TOTAL SYNTHESIS OF 7-HYDROXY-"9-OXA"-ANTHRACYCLINONE AND GLYCOSIDE DERIVATIVES

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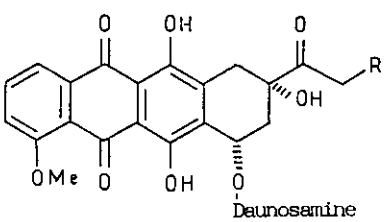
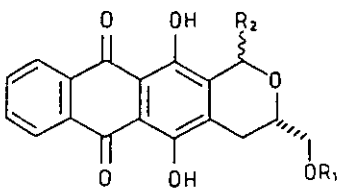
Abstract - The racemic title aglycone was prepared in seven steps from quinizarin 5 and its resolution achieved after glycosidation with 3,4-di-O-acetyl-2-deoxy-L-fucose.

When compared to the strong antitumour activity of anthracyclines 1, the lack of significant biological (i.e. antibiotic and/or antitumour) activity of "9-oxa"-anthracyclinones and "9-oxa"-anthracyclines of general structures 2 and 3[1] could be due either to the introduction of an oxygen atom at the 9-position in the A-ring of the molecule or to the change in the glycosidation position.



1 R = H, OH



2 R_1 = H ; R_2 = H, CH_3
3 R_1 = Sugar ; R_2 = H, CH_3

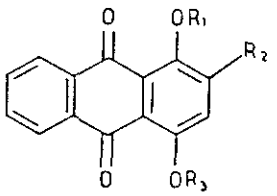
In order to establish clearly the origin of this lack of biological activity, it seemed of interest to achieve the synthesis of a simplified "9-oxa"-anthracycline (4a) bearing no side-chain at C-8 but a glycoside substituent at C-7α.

The synthetic strategy to elaborate the tetracyclic anthracyclinone skeleton followed the classical A + BCD scheme previously used in our laboratory for the synthesis of both anthracycline[2] and "9-oxa"-anthracycline[1] derivatives. The

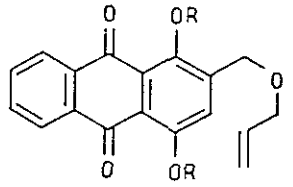
difficulties generally encountered in the synthesis of 4-hydroxyisochromans[3] corresponding to the AB rings segment of the molecule led us to use an intramolecular Marschalk reaction[4] during the last step of the synthesis of the aglycone, easily providing the hydroxy group at the required position.

Quinizarin (5) was converted in two steps into 1-hydroxy-2-hydroxymethyl-4-methoxy-9,10-anthraquinone (6) according to Krohn's procedure[5]. Methylation of 6 (Me_2SO_4, K_2CO_3, Me_2CO, reflux, 48 h) led in almost quantitative yield to 2-hydroxymethyl-1,4-dimethoxy-9,10-anthraquinone (7)[6] (mp 180°C). Condensation of 7 with an excess of allyl bromide in strong alkaline medium (NaH, DMF, r.t., 2h) afforded the benzylic ether 8 (mp 174°C) in 77 % yield. Removal of the two methyl protective groups was then achieved by treatment with aluminum chloride under anhydrous conditions[5] ($AlCl_3$, CH_2Cl_2, r.t., 10 min) to obtain 2-allyloxymethyl-1,4-dihydroxy-9,10-anthraquinone (9) (mp 128-129°C) in 44 % yield. Upon ozonolysis (O_3 stream, CH_2Cl_2, -78°C, 15 min ; then addition of Me_2S), 9 led in 87 % yield to the aldehyde 10 (mp 172°C), which was subjected to intramolecular alkylation under Marschalk conditions[4] to afford the required racemic (±)-4,5,12-trihydroxy-3,4-dihydro-1H-anthra[2,3-c]pyran-6,11-quinone (11) (mp 194°C) in almost quantitative yield.

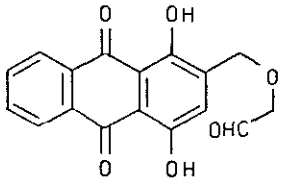
Glycosidation of (±)-11 by 3,4-di-O-acetyl-2-deoxy-L-fucopyranosyl chloride[8,9] (yellow HgO, $HgBr_2$, 4 Å molecular sieves, C_6H_6-CH_2Cl_2, r.t., 1 h)[10,11] finally led in 95 % overall yield to an equimolecular mixture of the two diastereoisomeric α-glycosides 4a (mp 228°C, $[\alpha]_D^{20}$ = +77° (c = 0.05, $CHCl_3$))[12] and 4b (mp 230°C, $[\alpha]_D^{20}$ = -245° (c = 0.05, $CHCl_3$))[13], easily separated after column chromatography (silica gel, CH_2Cl_2).



5 : $R_1 = R_2 = R_3 = H$
6 : $R_1 = H$; $R_2 = CH_2OH$; $R_3 = CH_3$
7 : $R_1 = R_3 = CH_3$; $R_2 = CH_2OH$



8 R = CH_3
9 R = H



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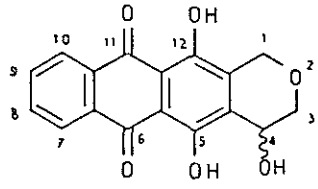
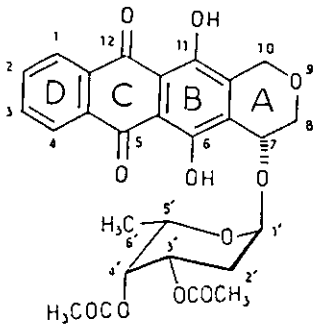
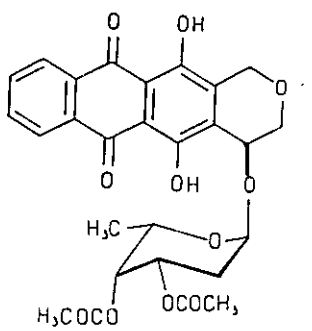


11
(systematic numbering)

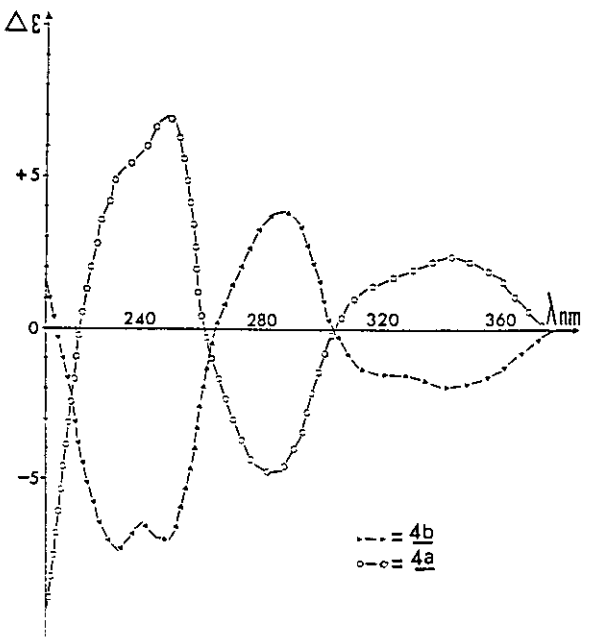
The absolute configuration at C-7 (anthracycline numbering) of these two compounds could be easily deduced from their cd curves (Scheme 1). Compound 4a with an α-configuration at C-7 (7R) exhibited a negative maximum at 287 nm whereas 4b with a β-configuration at C-7 (7S) showed a positive maximum at the same wavelength[14]. Deacetylated glycosides corresponding to 4a and 4b show no significant antitumour activity.



4a
(anthracycline numbering)



4b



Scheme 1

ACKNOWLEDGEMENTS

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11. H.S. El Khadem and D. Matsuura, Carbohydr. Res., 1982, 101, C1.
12. 4a : $C_{27}H_{26}O_{11}$; ^1H nmr ($CDCl_3$, TMS) : δ ppm : 13.45 and 13.10 (2 x 1H, 2s, D_2O exch., OH-6, OH-11), 8.24 (2H, m, H-1, H-4), 7.84 (2H, m, H-2, H-3), 5.60 (1H, d, J = 2Hz, H-1'), 5.26 (2H, m, H-7, H-3'), 5.09 (1H, d, J = 18Hz, H-10a), 4.76 (1H, narrow m, H-4'), 4.62 (1H, d, J = 18Hz, H-10b), 4.33 (1H, qd, J = 7Hz, J' = 1Hz, H-5'), 4.24 (1H, d, J = 12Hz, H-8a), 3.75 (1H, dd, J = 12Hz, J' = 1Hz, H-8b), 2.11 (3H, s, OAc), 2.05 (1H, m, H-2'a), 1.93 (3H, s, OAc), 1.91 (1H, m, H-2'b), 1.19 (3H, d, J = 7Hz, CH_3-6').
13. 4b : $C_{27}H_{26}O_{11}$; ^1H nmr ($CDCl_3$, TMS) : δ ppm : 13.57 and 13.09 (2 x 1H, 2s, D_2O exch., OH-6, OH-11), 8.35 (2H, m, H-1, H-4), 7.84 (2H, m, H-2, H-3), 5.40 (1H, d, J = 2Hz, H-1'), 5.25 (2H, m, H-7, H-3'), 5.15 (1H, d, J = 18Hz, H-10a), 5.01 (1H, narrow m, H-4'), 4.65 (1H, d, J = 18Hz, H-10b), 4.64 (1H, m, H-5'), 4.44 (1H, d, J = 13Hz, H-8a), 3.57 (1H, dd, J = 13Hz, J' = 1Hz, H-8b), 2.16 (3H , s, OAc), 2.11 (1H, m, H-2'a), 1.93 (3H, s, OAc), 1.89 (1H, m, H-2'b), 1.20 (3H, d, J = 7Hz, CH_3-6').
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