Base-induced Benzoyl Migrations in Diels–Alder Adducts of Benzoyl-1,4-benzoquinones

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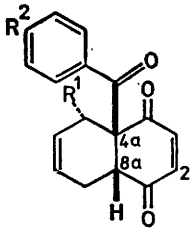
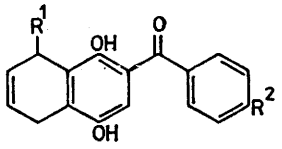
Summary Addition of buta-1,3-diene and *trans*-penta-1,3-diene to substituted benzoyl-1,4-benzoquinones affords the corresponding 4a-benzoyl-4a,5,8,8a-tetrahydro-1,4-naphthoquinones which, in pyridine and pyridine–methanol, undergo [1,5] and [1,2] benzoyl shifts to give 2-benzoyl-5,8-dihydro-1,4-dihydroxynaphthalenes; the effects of *para*-substituents in the benzoyl group on the kinetics and regiospecificity of the migration are described.

ADDITION of buta-1,3-diene to benzoyl-1,4-benzoquinone in the presence of trifluoroacetic acid gives, predominantly, the adduct (**1a**) (olefinic : enedione protons, 1 : 1 by ^{1}H n.m.r. spectroscopy) which smoothly isomerises in pyridine–methanol (1 : 1, v/v) at 25 °C into 2-benzoyl-5,8-dihydro-1,4-dihydroxynaphthalene (**2a**). Addition of *trans*-penta-1,3-diene to the quinone gives the adduct (**1b**) as the major product even in the absence of a proton acid; this adduct undergoes a similar rearrangement, although more rapidly, to give (**2b**). Monitoring the reaction progress with ^{1}H n.m.r. spectroscopy for a solution of (**1b**) in [$^2H_5$]pyridine–[$^2H_4$]methanol (1 : 1, v/v) reveals the accumulation and decay of an intermediate which, *inter alia*, shows a doublet at δ 0·89 (*J* 7 Hz) due to the methyl group, and a doublet of doublets at δ 6·34 (J_1 10 and J_2 1·2 Hz) and a doublet at δ 7·50 (*J* 10 Hz) assigned, respectively, to 3-H ($^6J_{3,8\beta}$ 1·2 Hz) and to 2-H of the enol (**3a**), in excellent agreement with the corresponding data[1] for the enol formed from the acetyl analogue (**4**).†

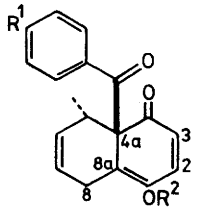


(1)



(2)

	R^1	R^2
a	H	H
b	Me	H
c	Me	OH
d	Me	OMe
e	Me	Me
f	Me	Br
g	Me	NO_2



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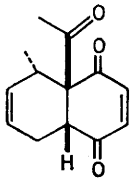


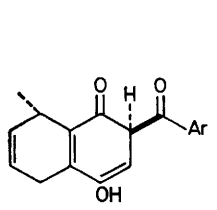
(4)

	R^1	R^2
a	H	H
b	Br	H
c	NO_2	H
d	Br	−ve
e	NO_2	−ve
f	Br	Ac

Pseudo-first order rate constants for the enolisation and rearrangement of several *para*-substituted benzoyl adducts (**1b**)—(**1g**) have been computed from the ^{1}H n.m.r. spectra of solutions in [$^2H_5$]pyridine and in [$^2H_5$]pyridine–[$^2H_4$]

† Isomerisation of the adducts (**1a**) and (**1b**) was first observed by J. M. Bruce and S. M. Mir-Saiedi in 1978. The intermediate from (**1b**) was detected and tentatively identified as the enol (**3a**).

methanol (1 : 1, v/v) at 35 °C assuming that aromatisation of the immediate product, (**5**), of the [1,5] benzoyl shift is fast relative to its formation. In each case the yield of the rearrangement product, observed spectroscopically, is *ca.* 95%; the remaining product is 5,8-dihydro-1,4-dihydroxy-5-methylnaphthalene resulting from competitive debenzoylation.



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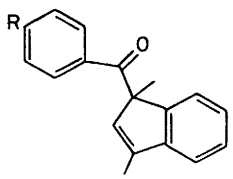


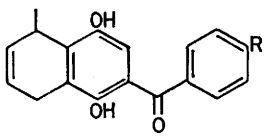
(6)

a R = SO_2Me
b R = H
c R = OMe

Electron-accepting substituents, R^2 in (**1b**)—(**1g**), increase the rate of enolisation by amounts consistent with the inductive enhancement of the acidity of 8a-H and electron-releasing substituents correspondingly decrease it, relative to R^2 = H. Contrarily, donor substituents (R^2 = OH, OMe, or Me) accelerate the [1,5] benzoyl shift relative to R^2 = H and acceptor substituents (R^2 = Br or NO_2) decelerate it. The effects are in the same sense for [$^2H_5$]-pyridine and for [$^2H_5$]pyridine–[$^2H_4$]methanol (1 : 1, v/v), both enolisation and migration being faster in the mixture.‡ The rate of enolisation of the 4a-acetyl compound[1] (**4**) is similar to those for the benzoyl series, but its rate of rearrangement is an order of magnitude greater, possibly consistent with the smaller size of the acetyl group.

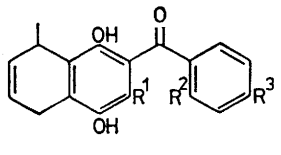
The decelerating effect of electron-accepting *para*-substituents on the [1,5] benzoyl shift is opposite to that observed[2] for the corresponding migration in the indens (**6a**)—(**6c**), but the magnitude of the substituent effect is relatively small for both systems, as expected for a sigmatropic shift, and may reflect differences in solvation.

The combination of an electron-accepting *para*-substituent, R^2 in (**1**), and [$^2H_5$]pyridine as solvent allows a high proportion (90% for R^2 = Br; > 95% for R^2 = NO_2) of the enols (**3b**) and (**3c**) to accumulate and survive sufficiently long for their ^{1}H n.m.r. spectra to be examined in detail; the results confirm the above assignments for the parent compound (**3a**) and the earlier results[1] for the enol of the acetyl analogue (**4**). Attempts to isolate the enols (**3b**) and (**3c**) have failed, only mixtures of the initial *cis*-adducts (**1f**) and (**1g**) and their *trans*-isomers being obtained, but the acetate§ of the enol (**3b**) is readily isolated following addition of acetic anhydride to the pyridine solution.



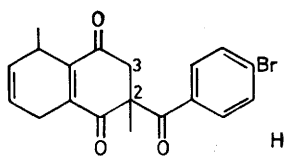
(7)

a R = Br
b R = NO_2



(8)

	R^1	R^2	R^3
a	H	Br	H
b	H	Me	H
c	Me	H	Br



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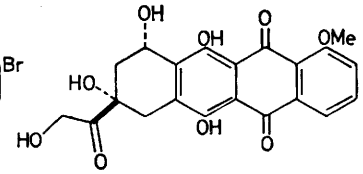

(10)

TABLE. Products of [1,5] benzoyl shifts in Diels–Alder adducts of benzoyl-1,4-benzoquinones.

Method[a]	Product	M.p. or Sublimn. temp. (°C/mmHg)[b]	Isolated yield/%	δ[c] OH	OH	3-H	8-Me[d]	Other
A	(**2a**)	162—163	80	12·13	8·20	6·88	—	—
A	(**2b**)	142—143	72	12·20	7·55	6·80	1·35	—
A	(**2c**)	157—159/0·001	72	12·11	8·80	6·92	1·30	—
A	(**2d**)	148—150/0·001	67	12·12	8·05	6·77	1·30	
A	(**2e**)	142—144/0·001	76	12·20	4·50	6·82	1·30	2·41[e]
A	(**2f**)	135—137/0·001	84	12·03	7·55	6·75	1·30	—
A	(**2g**)	142—145/0·001	74	12·00	4·60	6·65	1·30	—
A	(**8a**)	148/0·005	90	12·11	4·25	6·44	1·33	—
A	(**8b**)	182/0·05	80	12·35	7·97	6·54	1·34	2·25[f]
B	(**8c**)	200—205/0·005	86	[g]	6·75	—	1·28	1·87[h]

[a] A, 7% in pyridine at 35 °C for 24—120 h (*i.e.* until the conversion is complete); B, 7% in pyridine–methanol (1 : 1) at 65 °C for 6 h. [b] Compounds (**2**) and (**8**) are usually obtained as viscous oils. [c] In $CDCl_3$ except for (**2a**) in $CDCl_3$–$(CD_3)_2CO$ (1 : 1); δ 5·9 (m, 6-H, 7-H), 3·2—3·9 (5-H), and 7·1—8·3 [4(5)H, Ar]. [d] d, *J* 7 Hz. [e] 4′-Me. [f] 2′-Me. [g] The steric effect of R^1 = Me results in an upfield shift. [h] 2-Me.

‡ Pseudo-first order rate constants for the benzoyl series in [$^2H_5$]pyridine and in [$^2H_5$]pyridine–[$^2H_4$]methanol (1 : 1, v/v) at 35 °C lie in the ranges 1×10^{-4} to 1×10^{-3} and 5×10^{-4} to 5×10^{-3} s^{-1}, respectively, for enolisation and 1×10^{-5} to 5×10^{-6} and 1×10^{-4} to 5×10^{-5} s^{-1}, respectively, for migration. A detailed analysis will be presented elsewhere.

§ The reactions of this and of related enol acetates are being examined. Compound (**3f**) has δ ($CDCl_3$) 0·87 (d, *J* 7 Hz, 5-Me), 2·16 (dm, J_1 19 Hz, 8β-H), 2·23 (s, Ac), 3·04 (dm, J_1 19 Hz, 8α-H), 3·62 (m, J_1 7 and J_2 5 Hz, 5-H), 5·33 (m, 6-H), 5·80 (m, 7-H), 6·20 (dd, J_1 10 and J_2 1·4 Hz, 3-H), 7·04 (d, *J* 10 Hz, 2-H), and 7·35—7·80 [aromatic AA′BB′ system, dominated by 7·47 (d, *J* 8·4 Hz) and 7·67 (d, *J* 8·4 Hz)].

Rearrangement of the adducts (**1b**)—(**1g**) occurs regiospecifically in pyridine for all the *para*-substituents and in pyridine–methanol for R^2 = OH, OMe, Me, or H, giving (**2**), but for R^2 = Br or NO_2 up to 25% of the isomers (**7a**) and (**7b**) are also formed. This can be explained by a competing [1,2] shift of the benzoyl group from C-4a to C-8a in the enolates (**3d**) and (**3e**) prior to the [1,5] shift, as previously described[3] for the acetyl analogue (**4**), and is consistent with both the higher proportion of enolate expected in the methanolic solvent and the greater susceptibility to nucleophilic attack of the benzoyl carbonyl group when electron-accepting *para*-substituents are present.

The *o*-bromobenzoyl and *o*-toluoyl analogues of (**1b**) also undergo [1,5] benzoyl migrations, affording (**8a**) and (**8b**) when they are dissolved in pyridine.

The 2-methyl homologue of (**1f**) similarly yields (**8c**) but the use of pyridine alone to achieve overall regiospecificity is unnecessary because any competitive transfer of the benzoyl group to C-8a in the initial adduct followed by a [1,5] shift gives (**9**) which can not aromatise, but can undergo a further [1,2] shift[3] in which the benzoyl group is transferred to C-3, yielding (**8c**). A methyl group at C-2 of the initial Diels–Alder adduct thus ensures internal correction; the requisite 2-benzoyl-5-methyl-1,4-benzoquinones are readily prepared. Representative examples are listed in the Table.

The rearrangement products (**8**; R^1 = H, R^2 = Me and R^1 = Me, R^2 = H) contain the array of ring-carbon atoms and much of the key quinonoid oxygenation pattern of the aglycones, *e.g.* adriamycinone (**10**), of the anthracycline antitumour agents.[4] The use of the [1,5] benzoyl shift in the regiospecific synthesis of these compounds is being investigated.

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[3] F. B. H. Ahmad, J. M. Bruce, J. Khalafy, and K. Sabetian, preceding Communication.
[4] F. Arcamone in 'Topics in Antibiotic Chemistry,' ed. P. G. Sammes, Ellis Horwood, Chichester, 1978, Part C; W. A. Remers, 'The Chemistry of Antitumor Antibiotics,' Wiley, New York, 1979, vol. 1, ch. 2; T. R. Kelly, *Annu. Rep. Med. Chem.*, 1979, **14**, 288.