

CYCLOADDITION ROUTES TO POLYCYCLIC QUINONES: PART 1

BORON TRIACETATE AS A REGIOCHEMICAL DIRECTING AGENT

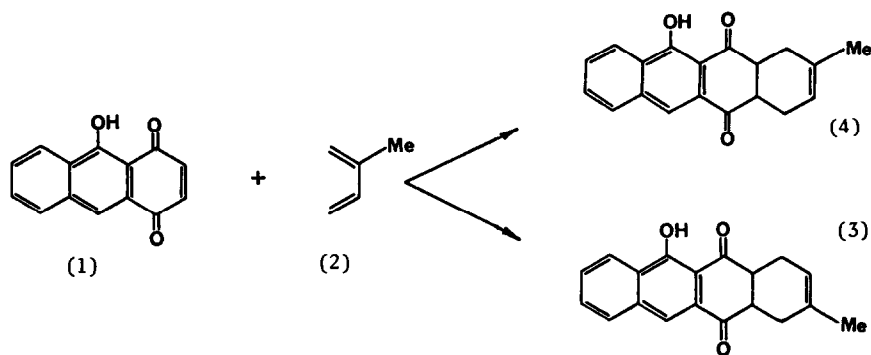
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Abstract: 9-Hydroxy-1,4-anthraquinone, a benzannulated juglone derivative, undergoes regio-specific cycloaddition with isoprene when conducted in the presence of boron triacetate. The structure of this regiomers has been determined by X-ray crystallography.

Cycloaddition reactions involving the addition of dienes to 5-hydroxynaphthoquinone (juglone) have played an important role in the synthesis of numerous naturally occurring anthraquinones^{1,2}, and more recently this approach has been applied to the synthesis of the antineoplastic agent daunomycin.^{3,4} Whilst the ability to control the regiochemical outcome of such cycloadditions has been a major synthetic challenge it is only recently that the large number of experimental results have been rationalised in terms of Frontier Molecular Orbital Theory.⁵ As predicted, cycloadditions involving non-polarised dienes, such as isoprene, show little regioselectivity unless a Lewis Acid is added to the reaction mixture. Unfortunately many dienes do not survive reaction conditions involving classical Lewis acids ($\text{BF}_3 \cdot \text{Et}_2\text{O}$ or AlCl_3) and any gain in regiospecificity is offset by a decrease in adduct yield. In an attempt to solve this problem Kelly and his co-workers introduced the mild Lewis Acid boron triacetate, $\text{B}(\text{OAc})_3$.⁶ This reagent caused a marked effect on the regiochemical outcome of many cycloadditives involving juglone and strongly polarised dienes. However the results obtained with non-polarised dienes showed a disappointing lack of regiospecificity.

As part of our synthetic program leading to anthracyclines we independently examined the role $\text{B}(\text{OAc})_3$ plays in the cycloaddition of isoprene into the anthracene analogue (1) of juglone.⁷ Our results clearly show that in this particular case $\text{B}(\text{OAc})_3$ induces a strong regioselectivity not present in the regular reaction. Thus in the absence of catalyst addition of (1) to (2) yielded a 11 : 10 mixture of the adducts (3) and (4); the ratio being measured by integrating the two resonances for the hydrogen-bonded hydroxyl protons.⁸ The addition of a three-fold excess of $\text{B}(\text{OAc})_3$ to this reaction resulted in the formation of a single isomer (3) in 60%



yield.^{9,10} This isomer was crystallised from CHCl_3 /petrol, m.p. 176-180°C, and its structure determined by single crystal X-ray analysis (fig. 1).

Crystals¹¹ of the hydroxyanthraquinone adduct (3), $\text{C}_{19}\text{H}_{16}\text{O}_3$, are monoclinic, space group $P2_1/c$, with $a = 5.032(1)$, $b = 13.517(3)$, $c = 22.131(4)$ Å, $\beta = 103.14(3)^\circ$, $V = 1465.9$ Å³, $D_c = 1.32$ g cm⁻³, $D_m = 1.33(1)$ g cm⁻³ and $Z = 4$. Intensity data were collected on a PICKER FACS-I automatic diffractometer (graphite-monochromated Mo K_α radiation, θ - 2θ scan technique). Of the 2555 independent reflections in the scan range $3^\circ > 2\theta > 50^\circ$, 1400 with $I > 3\sigma(I)$ were considered to be observed. The structure was solved by the MULTAN¹² series of programs and difference Fourier syntheses and refined by block-diagonal and full-matrix least-squares. Hydrogen atoms were located from difference Fourier syntheses and their parameters included as variables in the subsequent refinement. Full-matrix least-squares refinement with anisotropic thermal parameters for oxygen and carbon and isotropic temperature factors for hydrogen atoms converged to $R = 0.050$ ($R_w = 0.056$) for the 'observed' reflections.¹³ Bond angles and bond distances are shown in figures 2 and 3 respectively.

It is clear from the present work that fusion of the benzene ring to the 6,7-position of juglone, although well removed from the reaction site, dramatically effects the selectivity of its reactions. Since we have not yet established that the products arising from the present study are controlled by rate or equilibrium effects it is pointless to attempt to correlate our results with theory at this time.^{5,14} It should be noted, however, that magnesium iodide does partially reverse the selectivity [(3) : (4) = 2 : 3] in the reaction of (1) with isoprene although the yield ($\approx 10\%$) is poor.¹⁵

This result is the first example of a regiospecific addition of a non-polarised diene to a juglone-type derivative, catalysed by a non-destructive Lewis acid. Extensions of this result leading to regiospecific syntheses of anthracyclines will be presented in a forthcoming paper.

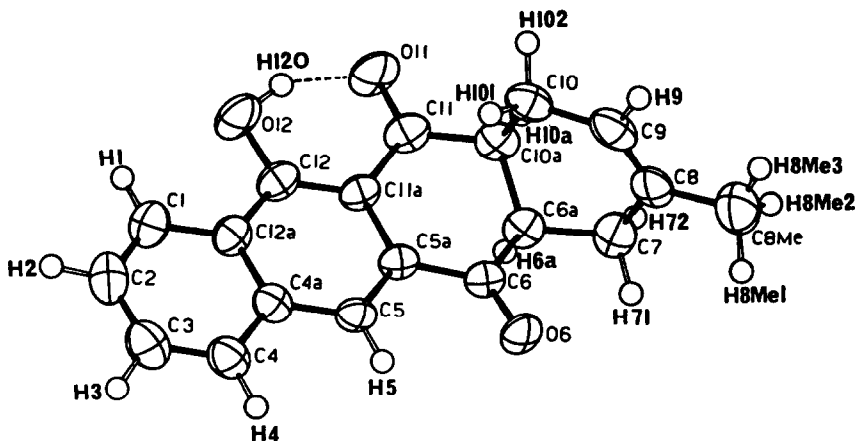
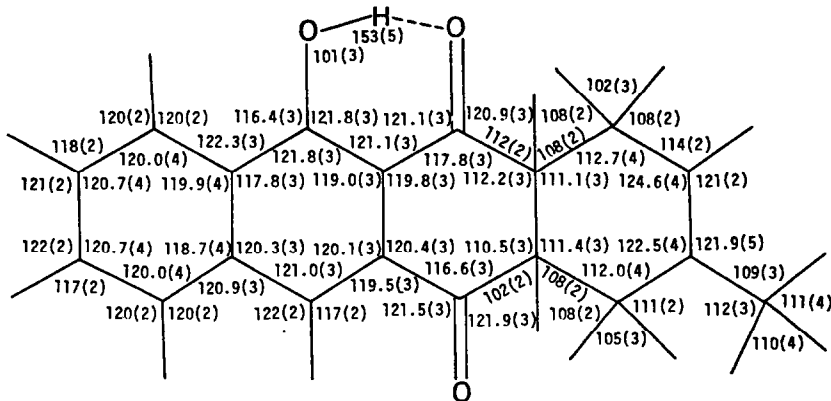


FIGURE 1. ORTEP diagram of isomer (3)



ANGLES NOT SHOWN IN DIAGRAM.

C10-C10a-C11	108.9(2)
C6-C6a-C7	112.3(3)
H6a-C6a-C10a	112(2)
H6a-C10a-C10a	105(2)
H71-C7-C8	110(2)
H72-C7-C6a	110(2)
H101-C10-C9	114(2)
H102-C10-C10a	112(2)
H8Me1-C8Me-H8Me3	104(4)
H8Me2-C8Me-C8	111(2)

FIGURE 2. Bond Angles ($^{\circ}$)

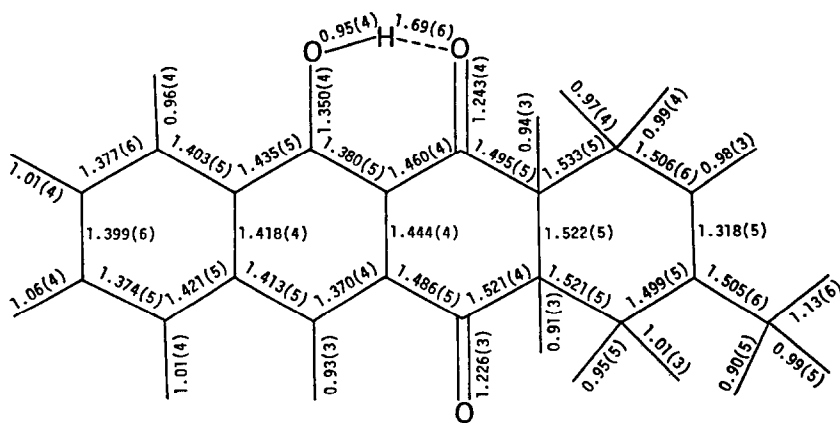


FIGURE 3. Bond Distances (Å)

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1. Birch, A. and Powell, V., *Tetrahedron Letters*, 1970, 3467.
2. Powell, V., *Tetrahedron Letters*, 1970, 3463.
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5. Boeckman, R.K., Dalak, T.M. and Culos, K.O., *J. Amer. Chem. Soc.*, 1978, 100, 7098.
6. Kelly, T.R. and Montury, M., *Tetrahedron Letters*, 1978, 4311.
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8. The ^1H -n.m.r. spectra (Varian CFT 20) of the regioisomers were superimposable with the exception of the hydroxyl resonances. In chloroform-*d* solution isomer (3) showed a hydroxyl resonance at δ 13.76 whilst (4) gave the corresponding resonance at δ 13.74. The low-field position of these resonances is consistent with the presence of a strongly H-bonded hydroxyl group and this is also evident in the X-ray structure (fig. 2).
9. Reactions not involving $\text{B}(\text{OAc})_3$ were conducted in benzene at 150° for 2 hrs. Catalysed reactions were more rapid and were conducted at room temperature.
10. A similar reaction using $\text{BF}_3 \cdot \text{Et}_2\text{O}$ yielded mainly polymeric material, whilst the use of boric acid as catalyst gave an isomer mixture (3):(4) = 10:2.8.
11. Crystals suitable for X-ray structure analysis were obtained by allowing hexane to slowly diffuse into a chloroform solution of the adduct.
12. Germain, G., Main, P. and Woolfson, M.M., *Acta Cryst.*, 1971, A27, 368.
13. Tables of positional and thermal parameters, observed and calculated structure amplitudes have been submitted for deposition at the Cambridge Crystallographic Data Centre.
14. Trost, B.M., Ippen, J. and Vladuchick, W., *J. Amer. Chem. Soc.*, 1977, 99, 8116.
15. Kelly and Montury⁶, noted a similar reversal with juglone.

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