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1,4-ANTHRAQUINONOID DIENOPHILES APPLICABLE TO SYNTHESIS OF LINEAR TETRACYCLES

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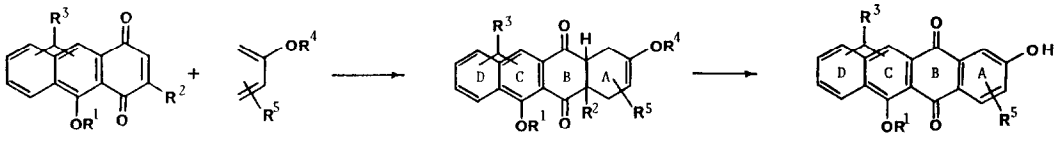
Abstract. Derivatives of 1,4-anthraquinones (3), (21) are shown to be good dienophiles for achieving strongly regiocontrolled synthesis of linear tetracycles, a property greatly enhanced by their ease of formation and of subsequent replacement of the chloride.

Important linear tetracycles should be easily accessible by cycloaddition of appropriate dienes to substituted 1,4-anthraquinones, the latter constituting the BCD-rings of the products (Scheme), and a wide range of A-rings being potentially available from current Diels-Alder methodology[1]. Representative target molecules include daunomycinone (1) and pretetramid (2), indicative of the considerable natural variation in oxidation levels of the BC-rings.

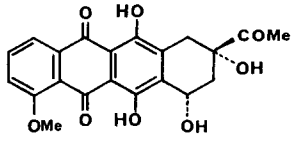


Scheme

The effectiveness of this approach depends on three requirements involving the dienophiles: (a) ready access to suitable 1,4-anthraquinones, systems far less well known than their 9,10-counterparts (b) their efficient cycloaddition to give adducts of independently determined regiochemistry (c) scope for elaborating the adducts to afford the BC-substitution patterns of target molecules, without unwanted decomposition elsewhere.

This paper establishes all three of these requirements in the context of derivatives of the 1,4-anthraquinone (3), originally derived[2] by heating quinizarin (4) in $SOCl_2$. With anticipated difference in directive influences of its chloro and hydroxy groups, (3) should react regioselectively with polarized dienes; indeed some examples of this have been reported by others during progress of the present work.[3,4] However in none of these examples was orientation of cycloaddition independently determined nor was a general procedure established for replacement of chloride under conditions compatible with a highly functionalized A-ring.

To investigate regiochemistry of addition, (3) and its methyl ether (5) were each heated with the polarised diene (6) in CH_2Cl_2. Without fractionation the resulting adducts were oxidatively aromatised (O_2/NaOH) and then methylated (Me_2SO_4/K_2CO_3). In this way (3) gave



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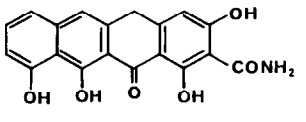

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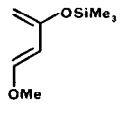


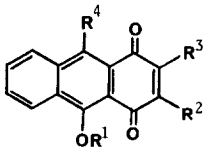
6

only the naphthacenedione (7) (70%) while (5) gave a mixture of (7) with its regioisomer (8) (91%, 1:1). Isomers (7) and (8) were inseparable by t.l.c. and were almost identical spectroscopically. Ratios were determined by addition of $Eu(fod)_3$, which induced differential shifts of the ^1H n.m.r. resonances of the α-methoxy groups.[5]

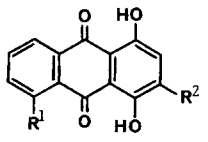
Analogous data were obtained without the chloro group. Thus the hydroxy quinone (9) with (6) led to an inseparable mixture of naphthacenediones (10) and (11) (79%, 3:1), while the methyl ether (12) gave the same two products with opposite regioselectivity (70%, 1:4). Pure samples of (10) and (11) respectively were obtained by recrystallisation of these mixtures. Again they were almost identical spectroscopically.

Proof of the two orientations (7), (10) and (8), (11) was provided by regiospecific reduction with $Na_2S_2O_4$/NaOH. This gave naphthacenone (13) from the former pair and its isomer (14) from the latter, dechlorination accompanying reaction of (7) and (8). The ^1H n.m.r. spectra of (13) and (14) were clearly distinguishable and open to first-order analysis in respect of A- and C-ring protons. For reduction (10) → (13) marked shielding was observed only for the ortho-coupled doublet due to H* (δ 8.32 → 7.49). The other two protons peri to carbonyl in (10) (δ 7.68, 8.68) were largely unshifted compared with the corresponding protons of (13) (δ 7.86, 8.78); this confirms the expected regiochemistry of reduction as involving only the carbonyl group peri to methoxy.[6] For the isomeric naphthacenone (14) relative to its parent quinone (11) analogous spectroscopic considerations applied except that the proton H*, which underwent strong shielding, was meta-coupled [δ_{H*} for (14) 7.02; for (11) 7.79].

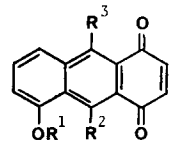
These data systematically establish regiochemistry of cycloaddition in the 1,4-anthraquinone series. The difference in effects of α-hydroxy and α-methoxy substituents parallels,



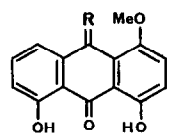
	R^1	R^2	R^3	R^4
3	H	H	H	Cl
5	Me	H	H	Cl
9	H	H	H	H
12	Me	H	H	H
15	H	Br	H	Cl
16	H	H	Br	Cl
17	Me	Br	H	Cl
18	Me	H	Br	Cl



	R^1	R^2
4	H	H
19	H	Br
20	H	Cl
22	OH	H

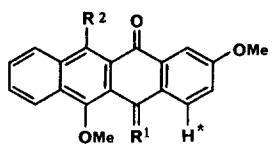


	R^1	R^2	R^3
21	H	OH	Cl
23	H	Cl	OH
24	H	OH	H
27	$-SO_2O-$		OH

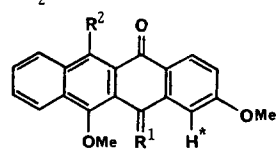


25 R = O

26 R = H_2



	R^1	R^2
7	O	Cl
10	O	H
13	H_2	H



	R^1	R^2
8	O	Cl
11	O	H
14	H_2	H

but is less sharp than, that for 1,4-naphthoquinonoid dienophiles.[7] The chloro group improves regioselectivity in the hydroxy series (3) relative to (9), and it diminishes it in the methoxy series (5) relative to (12).[3] In both cases the chloride reduces the influence of the carbonyl group peri to it; this could involve electronic or steric factors or both.

We have found that these same orientational principles also apply to 1:2-addition of 1,1-dimethoxyethene[8] to the 1,4-anthraquinones so far discussed. This gave regioisomeric pairs of trimethoxy naphthacenediones analogous to the dimethoxy systems (7), (8) and (10), (11).

As with simpler systems[9] the dienophilic reactivity of 1,4-anthraquinones is usefully enhanced by 2(3)-bromination or -chlorination and cycloaddition to polarized dienes then becomes essentially regiospecific under control of the introduced halo group. Thus (3) with Br_2 in AcOH gave a single isomer (15) (93%). Cycloaddition to (6) as above, led to a single product (7) (70%). The isomeric bromo derivative (16) was obtained indirectly through bromination of the methyl ether (5) giving isomers (17) (33%) and (18) (51%). After chromatographic separation these products were demethylated (BBr_3) to give (15) (δ_{OH} 14.46) and (16) (δ_{OH} 14.56) respectively. The overall direction of bromination agreed with that of simpler systems[10] as did the small, significant difference in δ_{OH} values of (15) and (16).[11] Known combinations of (15) and (16) underwent cycloaddition to (6), as above, to give the same portions of (7) and (8) (60-70%), consistent with regiospecificity within the limits of detection.

These observations thus provide a secure basis for derivatising system (3), so as to react with polarized dienes with strong regiochemical control. To be applicable to synthesis of natural tetracycles, e.g., (1), (2), the remarkable preparation of (3) simply by boiling (4) in $SOCl_2$ requires extension. Its scope is complex[12] and is under separate investigation.[13] Generalising it to unsymmetrical derivatives of (4) is further complicated by regiochemical factors. Thus 2-bromo quinizarin (19), originally reported[14] to give a single product in $SOCl_2$, is now shown to give a mixture of (15) and (16) (97%, 3:1); 2-chloro quinizarin (20)[12] similarly gives the dichloro analogs of (15) and (16) (95%, 6:1), these assignments following from the methodology already discussed.

More relevant to planned synthesis of (1) or (2), with D-ring oxygenation, is the new dienophile (21). This was obtained smoothly (86%) (δ_{OH} 10.80, 17.22) by standard treatment of the dyestuff 1,4,5-trihydroxy-9,10-anthraquinone (22)[15] in $SOCl_2$. None of its regioisomer (23) was detected. Its structure was supported by the strongly deshielded hydroxy group of the central ring and was confirmed by reductive dechlorination (H_2/Pd-$BaSO_4$) to give (24) (68%). The latter was independently synthesised from the known methyl ether (25).[16] Catalytic reduction (H_2/PtO_2) occurred peri to the methoxy group giving the anthrone (26) (45%) (δ_{OH} 11.82, 12.34). Demethylation (BBr_3) and reoxidation (chloranil) led to (24) (82%).

In one operation the conversion (22) → (21) secures three important requirements: (a) a 9,10-quinone, itself unsuitable for cycloaddition, is converted into a reactive 1,4-quinone (b) the latter has the potential for regioselective reaction (c) the conversion (22) → (21) is itself regiospecific. This resolves a fundamental problem towards formulating a regiospecific synthesis of e.g., anthracyclines (1), namely of being able to employ the substituent in the D-ring to differentiate reactive centres remotely located on the far side of the B-ring.[17]

Finally, and importantly, cycloaddition of dienophile (21) and of its derivatives is compatible with replacement of chloride following attachment of a correctly oriented A-ring. Reductive dechlorination, necessary for access to anthrone-like systems, e.g., (2), is accomplished by catalytic hydrogenation as in the conversion (21) → (24) above. Alternatively,

displacement of chloride by an oxygen substituent, necessary for access to anthracyclines, e.g., (1), is brought about in hot CF_3CO_2H. (Earlier approaches[2,3] involving stronger acid, alkali or severe heating are not generally compatible with sensitive groups elsewhere in the molecule). Thus brief warming of (21) in CF_3CO_2H effectively reversed its formation from (22), giving the latter quantitatively. While these two processes, reductive and hydrolytic dechlorination, are exemplified here in the context of tricyclic system (21) they have also been routinely applied to tri- and tetra- cyclic analogs.[18] An example in the context of anthracycline synthesis is reported elsewhere.[17]

All new compounds gave satisfactory analyses and spectroscopic data. We thank Bayer AG for samples of dyestuffs. We acknowledge financial support from the Anti-Cancer Council of Victoria and the Australian Research Grants Scheme, and Australian Postgraduate Research Awards (to C.C., M.W.F. and B.K.M.).

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