Oxidative Coupling of Furans and Naphthoquinones: a Potential Route to Anthracyclinones

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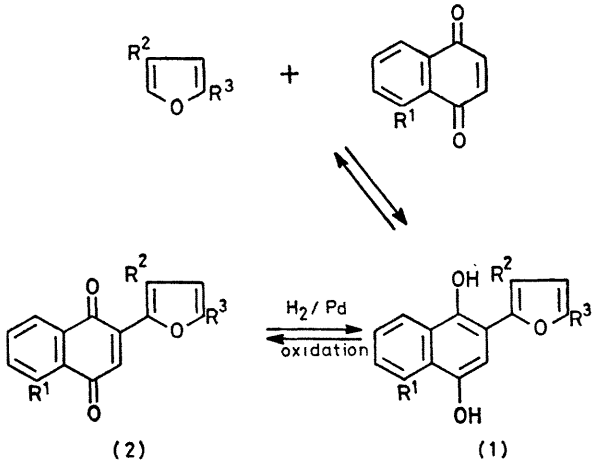
Summary 2-Furyl-1,4-naphthoquinones have been prepared by treatment of mixtures of furans and naphthoquinones with chloranil and other oxidants, and used to synthesize quinizarin and 6,11-dihydroxynaphthacene-5,12-dione in a reaction sequence which promises great versatility.

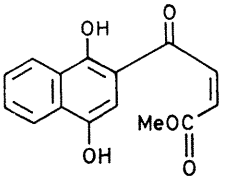
ANTHRACYCLINONE antitumour agents have recently been the subject of intense study and regiospecific total syntheses of the aglycones adriamycinone and daunomycinone have been published.[1] This communication reports a novel reaction of furans and naphthoquinones in the presence of oxidising agents, which, it is believed, will be the basis of an efficient, versatile synthetic route to these and related compounds. Eugster and his co-workers[2] have found furans to be unreactive towards naphthoquinones not bearing electron-withdrawing groups, and similarly Kraus and Roth[3] report that 2-t-butoxyfuran fails to react under all conditions (including Lewis acid catalysis) with unactivated quinones. If these failures reflect unfavourable equilibria rather than unfavourable rates, then *in situ* oxidation of the initial addition products (**1**) should circumvent the problem by removing those products from the equilibrium, provided that the oxidation itself is irreversible.

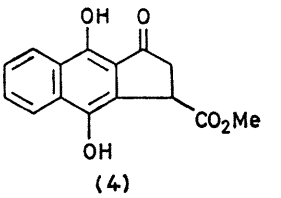
In this way moderate to excellent yields of the quinones (**2**) were obtained. For example, naphthoquinone with an equimolar quantity of chloranil refluxed in an excess of 2-methylfuran gave quantitatively (t.l.c.) a mixture of tetrachlorohydroquinone and (**2a**) which could be separated by recrystallisation or by column chromatography. Parallel results were obtained using 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ), and in the cases of (**2c**) and (**2d**) an excess of naphthoquinone itself proved capable of effecting oxidation. Thus a 2:1 mixture of naphthoquinone and 2-methoxyfuran stirred overnight in CH_2Cl_2 at room temperature gave a 70% yield of (**2c**). Juglone gave the

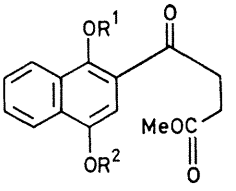
rather unstable (**2e**) in 52% yield; its structure awaits rigorous proof, though the behaviour of juglone towards other related nucleophiles[4] suggests the orientation of addition is as shown (Scheme).



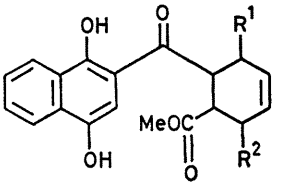
SCHEME. **a**; $R^1 = R^2 = H$, $R^3 = Me$
b; $R^1 = R^2 = R^3 = H$
c; $R^1 = R^2 = H$, $R^3 = OMe$
d; $R^1 = H$, $R^2 = NHCOPh$, $R^3 = H$
e; $R^1 = OH$, $R^2 = H$, $R^3 = OMe$.



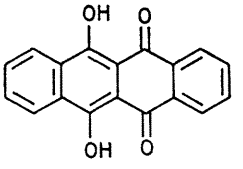




(5) a; $R^1 = R^2 = COMe$
b; $R^1 = H$, $R^2 = COMe$
c; $R^1 = R^2 = H$



(6) $R^1 = H$, $R^2 = OMe$ and $R^1 = OMe$, $R^2 = H$



Hydrogenation of the quinones (**2**) results in a rapid absorption of 1 equiv. of H_2 giving, presumably, (**1**) which rapidly decomposed. Further uptake of hydrogen, often non-stoicheiometric, gave complex mixtures from which naphthoquinol could be isolated, thus confirming the fragmentation of (**1**).

The furan ring in (**2c**) proved susceptible to acid hydrolysis (MeOH, H_2O, H_2SO_4, 0 °C, 1 h) and opened to give (**3**) in 89% yield; further treatment with $NaHCO_3$ resulted in quantitative cyclisation to (**4**). Reductive acetylation of (**2c**) (Zn dust, acetic anhydride) followed by a similar acid hydrolysis gave the diacetate (**5a**) from which (**5b**) and (**5c**) could be obtained by stepwise hydrolysis. Cyclisation of (**5c**) with concurrent oxidation (H_2SO_4, air, 100 °C, 5 min) gave quinizarin quantitatively. This led to the expectation that a more elaborate analogue of (**5c**) might be cyclised to a four-ring system. Accordingly (**3**) was allowed to stand with 1-methoxybutadiene for 3 days to give quantitatively a 2:3 mixture of regioisomers (**6**) Sulphuric acid-induced cyclisation of (**6**) with simultaneous aromatisation gave, in low yield (13% after sublimation), 6,11-dihydroxynaphthacene-5,12-dione (**7**), identified by comparison of its spectral properties with published values.[5] Thus, although a more elegant and efficient cyclisation procedure is clearly needed, the synthetic utility of (**3**) has been demonstrated.

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