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SYNTHESIS OF HYDROXYTETRAHYDRONAPHTHACENEQUINONES BY ANNELATION OF HYDROXYANTHRAQUINONE DERIVATIVES

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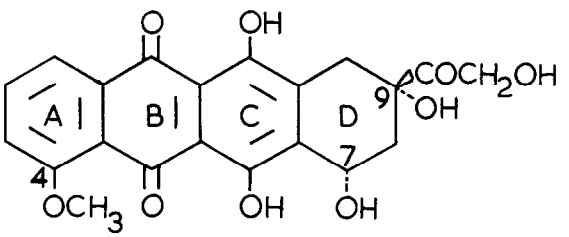
There is at present intense interest in the development of synthetic routes to the aglycones of the anthracycline antibiotics[1]. There are two facets, firstly synthesis of the aglycones themselves e.g. adriamycinone 1 , and secondly the design and preparation of analogues with the aim of



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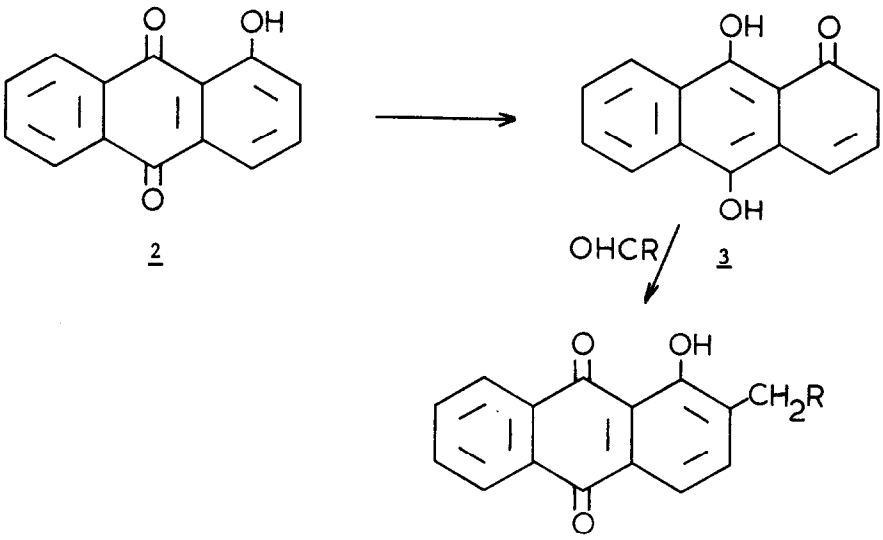
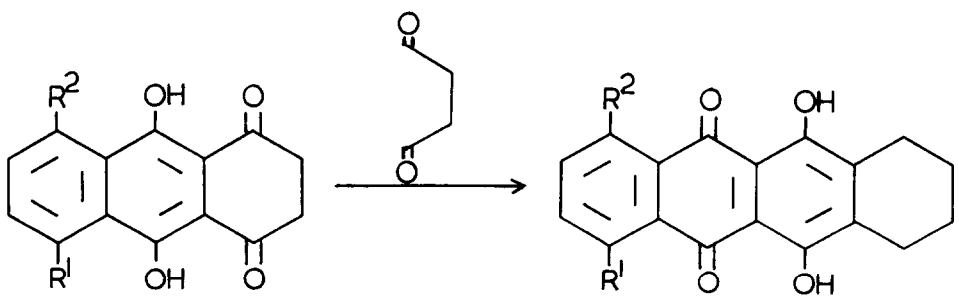
developing improved drugs. In the former case, a regiospecific route is essential. In the latter case this is less important since deletion of the 4-OCH_3 actually leads to enhancement of activity[2]. Also the 9-substituent is not vital for the molecular action of these drugs[3]. We have therefore sought a direct route to the 6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione ring skeleton, bearing in mind that the route must still allow the introduction of substituents into the A and D rings. A relatively neglected reaction is the Marschalk reaction[4] by which an alkyl group can be introduced into the 2-position of 1-hydroxyanthraquinone 2, by reaction of an aldehyde with the leuco- (dihydro-) derivative 3 of the hydroxyanthraquinone yielding compounds of general structure 4. Similarly an alkyl group can be introduced into the 2-position of quinizarin (1,4-dihydroxyanthraquinone); and with formaldehyde the 2,3-dimethyl- derivative can be obtained[4].



2 3 4

We have investigated the reaction of leucoquinizarin[5] with succindialdehyde[6]. Leucoquinizarin 5, was prepared by dithionite reduction of quinizarin, then reacted with a 2M xs of succindialdehyde (Na_2CO_3 solution, oxygen-free atmosphere, 1 hr at 90°C, followed by oxygenation) yielding 6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenequinone 6 (62% yield after



5 R^1=H; R^2=H
7 R^1=OH; R^2=H
10 R^1=OCH_3; R^2=H

6 R^1=H; R^2=H
8 R^1=OH: R^2=H
9 R^1=OH; R^2=OH
11 R^1=OCH_3; R^2=H

recrystallization from DMF: m.p. 323-327°: Calcd. for $C_{18}H_{14}O_4$, 294.0892; Found, 294.0894: λmax EtOH 485 nm, shifting 65 nm with base)[7].

Similarly, the leuco-derivative 7 of 1,4,5-trihydroxyanthraquinone yielded the corresponding 4,5,11-hydroxy-tetracycle 8 (a 2M xs of dithionite was used in this and subsequent reactions). Residual starting material could only be removed by washing with DMF/H_2O (with loss of product!), evenso a yield of 50% was obtained after recrystallization of the washed product from 1-butanol (m.p. > 320°: Calcd. for $C_{18}H_{14}O_5$, 310.0841; Found, 310.0850: λmax EtOH 496 and 531 nm, shifting 65 nm with base). This trihydroxy compound can then be oxidised to the tetrahydroxy- analogue 9 by the Bohn-Schmidt reaction[8] (9 was separated from starting material by column chromatography on silica gel, eluting with EtOAc then DMF followed by recrystallization from AcOH: λmax EtOH 547 and 560 nm, shifting 46 nm with base). To complete the analogy with adriamycinone, the reaction was repeated using the leuco- derivative 10 of 1,4-dihydroxy-5-methoxyanthraquinone. The parent compound was prepared from 1,4,5-trichloroanthraquinone by methoxylation[9] then selective demethylation[10] at the 1,4-positions. In the annelation reaction, alcohol was added to aid solubility, and the tetracyclic analogue 11 obtained in 82% yield after recrystallization from EtOH (m.p. 204°C: Calcd. for $C_{19}H_{16}O_5$, 324.0998; Found, 324.0990: λmax EtOH 498 nm and 532 nm, shifting 65 nm with base).

Marschalk reaction of the leuco- derivatives of 1,4-dihydroxyanthraquinones with succindialdehyde therefore provides a simple preparation of the 6,11-dihydroxy-7,8,9,10-tetrahydro-5,12-naphthacenedione ring skeleton as a precursor for preparation of anthracycline analogues. The Marschalk reaction is particularly flexible as a means of entry into this group of compounds for example alkyl groups can be introduced regiospecifically into 1,4,5-trihydroxyanthraquinone[11] and one feature which has not yet been exploited is the ability to isolate the reaction intermediates bearing a benzylic alcohol function[12].

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