidine in benzene solution at room temperature gave 4-acetyl-5-hydroxy-3-methyl-2-piperidino-2,3-dihydrobenzo[*b*]furan (2b) in 80% yield, as an orange oily liquid: IR (film): 1625 cm⁻¹; ¹H-NMR⁹ δ;

6.98 (d, 1H, $J \sim 9\text{Hz}$), 6.81 (d, 1H, $J \sim 9\text{Hz}$), 4.96 (d, 1H, $J \sim 1.8\text{Hz}$), 3.63 (dq, 1H, $J \sim 1.8\text{Hz}$), 2.40-2.84 (m, 4H), 2.70 (s, 3H), 1.40-1.70 (m, 4H), 1.38 (d, 3H). Treatment of **2b** in the same experimental conditions as those for the transformation **2a** \rightarrow **3** afforded 5-hydroxy-8-methyl-1,4-naphthoquinone (**4a**) in low yield¹⁰ (15%): m.p. 162-163° [from cyclohexane (lit.¹¹ 160-163°)] ¹H-NMR: δ ; 12.47 (s, 1H), 7.43 (d, 1H, $J \sim 9\text{Hz}$), 7.16 (d, 1H, $J \sim 9\text{Hz}$), 6.89 (s, 2H), 2.64 (s, 3H).

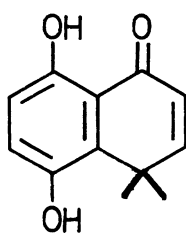
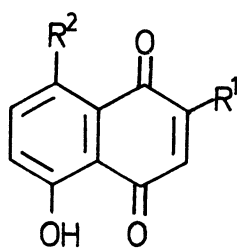
Better results were obtained when **2b** was rearranged in refluxing acetone-10% sulfuric acid solution (1:1) which gave **4a** in 60% yield. On the other hand treatment of **2b** with benzoyl chloride in pyridine produced 1,4,5-tribenzoyloxy-8-methylnaphthalene (**5**) in 50% yield. IR (Nujol): 1754 and 1740 cm^{-1} ; ¹H-NMR: δ ; 8.40-6.80 (m, 19H), 2.80 (s, 3H).



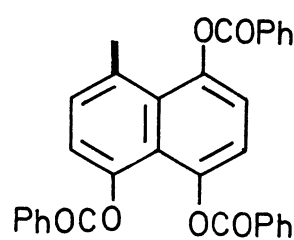
- 1a.** $R^1 = \text{Me}, R^2 = \text{H}$
b. $R^2 = \text{OMe}, R^1 = \text{H}$
c. $R^3 = \text{Me}, R^2 = \text{OMe}$



- 2a.** $R^1 = R^2 = \text{Me}, R^3 = \text{Pip.}, R^4 = \text{H}$
b. $R^1 = \text{Me}, R^2 = R^4 = \text{H}, R^3 = \text{Pip.}$
c. $R^1 = \text{Me}, R^2 = \text{H}, R^3 = \text{Pip.}, R^4 = \text{OMe}$
d. $R^1 = \text{Me}, R^2 = \text{H}, R^3 = \text{OH}, R^4 = \text{OMe}$
e. $R^1 = R^2 = R^4 = \text{H}, R^3 = \text{OH}$

**3**

- 4a.** $R^1 = \text{H}, R^2 = \text{Me}$
b. $R^1 = \text{OMe}, R^2 = \text{Me}$
c. $R^1 = R^2 = \text{H}$

**5**

In order to obtain a substituted juglone in the quinone ring in a similar fashion to that presented above, the reaction of 5-acetyl-2-methoxy-1,4-benzoquinone¹² (**1c**) and N-propenylpiperidine¹² was carried out, isolating the corresponding 2,3-dihydrobenzo[*b*]furan **2c** in 59% yield. IR (KBr): 1610 cm^{-1} ; ¹H-NMR: δ ; 12.95 (s, 1H), 6.36 (s, 1H), 6.05 (s, 3H), 5.02 (d, 1H, $J \sim 1.8\text{Hz}$), 3.60 (dq, 1H,

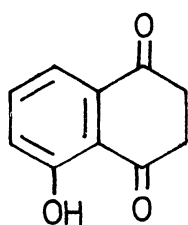
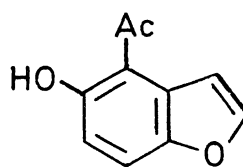
$J \sim 1.8\text{Hz}$), 3.00-2.40 (m, 4H), 2.66 (s, 3H), 1.70-1.35 (m, 4H), 1.37 (d, 3H).

Although two chiral centers appeared at C-2 and C-3 in the formation of the furans **2b** and **2c**, only one product was isolated in both cases. According to the proton coupling constant $C_2\text{-H}$ and $C_3\text{-H}$ ($\sim 1.8\text{Hz}$), it seems reasonable to attribute, in principle, stereochemistry *trans* to those heterocycles^{13,14}, notwithstanding the finding of Zalkow and Thosal^{15,16}.

Prolonged heating of the furan **2c** in 10% sulfuric acid gave 5-hydroxy-2-methoxy-8-methyl-1,4-naphthoquinone (**4b**) in low yield (21%). IR (KBr): 1670 and 1630 cm^{-1} ; $^1\text{H-NMR}$: δ ; 12.71 (s, 1H), 7.24 (2d, 2H, $J \sim 9\text{Hz}$), 6.04 (s, 1H), 3.90 (s, 3H), 2.62 (s, 3H). During the acid treatment of compound **2c**, it was possible to isolate a reaction product characterized by its $^1\text{H-NMR}$ spectrum as the hemiacetal **2d**, which by treatment with 10% sulfuric acid gave the juglone **4b**.

From these results it was supposed that the transformation **2b** \rightarrow **4a** and **2c** \rightarrow **4b** is initiated by hydrolysis of the O,N-acetalic grouping followed by cyclization, in an aldol type fashion, of the open form of the hemiacetals, aromatization and, finally, air oxidation.

Taking into account the participation of hemiacetals in the formation of juglones **4a** and **4b**, acid treatment of hemiacetal **2e**³ gave 2,3-dihydrojuglone (**6**) in fair yield (44%) m.p. 96-97° [from cyclohexane (lit.¹⁷ 96-97°)] and juglone (**4c**) in low yield (15%). The latter was identified by comparison with an authentic sample. When the above reaction was carried out in the presence of diluted hydrogen peroxide, only juglone was isolated in 62% yield.

**6****7**

It is interesting to note that the dihydrofuran **2e** by treatment with *p*-toluenesulfonic acid in benzene solution produced quantitatively 4-acetyl-5-hydroxybenzo[*b*]furan (**7**). IR (KBr): 1620 cm^{-1} ; $^1\text{H-NMR}$: δ ; 12.95 (s, 1H), 7.72 (d, 1H, $J \sim 2\text{Hz}$), 7.60 (d, 1H, $J \sim 9\text{Hz}$), 6.95 (d, 1H, $J \sim 2\text{Hz}$), 6.90 (d, 1H, $J \sim 9\text{Hz}$), 2.80 (s, 1H).

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9. a) All new compounds gave satisfactory data in elemental analysis; b) All ¹H-NMR spectra were run in a VARIAN XL-100 Spectrometer using CDCl₃ as solvent and TMS as internal standard.
10. All juglones were purified by column chromatography on silica gel and the yield are based on the pure products. No further attempts were made in order to improve the yields.
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