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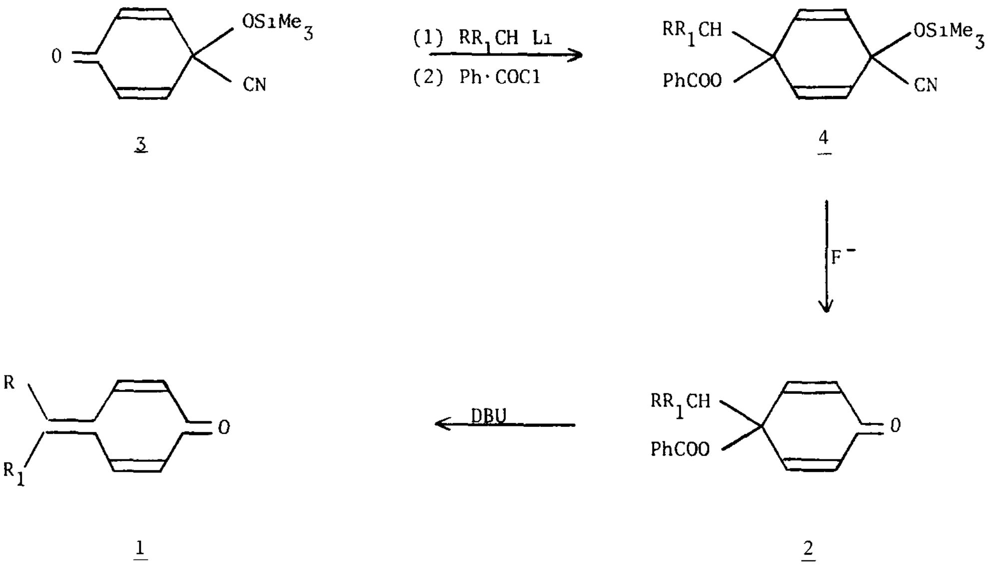
# THE SYNTHESIS OF QUINONE METHIDES FROM p-QUINOL BENZOATES

Allen J Guildford and Ralph W Turner*
Pharmaceuticals Division, Imperial Chemical Industries P.L.C.
Alderley Park, Macclesfield, Cheshire

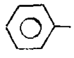
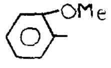
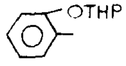
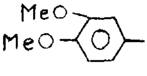
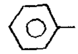
Abstract: A simple route to the quinone methides $(1,R=Ar,R_1=CO_2Me)$ is described.

As part of a programme of research directed towards the synthesis of novel antifungal agents we became interested in developing a facile route to quinone methides of the types (1, R = Ar) and (1, R = $CH_2Ar$) from p-quinol precursors. The formation of quinone methide intermediates has been implicated in certain rearrangements of p-quinol ethers [1] and recently Evans [2] has utilised the conversion of p-quinone monoketals into p-quinone methide ketals in the synthesis of the alkaloid cherylline. In this communication we describe the conversion of certain p-quinol benzoates (2) into the quinone methides (1) and also report a new synthesis of 4-hydroxystilbenes.



A model reaction of the masked quinone (3)[3] with benzyl magnesium bromide gave, after deprotection with sodium fluoride, the required 4-benzyl-4-hydroxycyclohexadienone in 25% yield. This p-quinol was unstable [4] slowly undergoing the dienone-phenol rearrangement even on storage at 0°C. In order to circumvent the problem of this dienone-phenol rearrangement we utilised the anions [5] of esters of phenylacetic acids and benzyl phenyl sulphone instead of the benzyl anion, added the protected quinone (3) to the anion at -70°C and then trapped, still at -70°C, the resultant p-quinol anion with benzoyl chloride. Sodium fluoride deprotection gave the stable p-quinol benzoates (2) and the results of these experiments are summarised in Table 1. In contrast to these observations, when the anion generated from benzyl phenyl sulphide was used in this reaction sequence, only the rearranged benzoate (5) mp 138 - 140°C (hexane/benzene) was isolated, demonstrating the importance of an electron-withdrawing substituent in the benzyl function if rearrangement is to be avoided

Table 1 p-Quinol benzoates (2)

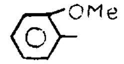
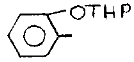
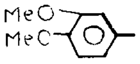
| | R | $R_1$ | m.p.$^{(a)}$ °C | Yield % |
|---|---|---|---|---|
| 2a |  | $CO_2Et$ | 122 - 123 | 64 |
| 2b |  | $CO_2Me$ | 128 - 129 | 55 |
| 2c |  | $CO_2Me$ | foam$^{(b)}$ | 46 |
| 2d |  | $CO_2Me$ | 139 - 141 | 55 |
| 2e |  | $SO_2Ph$ | 149 - 150 | 63 |

(a) recrystallised from toluene/hexane

(b) obtained as a mixture of diastereoisomers

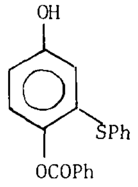
Reaction of the p-quinol benzoates (2a) and (2e) with either DBU or potassium t-butoxide in dry toluene gave only a multispot mixture.[6] However, the three substituted benzoates (2b), (2c) and (2d) under these conditions produced the required quinone methides, isolated as stable crystalline solids (see Table 2).

Table 2 Quinone methides (1)

| | Base | Reaction Time | R | $R_1$ | m.p. °C | yield % |
|---|---|---|---|---|---|---|
| 1a | DBU | 4 hr |  | $CO_2Me$ | 84-86[(a)] | 35 |
| 1b | DBU | 1.3hr |  | $CO_2Me$ | 237 [(b)] | 45 |
| 1c | $KOBu^t$ | 0.5hr |  | $CO_2Me$ | 105-106[(b)] | 35 |

(a) recrystallised hexane/toluene. (b) recrystallised ether/hexane.

The intense yellow quinone methides exhibited characteristic I.R. spectra, showing a split carbonyl band centred between 1720 - 1740 $cm^{-1}$ and a quinone carbonyl band at 1665 - 1670 $cm^{-1}$. These quinone methides readily react with nucleophiles, for example the methide (1a) on treatment with imidazole furnished the addition product (6), mp 222°C in almost quantitative yield. [7] It would appear from these preliminary results that o- and p-electron donating substituents can confer stability on quinone methides of the type (1, R = Ar, $R_1$ = $CO_2Et$).



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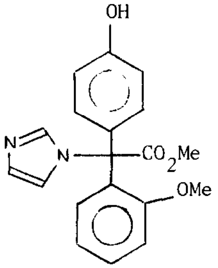

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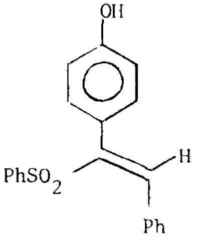

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In an attempt to generate the quinone methide (1, R = $CH_2Ph$) by an analogous sequence developed for the compounds (1, R = Ar), the lithium derivative of phenyl phenylethyl sulphone was reacted with the protected quinone (3) and the resultant anion trapped with benzoyl chloride to give the p-quinol benzoate (2, R = $CH_2Ph$, $R_1$ = $SO_2Ph$), mp 153 - 154°C (hexane/EtoAc) in 75% yield. [8] Predictably the isolation of the less stable quinone methide (1, R = $CH_2Ph$, $R_1$ = $SO_2Ph$) was not possible, treatment of the p-quinol benzoate with DBU gave the stilbene derivative (7), mp 234 - 235°C (hexane/EtoAc) in 70% yield. All reactions designed to trap the quinone methide intermediate with imidazole failed. The structure of (7) was confirmed by removal of the phenylsulphonyl group with aluminium amalgam to give trans-4-hydroxystilbene.

The quinone methide (1b) and related compounds should serve as precursors for a new grisan and/or xanthene synthesis, providing an alternative approach to the well established oxidation of dihydroxybenzophenones, which gives both grisans and xanthenes [9].

## References and Notes

1 M Karhu, J.C.S. Perkin 1, 1661 (1979).

2 D J Hart, P A Cain, and D A Evans, J.Am.Chem.Soc., 100, 1548 (1978).

3 D A Evans, J M Hoffmann and L K Truesdale, J.Am.Chem.Soc., 95, 5822 (1973).

4 The p-quinol was purified by a rapid flash chromatography on Merck silica gel 60 eluting with toluene/ethyl acetate (20:3), followed by removal of solvent at ambient temperature

5 The anions were generated in THF solution at -70°C using lithium diisopropylamide.

6 After a few minutes a transient yellow spot was observed on TLC which rapidly decomposed The quinone methide (1, R = Ph, $R_1$ = $CONEt_2$) however has been isolated. J Ficini and A Krief, Tetrahedron Lett., 2497 (1967).

7 In the case of the p-quinol benzoates (2a) and (2e), which did not give stable quinone methides, trapping of the quinone methides could be achieved by treating (2a) or (2e) with DBU in the presence of imidazole.

8 Various 4-phenylethyl-4-hydroxycyclohexadienone derivatives have been synthesised using the reaction of arylethyl phenyl sulphone anions with quinone monoketals.
D A Evans, P A Cain and R Y Wong, J.Am.Chem.Soc., 99, 7083 (1977).

9 B Franck and U Zeidler, Chem.Ber., 106, 1182 (1973)

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