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STUDIES DIRECTED TOWARD THE SYNTHESIS OF ADRIAMYCIN: A DIELS-ALDER APPROACH

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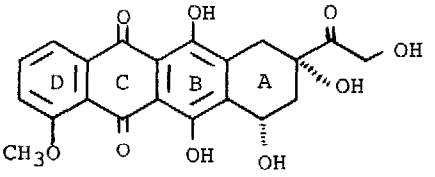
In the preceding Letter[2] we have shown that the synthesis of tetracyclic precursors of adriamycinone (1) by the Diels-Alder reaction between 1,4,9,10-anthradiquinones and 1,3-disubstituted dienes is largely frustrated by the obtrusion of an alternate mode of reaction. As a



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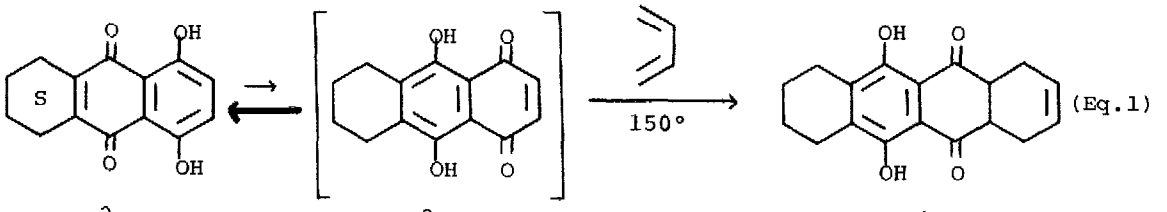
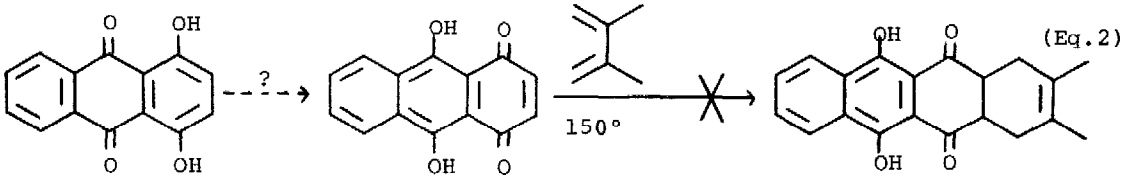
consequence, it became worthwhile to explore alternative DCB→DCBA approaches to functionalized anthracycline tetracycles. In the present communication we report a partial solution to this problem which also provides insight into the orientational aspects of the Diels-Alder reaction between unsymmetrical quinones and dienes.

Fariña and coworkers[3] have reported that the Diels-Alder reaction between 2 and butadiene proceeds via 2a, the less stable tautomer of 2, to give the linearly annulated adduct 3 (Eq. 1).



2 2a 3 (Eq.1)

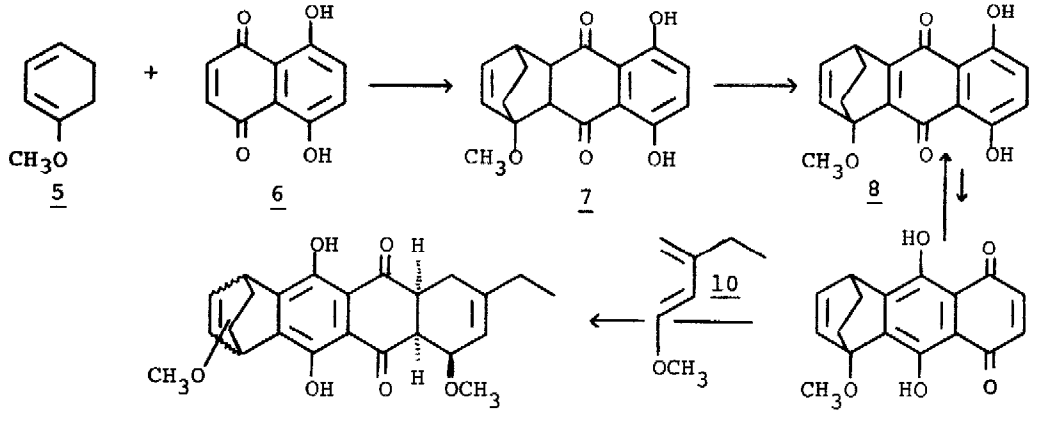
As anticipated, attempts in our laboratory to extend this approach using quinizarin (4), which would provide adducts possessing the requisite aromatic D ring, were unavailing. The quinizarin appears inert to the reaction conditions, and only slow destruction of the diene occurs (Eq. 2).



4 (Eq.2)

It thus became apparent that extension of the approach implicit in Equations 1 and 2 requires that the aromaticity of the potential D ring of adriamycinone must be initially incorporated in a latent form. One solution to this problem, which is at once both an amalgamation and extension of previous work by Fariña and coworkers[3] and by Powell[4] and Birch[5], is outlined in Scheme 1.

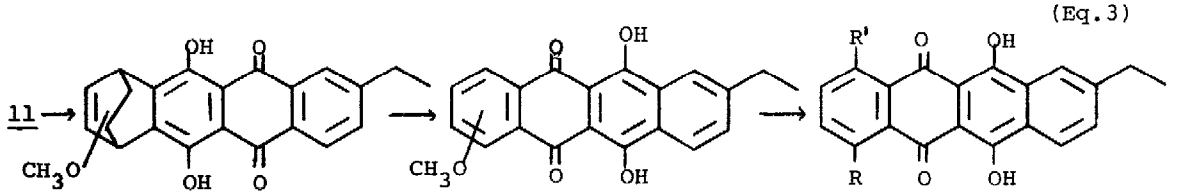
Scheme 1



Reaction of 1-methoxycyclohexa-1,3-diene (5)[6] with naphthazarin (6)[7] affords the pale yellow adduct 7* (mp. 165-166°, 72%) after recrystallization from ethanol which, upon treatment with aqueous base in the presence of oxygen[3], suffers simultaneous tautomerization and oxidation to give the annulated naphthazarin 8, as deep red crystals (mp. 167-169°) in 73% yield after chromatography. In solution, 8[8] is in a facile but unfavorable equilibrium with 9, and addition of excess 10[2] to 8 in methylene chloride at 20° results in the rapid formation of 11 in 94% yield (crude). The overall yield of 11, which contains the tetracarbocyclic nucleus of adriamycinone and its analogs, is 49.4% based on napthazarin.

Adduct 11 is obtained as a non-crystalline mixture of isomers, but since all but one of the five asymmetric centers would be subsequently destroyed, a lack of stereospecificity in the cycloaddition is of no great moment. For precursors of adriamycin analogs which possess substituents in the D ring, however, the regiospecificity of the reaction is of substantial consequence and it was therefore determined using the sequence outlined in Equation 3.

(Eq.3)



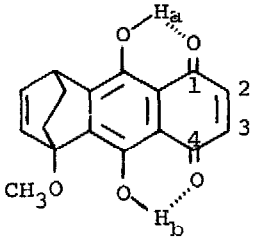
Reaction[3] of 11 (as a mixture) with oxygen and aqueous alkali gives the oxidized, aromatized derivative 12 as orange crystals (mp. 151°, decomp., 58% yield), which, when heated[4] at 155°, eliminates ethylene to give the red napthacenequinone 13 (mp. 196-201°) in 52% yield.

*All compounds described herein gave spectra completely consistent with assigned structures.

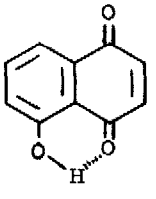
Demethylation[9] of 13 with boron tribromide at -70° gives the corresponding red trihydroxynaphthacenequinone (mp. 157°, 59%) which could, a priori, be 14, 15 or a mixture of the two.[10,11] Comparison of the infrared spectrum of the ethyltrihydroxynaphthacenequinone derived from 11 with infrared spectra[12] of authentic samples of 14 and 15 revealed that it is a mixture (which we have been unable to separate) of 14 and 15, with 15 as the major (80+%) component. Since the regioselectivity desired for the synthesis of adriamycinone requires 14 to be the sole or major degradation product of 11, we can conclude that the Diels-Alder reaction between 9 and 10 proceeds primarily in the regiochemically undesired sense.

Nevertheless the efficient, high-yield synthesis of 11 provides, with appropriate modification and extension, a potentially short and flexible route to numerous analogs of adriamycin.

The preferential formation of the undesired regioisomer of 11 can be accounted for either on the basis of Chisholm's first law[13] or hydrogen bonding considerations. In the latter explanation, hydrogen bonding in 9a could be stronger between H_a and the C-1 carbonyl than between H_b and the C-4 carbonyl because of the potential competition for hydrogen bonding between H_b and the methoxy group. If this is true the C-1 carbonyl would be the more electron withdrawing substituent on the dienophilic C-2, C-3 double bond and the observed regiochemical outcome should obtain.[14] A similar rationale has been suggested by Birch and Powell[5] to account for the regiospecificity observed in the reaction of juglone (16) with a number of 1-methoxycyclohexa-1,3-dienes. Inhoffen, Muxfeldt and coworkers have also reported substituent-dependent regiochemical



9a



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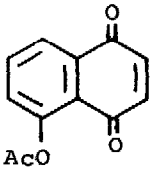

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outcomes in the reaction of 16 and 17 with 1-acetoxybutadiene.[15] Their results can be rationalized, in part, by using similar considerations.[16]

In view of the above results, it would appear that any regiospecific synthesis of adriamycinone and its analogs which employs a Diels-Alder reaction will require a careful appraisal of seemingly-remote-substituent effects. Application of the understanding gained from the results described herein will be reported in due course.

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Footnotes and References

1. Recipient of NIH Research Career Development Award, 1975-80.

2. T.R. Kelly, R.N. Goerner, Jr., J.W. Gillard and B.K. Prazak, Tetrahedron Letters, see accompanying letter.

3. F. Fariña and J.C. Vega, ibid., 1655 (1972); S. Alvarado, F. Fariña and J.L. Martin, ibid. 3377 (1970).

4. V.H. Powell, ibid., 3463 (1970).

5. A.J. Birch and V.H. Powell, ibid., 3467 (1970).

6. A.J. Birch and G.S.R. Subba Rao, ibid., 3797 (1968).

7. L.F. Fieser, J. Amer. Chem. Soc., 50, 439 (1928). See also L.A. Cort and P.A.B. Rodriguez, J. Chem. Soc, (C), 949 (1967) and references therein.

8. That 8 is the predominant tautomer of the 8⇄9 equilibrium is indicated[3] by the chemical shift (δ 7.1) of the aromatic protons.

9. Z. Horii, Y. Ozaki, S. Yamamura, T. Nichikado, Y. Hanaoka and T. Momose, Chem. Pharm. Bull. (Tokyo), 22, 93 (1974); Z. Horii, Y. Ozaki, S. Yamamura and T. Momose, ibid., 20, 2502 (1972). We thank Dr. Mervyn Israel, Children's Cancer Research Foundation, for bringing these references to our attention.

10. Compounds 14 and 15 possess identical melting points of 206°.[11] An equal mixture of 14 and 15 melts at 173-5°.[11] The low-but sharp-melting point of the 11-derived mixture of 14 and 15 may be due to polymorphism or to a dramatic dependence of the value of the mixed melting point on the proportion of 14 and 15 in the mixture. The ethyltrihydroxynaphthacenequinone mixture derived from 11 gave the correct molecular ion in its mass spectrum; its UV-visible spectrum in cyclohexane is identical to those reported for 14 and 15[11] but its visible spectrum in conc. H_2SO_4 [λ_{max} (ϵ):533 (26,000), 575 (54,000)] is consistent with only 15 or a mixture of 14 and 15 which is predominantly 15 [lit.[11] $\lambda_{max}^{conc.\ H_2SO_4}$($\epsilon$), 14: 536 (27,500), 578 (54,000); 15: 532 (28,000), 574 (56,000)]. The IR spectra of 14 and 15[12] are distinctly different.

11. H. Brockmann and R. Zunker, Tetrahedron Letters, 45 (1966); H. Brockmann, R. Zunker and H. Brockmann, Jr., Ann. 696, 145 (1966). For an alternate preparation of 14 see ref. 9.

12. We thank Professor Brockmann for copies of the IR spectra of 14 and 15.

13. Also known as Murphy's Law: "If anything can go wrong, it will." See F.P. Chisholm in "A Stress Analysis of a Strapless Evening Gown and Other Essays for a Scientific Age," R.A. Baker, Ed., Doubleday-Anchor, Garden City, N.Y., 1969, p.1.

14. For reviews of the Diels Alder reaction see, inter alia, W. Carruthers, "Some Modern Methods of Organic Synthesis," Cambridge University Press, Cambridge, 1971, Chapter 3; and A.S. Onishchenko, "Diene Synthesis," Israel Program for Scientific Translations, Jerusalem, 1964.

15. H.H. Inhoffen, H. Muxfeldt, H. Schaefer and H. Kramer, Croat. Chem. Acta, 29, 329 (1957); H. Muxfeldt, Angew. Chem. 74, 825 (1962).

16. For the use of Lewis acid catalysis to reverse the regiochemistry in the Diels Alder reaction of 2,6-xyloquinone see R.A. Dickinson, R. Kubela, G.A. MacAlpine, Z. Stojanac and Z. Valenta, Can. J. Chem., 50, 2377 (1972).