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LINEAR ANNELATION OF TRICYCLIC QUINONES BY SITE SELECTIVE REACTION WITH DIENES.

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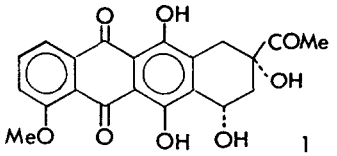
Summary. Diels Alder reactions involving tricyclic quinones of type (3) proceed at the internal pi-bond unless the terminal pi-bond is substituted with an activating substituent. e.g. SO_2Ar. Thermal isomerisation of the internal adducts leads to the formation of linear but aromatised products some of which can be made to retain their bridge.

The naphthacene nucleus has recently come into prominence since it is the basic ring-system present in the aglycone portion of a number of important antitumor agents. Early approaches[1] to the synthesis of the naphthacene-5,12-quinone (**1**), corresponding to the aglycone of daunomycin, involved the Diels-Alder addition of substituted butadienes to diquinones of type (**2**). This approach proved unreliable owing to the understandable preference for many dienes to react with the doubly activated internal pi-bond of (**2**), rather than the singly activated, terminal pi-bond. Modifications of this strategy have been reported[2] subsequently which achieve selective terminal annelation of derivatives of (**2**) in the Diels-Alder step.The present communication reports an alternative solution to control site selectivity in reactions of ambinucleophilic quinones which involves the use of bridged quinones of type (**3**) as synthons for (**2**). This strategy is applied to the synthesis of naphthacene-5,12-quinones and some novel bridged derivatives thereof.



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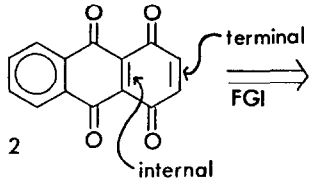

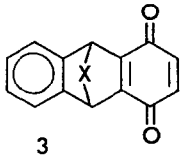

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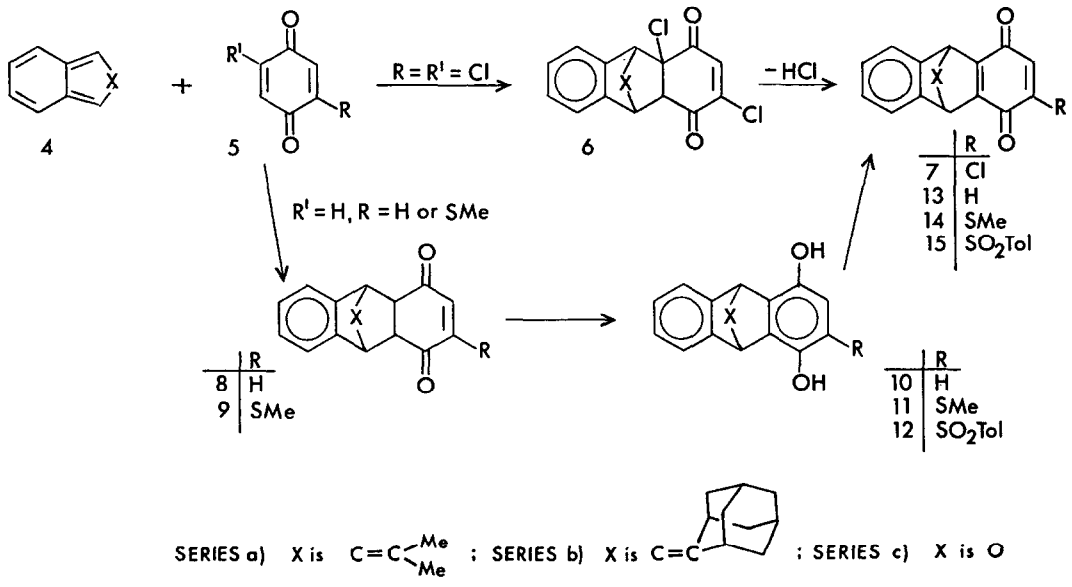
The starting materials for our work, the 9,10-bridged-1,4-anthraquinones (**7,13-15**) were prepared as outlined in Scheme 1. Reaction conditions and physical properties of the various products are summarised in reference 3. The bridging groups were introduced to modify the reactivity of the internal pi-bond,[6] and selected on the basis of their known ability to be removed in later reactions.[5]

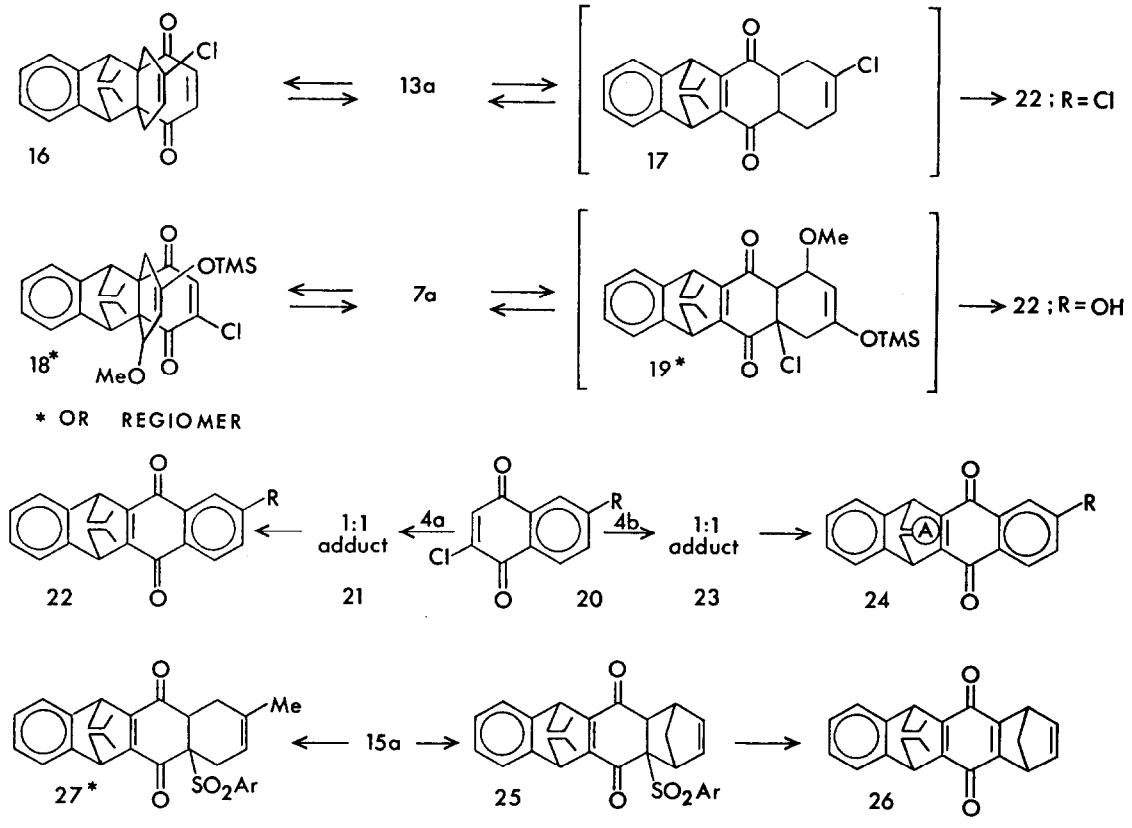
Reaction of the dimethylvinylidene-bridged-1,4-anthraquinone (**13a**) with chloroprene (80°/2h) forms the 1:1-adduct (**16**) in quantitative yield (Scheme 2). Pmr spectroscopy



SCHEME 1: PREPARATION OF BRIDGED ANTHRACENE-1,4-QUINONES.

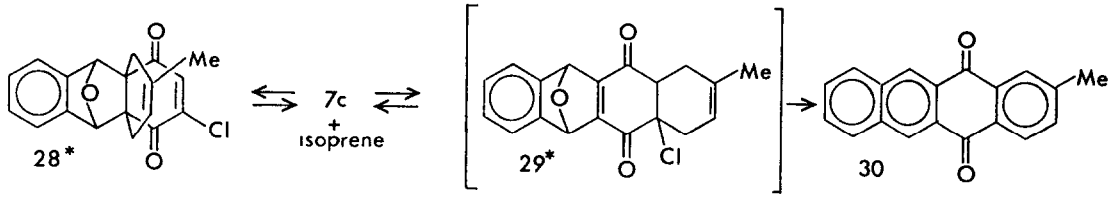
shows[8] that the reaction occurs exclusively at the internal pi-bond.[9] Adduct (**16**), upon heating (140°/5h), is transformed into an aromatic product, the naphthacene derivative (**22**; R=Cl) in 97% yield. The intermediacy of the linear adduct (**17**) is logically implicated in this transformation. To further probe this reaction and to offer a method of controlling regiospecificity in these Diels-Alder reactions, substituents were introduced at the terminal pi-bond of the 1,4-anthraquinones (**13**). The nature of these substituents dramatically influenced the site of reaction with dienes. Chloro or methylthio groups gave internal adducts, while the activating toluenesulfonyl group promoted reaction at the terminal pi-bond. Thus reaction of the chloroquinone (**7a**) with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (Danishefky's diene)[10] occurred rapidly at room temperature to form the internal adducts (**18**). These adducts are thermally labile and were only characterised by pmr spectroscopy.[8] By conducting the reaction in the presence of pyridine the naphthacene-5,12- quinone derivative (**22**; R=H) is formed; in this case the transient terminal 1:1-adduct (**19**) is implicated, being trapped by the pyridine, acting as a base, and eliminating the elements of hydrogen chloride and methanol. Interestingly, the related chloroquinone (**7b**) in the adamantylidene series also forms internal 1:1-adducts in spite of the additional steric crowding on the *exo*-face of the internal pi-bond. Thus 1-methoxy-1,3-butadiene reacts (80°/15 min) with chloroquinone (**7b**) to form a mixture of internal 1:1-adducts (pmr monitor) which were not isolated but heated (140°/12 h) to produce the naphthacene derivative (**24**; R=H).[11]

Treatment of the toluenesulfonylquinone (**15a**) with cyclopentadiene occurred rapidly at R.T. to yield a single product (oil) in 84% yield, shown by pmr spectroscopy[12] to be the terminal adduct (**25**). Further evidence to support structure (**25**) is obtained by treatment of adduct (**25**) with diazabicyclononene (DBN) to yield the norbornadiene (**26**). Reaction of (**15a**) with isoprene yielded a mixture of terminal adducts (**27**) in 66% yield but these were not separated into pure isomers.



SCHEME 2: PREPARATION OF LINEAR ANNELATED PRODUCTS.

The oxa-bridged chloroquinone (**7c**) was also investigated (Scheme 3). Again, internal adduct formation occurred with isoprene to yield a regiomeric mixture (1:1, 100%) of adducts. These adducts (**28**) were thermally labile and heating (sealed tube, 140°/12 h) formed 2-methyl-5,12-naphthacene quinone (**30**) (m.p. 170°, 27%). This sequence can be carried out as a one pot reaction and offers a rapid entry into the fully aromatised 5,12-naphthacene-5,12-quinone system.



SCHEME 3: NEW ROUTE TO NAPHTHACENE-5,12-QUINONES.

Thus we have developed methods whereby linear aromatic naphthacene quinones can be prepared in which there is no bridge (series c) or a substituted vinylidene bridge (series a, b) which is capable of modification at a later stage.[6] Using the toluenesulfonyl group to activate the

terminal pi-bond, non-aromatic A-ring compounds can be produced.

References and Notes

1. T.R. Kelly, R.N. Goener, J.W. Gillard and B.K. Prazak, *Tetrahedron Lett.* 1976, 3869; W. Whee, A.P. Martinez, T.H. Smith and D.W. Henry, *J. Org. Chem.*, 1976, **41**, 2296; A.S. Kende, Y.S. Tsay and J.E. Mills, *J. Am. Chem. Soc.*, 1976, **98**, 1967.
2. M. Chandler and R.J. Stoodley, *J. Chem. Soc., Perkin Trans. I*, 1980, 1007.
3. The required isobenzofurans (ref. 4) or isobenzofulvenes (ref. 5) were prepared by the tetrazine method and reacted *in situ* with the appropriate dienophile. (**6a**), not isolated; treated with s-collidine in benzene, R.T., 2 h, to form (**7a**), 200°, 87%; (**6b**), 182°, 91%; (**7b**), 170°, 82%; (**7c**), 60-63°, 16%; (**9a**), 172°, 88%; (**11a**), HOAc at reflux, 217°, 81%; (**14a**), $Ce(NH_4)_2(NO_3)_6/NaBrO_3$, 207°, 100%; (**8a**), 97% as mixture of isomers; (**10a**), HOAc at reflux, 300° dec, 84%; (**13a**) DDQ, 200° dec, 95%; (**12a**), sodium toluene sulfinate on (**13a**), 194°, 85%; (**15a**) DDQ, red oil, 100%.
4. R.N. Warrener, B.C. Hammer and R.A. Russell, *J. Chem. Soc., Chem. Commun.*, 1981, 942.
5. R.A. Russell, E.G. Vikingur and R.N. Warrener, *Aust. J. Chem.*, 1981, **34**, 131.
6. It was anticipated that these bridging groups would deactivate the internal pi-bond and make the quinone moiety similar in reactivity to that of a 2,3-dialkylquinone, i.e. react at the unsubstituted terminal pi-bond. As reported herein this is not the case and we ascribe the increased reactivity of the internal pi-bond to an orbital interaction between the pi-electrons of the bridge (or the oxygen lone pair) with the internal pi-bond (c.f. ref. 7).
7. H.R. Pfaendler, H. Tanida and E. Haselbach, *Helv. Chim. Acta*, 1974, **57**, 383; M.N. Paddon-Row, H.K. Patney and R.N. Warrener, *J. Org. Chem.*, 1979, **44**, 3908.
8. Two features are diagnostic for the internal adducts, (i) the upfield shift of the bridgehead protons (δ 3.86) compared with the starting quinone (δ 4.93), (ii) the preservation of the terminal vinylic protons (δ 6.12). [Figures quoted are for (**16**)].
9. Adducts similar to (**16**) were formed from (**13a**) with isoprene (115°, 5 min, 68%, oil) and with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene[10] (R.T., 2 min, 100%, oil).
10. S. Danishefsky, T. Kitahara, C.F. Yan and J. Morris, *J. Am. Chem. Soc.*, 1979, **101**, 6996.
11. The overall yield in this reaction is poor (18%), and (**24**; R=H) is better prepared by reaction of 8,8-adamantylideneisobenzofulvene (**4b**) with 2-chloronaphthoquinone (**20**; R=H) to form adduct (**23**)(95%, m.p. 196°) which produces (**21**; R=H)(47%, m.p. 291-94°) upon treatment with collidine in benzene (R.T./12 h). This is a general reaction.
12. *inter alia*, only one set of vinylic protons are present (δ 5.42, 5.56, dd, J = 6.0, 3.0 Hz), typical of the norbornenyl pi-system.

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