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A FACILE SYNTHESIS OF BENZ[a]ANTHRACENE-7,12-DIONES

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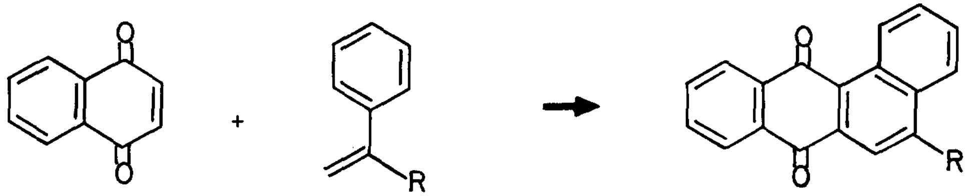
The synthesis of the potent carcinogen 7,12-dimethylbenz[a]anthracene, DMBA, 4a and its many derivatives has been difficult in the past due to the lack of commercially available starting materials. Of the various methods available for its synthesis(1-4), the simplest involves the addition of methylmagnesium iodide to a benz[a]anthracene-7,12-dione precursor.(2,3) This reaction does not provide easy access to the wide range of DMBA derivatives that are needed for the investigation of its biological activity because of the difficulty in obtaining the appropriately substituted quinones. To make use of this simple Grignard reaction, a facile synthesis of benz[a]anthracene-7,12-diones was necessary. We have developed such a synthesis by employing a Diels-Alder reaction between styrenes and naphthoquinone. The Diels-Alder type of reaction(5) has been successfully used in the past to prepare numerous naphthoquinones(6), anthraquinones(7), phenanthraquinones(8) and chrysenequinones.(9) There has been only one report of the formation of a benzanthraquinone derivative, 1,2,3,4,-tetrahydro-5-chlorobenz[a]anthracene-7,12-dione, which was formed from the reaction of 1,4-naphthoquinone with α-chlorovinylcyclohexene.(10) However, there have been no reports of the successful reaction of 1,4-naphthoquinones with styrenes, even though considerable work has been done with benzoquinones and styrenes.(11,12)

We have been successful in preparing benz[a]anthracene-7,12-dione (3a) in a reasonably good yield from 1,4-naphthoquinone (1) and styrene (2a). The use of α-methylstyrene (2b) has led to the formation of 5-methylbenz[a]anthracene-7,12-dione (3b).



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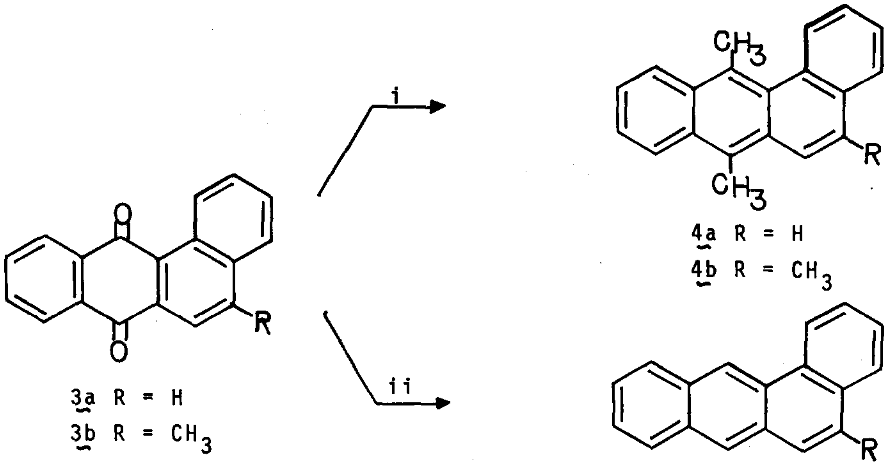
2a R = H
2b R = CH$_3$

3a R = H
3b R = CH$_3$

These diones (3a and 3b) can then be reacted with methylmagnesium iodide (2,3) in the classical way to produce the 7,12-dimethyl derivatives (4a and 4b) or they can be reduced to the benz[a]-anthracenes (5a and 5b) utilizing aluminum tricyclohexoxide.(13)



3a R = H
3b R = CH$_3$

4a R = H
4b R = CH$_3$

5a R = H
5b R = CH$_3$

i = CH$_3$MgI, HI,SnCl$_2$

ii = Aluminum Tricyclohexoxide

In a typical experiment, 1,4-naphthoquinone (1.58g) and α-methylstyrene (1.18g) were added to 5 ml of benzene and the mixture was stirred at 85° for one week. The benzene was evaporated and the crude residue was chromatographed on a silica gel column eluting first with hexane and then with benzene. Evaporation of the benzene gave 0.55g (20%) of 5-methylbenz[a]anthracene-7,12-dione (3b), m.p. 175.5-176.5° (lit 176-7°) (14); mass spectrum (70eV) m/e 272 (parent peak);

NMR ($CDCl_3$), δ2.81 ($3,s,CH_3$), 7.60-7.81 (4,m,aromatic H), 8.00-8.32 (4,m,aromatic H), 9.71 (1,d,aromatic H). Benz[a]anthracene-7,12-dione (3a) was similarly produced in a 12% yield, m.p. 169-170° (lit 169°)(15,16). When 3a was reacted with methylmagnesium iodide, hydriodic acid and stannous chloride according to the procedure of Flesher, et al(17), 7,12-dimethylbenz[a]anthracene (4a) was produced in a 47% yield(16), mp 120-1° (lit 122-3°)(3). 5,7,12-Trimethylbenz[a]-anthracene (4b) was produced in a 20% yield by the same procedure, m.p. 126-8° (lit 127.5-129.5°)(18); mass spectrum (70eV) m/e 270 (parent peak); NMR (CCl_4), δ2,42 ($3,s,CH_3$), 2.75 ($3,s,CH_3$), 3.03 ($3,s,CH_3$), 7.13-7.47 (4,m,aromatic H), 7.49-7.82 (2,m,aromatic H) 7.87-8.27 (3,m,aromatic H). The diones 3a and 3b were also reduced with aluminum tricyclohexoxide according to the procedure of Ahmed, et al.(13) Benz[a]anthracene (5a) was produced in an 86% yield(16), m.p. 161-2° (lit 159.5-160.5)(19); and 5-methylbenz[a]anthracene (5b) was produced in a 90% yield, m.p. 155-7° (lit 155.9-156.9°)(20); mass spectrum (70eV) m/e 242 (parent peak); NMR ($CDCl_3$), δ2.71 ($3,s,CH_3$), 7.40-7.80 (6,m,aromatic H), 7.90-8.20 (2,m,aromatic H), 8.24 (1, broad s, aromatic H), 8.75-8.98 (1,m,aromatic H), 9.11 (1, broad s, aromatic H).

We are presently investigating the general nature of this reaction and feel that most derivatives of benz[a]anthracene and 7,12-dimethylbenz[a]anthracene can be easily prepared by this method. The results of these ongoing investigations will be reported in the near furture.

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