4a,9a-Epoxy-4a,9a-dihydroanthracene-1,4,9,10-tetrone: a Versatile Synthon in Anthracyclinone Synthesis

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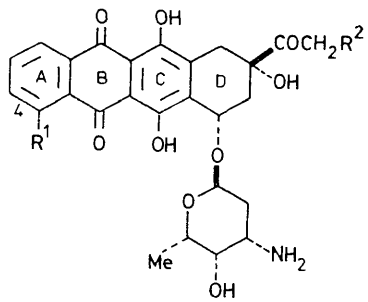
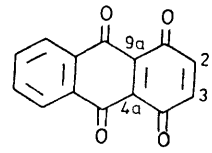
Summary The title compound (**3a**) undergoes Diels–Alder reactions with isoprene, cyclopentadiene, and cyclohexa-1,3-diene; the adducts (**4**) and (**5a,b**) can be transformed into the leucoquinizarins (**6**) and (**7a,b**) which are potentially valuable precursors of anthracyclinone analogues.

ADRIAMYCIN (**1**) and daunomycin (**1b**), members of the anthracycline group of antibiotics, are of considerable current interest because of their potent antitumour properties.[1] To acquire a better understanding of structure–activity relationships involving this class of compounds, we have initiated a programme aimed at the synthesis of analogues with altered aglycones. At the outset of our work it was known that the 4-methoxy-group of ring A was not essential since carminomycin (**1c**)[2] also displayed pronounced cytotoxic activity. Our initial objective therefore was to prepare derivatives, with modifications to ring D, which lacked the 4-substituent of ring A. Significantly, a recent report has revealed[3] that 4-demethoxydaunomycin (**1d**) is 4—8 times more active than daunomycin (**1b**).

In principle, a simple and versatile approach to precursors of the required anthracyclinones involves the cycloaddition of a diene at the 2,3-positions of the diquinone (**2**). In practice, however, this route is limited by the tendency of many dienes to react preferentially with the 4a,9a-double bond.[4–6] No obvious correlation exists between the structure of the diene and the site of its cycloaddition, although 2-substituted butadienes add predominantly to the 4a,9a-double bond. An obvious solution to the foregoing problem involves the protection of the internal double bond of the diquinone (**2**). The choice of the substituents X and Y in such a protected compound, *i.e.* (**3**), is governed by three considerations. First, it is desirable

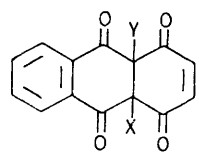


(1)

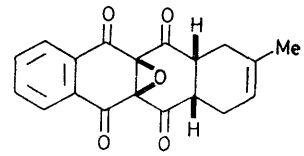


(2)

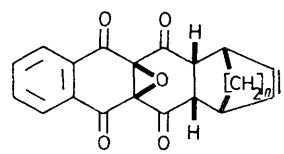
a; R^1 = OMe, R^2 = OH
b; R^1 = OMe, R^2 = H
c; R^1 = OH, R^2 = H
d; R^1 = R^2 = H



(3)
a; X = Y = O



(4)



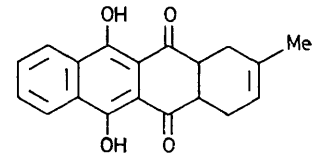
(5)
a; *n* = 1
b; *n* = 2

that they can be added exclusively to the 4a,9a-double bond of the diquinone (**2**). Second, they should not interfere with the dienophilic properties of the compound (**3**). Third, they should be capable of elimination from the derived cycloadducts. We now report that the epoxy-derivative (**3a**),† m.p. 166—180 °C (decomp.) (from $CHCl_3$), obtained (50%) by treating the diquinone (**2**)[7] with *m*-chloroperbenzoic acid in dichloromethane, fulfils these requirements.

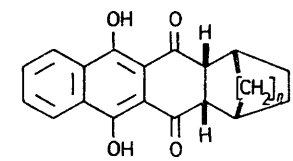
When heated with an excess of isoprene‡ in boiling benzene, the epoxy-compound (**3a**) was converted (90%) into the cycloadduct (**4**),† m.p. 152—154 °C (decomp.) (from $CHCl_3$–Et_2O). Similarly, cyclopentadiene§ and cyclohexa-1,3-diene¶ reacted with the derivative (**3a**) to give the cycloadducts (**5a**) and (**5b**). The former product, m.p. 208—220 °C (decomp.) (from C_6H_6), was isolated in 85% yield and the latter product, m.p. 208—212 °C (decomp.) (from $CHCl_3$–Et_2O), in 75% yield. The stereochemistries of the cycloadducts were inferred on the expectation that the cycloadditions occurred by way of the least-hindered *endo*-transition states.

Although we were unable to effect the direct deoxygenation of the derivatives (**4**) and (**5**), reductive deoxygenations were achieved. Thus, sodium dithionite–methanol effected the conversions of the compound (**4**) into the leucoquinizarin (**6**)† (35%), m.p. 238—239 °C (from EtOAc–light petroleum), and of the compound (**5a**) into the leucoquinizarin (**7a**) (70%), m.p. 147—148 °C (from $CHCl_3$–Et_2O) (lit.[8] m.p. 143—144 °C). The compound (**5b**) was transformed into the leucoquinizarin (**7b**)† (60%), m.p. 203—204 °C (from $CHCl_3$–Et_2O), by zinc–acetic acid.

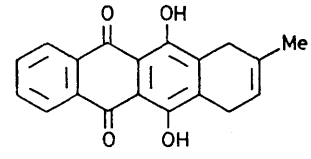
Sequential treatment of the leucoquinizarins (**6**) and (**7a,b**) with lead tetra-acetate in acetic acid, and triethylamine in boiling benzene afforded the quinizarins (**8**)† (80%), m.p. 287—288 °C (from $CHCl_3$–Et_2O), (**9a**) (70%), m.p. 222—224 °C (from $CHCl_3$–Et_2O) (lit.[8] 225—227 °C), and (**9b**)† (45%), m.p. > 340 °C (from $CHCl_3$).



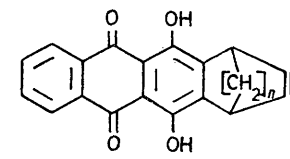
(6)



(7)
a; *n* = 1
b; n = 2



(8)



(9)
a; *n* = 1
b; *n* = 2

These results extend the scope of the Diels–Alder route to anthracyclinones; in principle they allow for the derivation of compounds with a wide range of functionality in ring D.

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† The compositions of new compounds were confirmed by elemental analyses. Structural assignments were based upon n.m.r., i.r., and u.v. spectroscopic evidence.

‡ Isoprene has been reported (ref. 6) to react with the 4a,9a-double bond of the diquinone (**2**).

§ Cyclopentadiene affords a mixture of mono- and di-adducts with the diquinone (**2**).

¶ Cyclohexa-1,3-diene reacts with the diquinone (**2**) to give predominantly the 2,3-cycloadduct (70%).

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