Regiocontrolled Diels–Alder Reactions of 9-Chloro-10-hydroxyanthracene-1,4-dione

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The title compound reacts with isoprene in the presence of aluminium chloride or boron trifluoride–ether to give the 2-methyl derivative of 6-chloro-11-hydroxy-1,4,4a,12a-tetrahydronaphthacene-5,12-dione; in the presence of boron triacetate, the 3-methyl isomer is the major product.

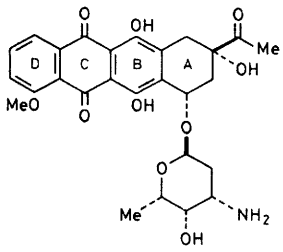
Because of the clinical value of certain anthracycline antibiotics, *e.g.* daunomycin (**1**), in the treatment of cancers, much effort is currently being devoted to the synthesis of such compounds and their analogues.[1] Quinizarin (**2a**) and 5-hydroxyquinizarin (**2b**), important intermediates in the dyestuff industry, represent potentially powerful BCD-ring synthons for the aglycone components of these anticancer agents. To date, three procedures have been developed to effect A-ring annelations of type (**3**) on such compounds or their products: the Diels–Alder reaction,[2–4] the double Marschalk reaction,[5] and the Michael–Marschalk reaction sequence.[6] Only the last-mentioned method has, so far, been developed for a regiocontrolled annelation.[6]

As a prelude to attempting to effect regiocontrolled Diels–Alder reactions of anthracenediones derived from compound (**2b**), we have re-examined the behaviour of anthracenedione (**4a**), readily prepared from quinizarin (**2a**) and thionyl chloride,[7] towards isoprene.[3] The outcome of the reaction can be controlled by the choice of Lewis acid.

In accord with a recent report,[4] it was found that the crude product (88%), from the reaction of the anthracenedione (**4a**) and isoprene in boiling benzene for 35 h, was a 1:1 mixture† of the cycloadducts (**5**) and (**6a**). Recrystallisation of the mixture from dichloromethane gave buff needles, m.p. 182—184 °C, which were a 3:1 mixture† of cycloadducts.

It is well established that Lewis acids can enhance the regioselectivity of Diels–Alder reactions. In particular, it has been shown[8] that the reaction of juglone (**7**) with isoprene leads, following aromatisation, to 7.3:1 and 4.5:1 mixtures of the anthraquinones (**8**) and (**9**) in the presence of BF_3–Et_2O and aluminium chloride, respectively; a 1:1.2 mixture of anthraquinones (**8**) and (**9**) was produced in the uncatalysed reaction.

On the basis of the aforementioned results, it was expected that the corresponding Lewis-acid mediated reactions of the anthracenedione (**4a**) with isoprene would afford predominantly the cycloadduct (**5**). Indeed, the crude product (70%) from the boron trifluoride-induced reaction, which was obtained after 3 h at 23 °C in benzene, contained essentially one cycloadduct.† Similarly, the crude product (68%) from the aluminium chloride-mediated reaction, which was isolated after 1.5 h at 80 °C, was the same cycloadduct;† recrystallisation of the product gave a pure compound,† m.p. 204—205 °C, presumed to possess the structure (**5**).



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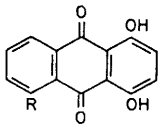
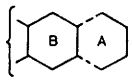
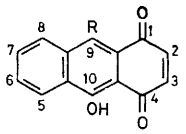


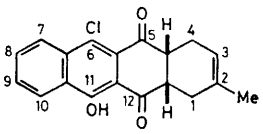
(2) a; R = H
b; R = OH



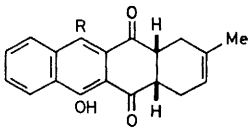
(3)



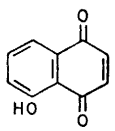
(4) a; R = Cl
b; R = H



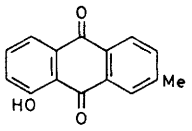
(5)



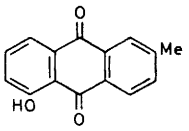
(6) a; R = Cl
b; R = H



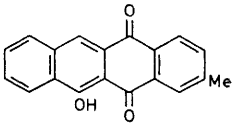
(7)



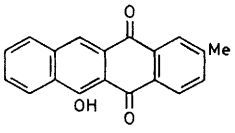
(8)



(9)



(10)



(11)

† The ratio of products in diastereoisomeric mixtures and the homogeneity of pure diastereoisomers were established by 220 or 360 MHz n.m.r. spectroscopy.

To establish unequivocally the structure of the aforementioned cycloadduct, a chemical correlation with the naphthacenedione (**6b**),[9] whose structure is secure on the basis of an *X*-ray analysis, was sought. Attempts to effect the reductive dechlorination of the 1 : 1 mixture of cycloadducts (**5**) and (**6a**) were unrewarding. However, treatment of the mixture with hot aqueous sodium hydroxide solution followed by triethylamine in dichloromethane and recrystallisation of the product gave a 1 : 1.5 mixture† of naphthacenediones (**10**) and (**11**), m.p. 235—238 °C.

Under corresponding conditions, the crude cycloadduct [presumed to be (**5**)], obtained from the aluminium chloride-mediated reaction, gave the naphthacenedione [presumed to be (**10**)]† [61% yield, based upon (**4a**) after recrystallisation], m.p. 255—256 °C (decomp.). The crude cycloadduct (**6b**), prepared by the published method,[9] was converted into a 1 : 6 mixture† of naphthacenediones (**10**) and (**11**) [63% yield, based upon (**4b**) after recrystallisation], m.p. 233—235 °C (decomp.), by reaction with triethylamine.

It is noteworthy that compound (**6b**) was prepared from the anthracenedione (**4b**) and isoprene in the presence of boron triacetate.[9] Accordingly, the behaviour of the anthracenedione (**4a**) towards isoprene in the presence of this reagent was examined. The crude product, obtained from the reaction in benzene after 1 h at 20 °C, was treated with sodium hydroxide followed by triethylamine to give a 1 : 10 mixture† of naphthacenediones (**10**) and (**11**) [72% yield, based upon (**4a**) after recrystallisation], m.p. 233—235 °C (decomp.); several recrystallisations of the crude cycloadduct gave pure compound (**6a**),† m.p. 181—182 °C.

In a re-examination of Boeckman's work,[8] juglone (**7**) was treated with isoprene in toluene at 0 °C in the presence of BF_3–Et_2O. Aromatisation of the crude cycloadduct with triethylamine in dichloromethane gave an 8 : 1 mixture of anthraquinones (**8**) and (**9**) (66%), m.p. 152—154 °C; recrystallisation of the mixture gave the pure anthraquinone (**8**),† m.p. 183—184 °C. Juglone (**7**) reacted with isoprene in the presence of boron triacetate, in benzene at 20 °C over 0.5 h, to give, following aromatisation, a 1 : 7 mixture† of anthraquinones (**8**) and (**9**) (63%), m.p. 128—130 °C; recrystallisation of the mixture gave pure anthraquinone (**9**),† m.p. 146—147 °C (lit.[10] 147 °C).

These results show, for the first time, that it is possible to alter substantially the regioselectivity of addition of a non-polarised diene to a hydroxyquinone, by the choice of Lewis acid. Hitherto, such control has been noted[11] in reactions of hydroxyquinones with strongly polarised dienes. No regiocontrol was observed with non-polarised dienes and, in that situation, the directing effects of BF_3–Et_2O and boron triacetate were comparable.[11]

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