CHIRAL POOL SYNTHESIS OF 8-HYDROXYMETHYL-"9-OXA"-ANTHRACYCLINONES

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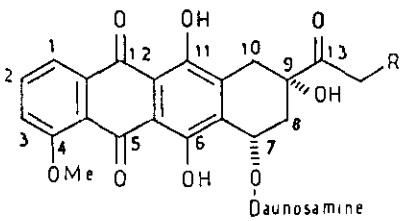
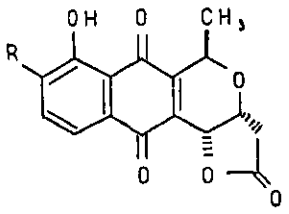
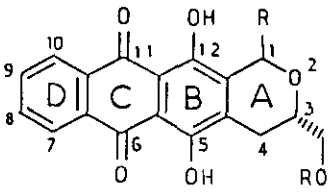
Abstract - The synthesis of title compounds from (R)-2,3-O-isopropylidene-glyceraldehyde and leucoquinizarin is reported.

Doxorubicin (1) and daunorubicin (2) are glycoside antibiotics widely used in the chemotherapic treatment of different human cancers[1].







1 R = OH
2 R = H

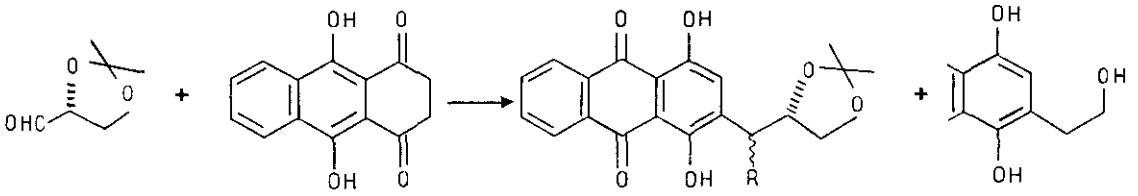
3 R = H
4 R = β (N-dimethylacosamine)

5 R= H or sugar

On the other hand, different pyranonaphthoquinone antibiotics including kalafungin (3) or its enantiomer nanaomycin D and closely related nanaomycin A have been shown to possess significant antimicrobiological properties[2]. It has also been postulated that these compounds would possess some antineoplastic activities as bioreductive alkylating agents[3]. This has been supported by the recent discovery of lactoquinomycin (4)[4], an amino-glycoside of kalafungin which displayed antitumor activity although its mechanism of action has not yet been reported.

Synthesis of new analogs of 1 and 2 with an oxygen in the A ring instead of both the side-chain and axial OH at C-9 and with a hydroxymethyl side-chain at C-8 such as the 5,12-dihydroxy-3-hydroxymethyl-3,4-dihydro-1H-anthra[2,3-c]pyran-6,11-dione (R = H), has been undertaken. Intercalation with native DNA must be less marked with these new glycosides of general formula 5 than with 1 and 2 since it

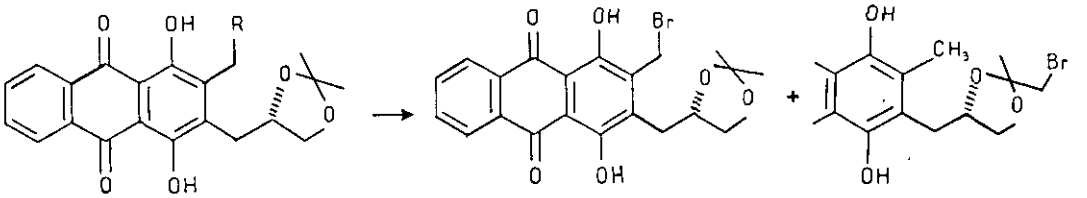
has been shown on different models[5] that 9-OH and 13 C=O strongly participate but, in contrast, they could act as more powerful alkylating agent after bioreduction[3]. A synthetic strategy to elaborate such a tetracyclic skeleton followed the general A + BCD route which has been already successfully used in our laboratory[6]. With the same goal in mind to synthesize enantiomerically pure compounds to avoid the complex and wasteful separation of diastereoisomers after glycosidation with loss of the valuable amino-sugar moiety, (R)-2,3-O-isopropylideneglyceraldehyde (6) was used as chiral precursor[7] of ring A. Aldol condensation of this latter with anion of leucoquinizarin (7), precursor of rings BCD could be a possible way to obtain under Marschalk conditions[8] and in the first step, a chiral β-alkylanthraquinone. Since this reaction gave three products in a temperature-dependent ratio, efforts were directed towards conditions which gave the desired compound 8 as major product. Thus at 40°C, 8 (m p 149-152°C ; $[\alpha]_D^{20}$ -40° in CH_2Cl_2)[9] was isolated in 46 % yield along with a small amount of the corresponding hydroxy-derivative (9) (mixture of diastereoisomers[10], 7 %) and 24 % of 10 (m p 143-145°C)[11]. A second alkylation of 8 under Marschalk conditions with formaldehyde at room temperature for 1 h, afforded 11 (m p 149°C ; $[\alpha]_D^{20}$ -122° in CH_2Cl_2) which was isolated in 98 % yield.



6 7 8 R = H 9 R = OH 10

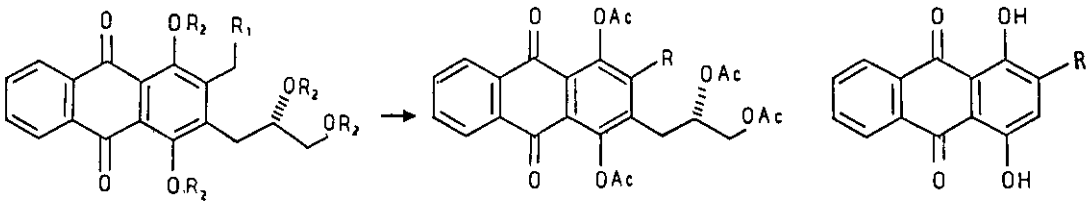
Photochemical bromination of 11 (NBS, 2,2'-azobis(2-methylpropanenitrile), CCl_4, 2 h) led to 13 in 20 % yield (m p 105°C, $[\alpha]_D^{20}$ -106° in CH_2Cl_2) along with the mixture of compounds 14 resulting from bromination of one of the two methyl groups of the acetal ring. Owing to this difficulties, in a further attempt, the acetal ring of 11 was removed under acidic conditions (1N HCl-MeOH, room temperature, 2 h) to give 15 in quantitative yield (m p 174°C ; $[\alpha]_D^{20}$ -107° in MeOH). After peracetylation of 15 (Ac_2O, C_5H_5N, room temperature, 48 h), giving 16 (m p 135°C ; $[\alpha]_D^{20}$ +33° in $CHCl_3$) in quantitative yield, benzylic bromination was performed by irradiation of 16 (1,3-dibromo-5,5'-dimethylhydantoin, CCl_4, 2 h)[12] to obtain 19 (m p 140°C) in 77 % yield.

On the other hand, ortho-dialkylquinizarin (12) must be prepared in a way different from that previously used to synthesize 11 since Marschalk condensation of 8 with CH_3CHO led to 21 (m p 148-150°C). Nevertheless, 12 (m p 158°C ; $[\alpha]_D^{20}$ -50° in CH_2Cl_2) could be obtained in 16 % yield starting from 2-ethylquinizarin (22) by aldol condensation with (R)-2,3-O-isopropylideneglyceraldehyde. Access to 20 (mixture of diastereoisomers) involved the same sequence of reactions as that previously used for the synthesis of 19 : i) cleavage of the acetal ring , ii) peracetylation , iii) photochemical bromination (12 → 17 → 18 → 20).



11 R = H
12 R = CH_3

13 14



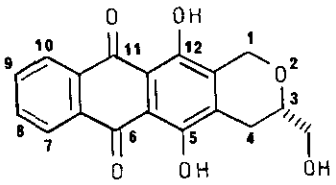
	R_1	R_2
15	H	H
16	H	Ac
17	CH_3	H
18	CH_3	Ac

19 R = CH_2Br
20 R = $CH(Br)CH_3$

21 R = 
22 R = C_2H_5

Heating 19 under reflux in a methanolic solution previously saturated with HCl gas gave quantitatively the required aglycon (23)[13] (m p 190°C ; $[\alpha]_D^{20}$ -139° in $CHCl_3$). The same reaction applied to 20 led in 60 % overall yield to an equimolecular mixture of diastereoisomers 24[14] (m p 200°C ; $[\alpha]_D^{20}$ -113° in $CHCl_3$) and 25[15] (m p 238°C ; $[\alpha]_D^{20}$ +20° in $CHCl_3$) easily separated after column chromatography (silica gel, CH_2Cl_2). The absolute configuration at C-1 of both compounds could be established from their ^{13}C nmr spectra. The spectrum of 24 exhibits two aliphatic CH signals at 71.8 and 73.3 ppm which correspond to the presence of two pseudo-axial substituents at C-3 and C-1 whereas the corresponding signals located at 65.8 and 68.3 ppm for 25 indicate a pseudo-axial and a pseudo-equatorial substituent on the A ring. Furthermore, these latter values were in good agreement

with the data published for nanaomycin A[16]. From these spectra, it could be deduced that the configurations were (1S,3S) for 24 and (1R,3S) for 25



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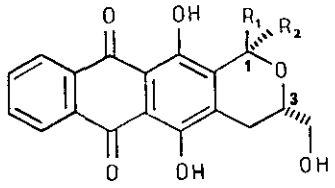

24 $R_1 = H$; $R_2 = CH_3$
25 $R_1 = CH_3$; $R_2 = H$

Several glycoside derivatives with amino-deoxy-sugar or deoxy-sugar have been prepared with both new aglycons. They have shown no significant antibiotic or antitumour activity and details for their preparation and for biological results will be reported later on.

ACKNOWLEDGMENTS

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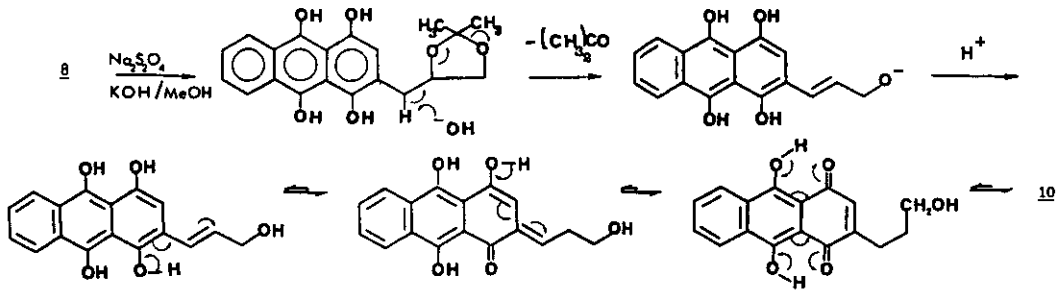
9. All new compounds gave i.r., n.m.r., m.s. and h.r.m.s. or combustion analysis consistent with their assigned structures.
10. Since the 7-OH (anthracycline numbering) as present in 9 was not required for

the present synthesis, the stereochemical course of the reaction was not determined.

11. The formation of 10 can be explained by the following mechanism :



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13. 5,12-dihydroxy-3-hydroxymethyl-3,4-dihydro-1H-anthra[2,3-c]pyran-6,11-dione (23) : $C_{18}H_{14}O_6$; ^{1}H n.m.r. ($CDCl_3$, TMS) δ ppm : 13.67 and 13.62 (2 x 1H, 2s, D_2O exch., OH-5, OH-12), 8.37 (2H, m, H-7, H-10), 7.84 (2H, m, H-8, H-9), 4.93 (1H, d, J = 10Hz, H-1a), 4.87 (1H, d, J = 10Hz, H-1b), 4.13 (1H, m, H-3), 3.78 (1H, dd, J = 11Hz, J'= 4Hz) and 3.60 (1H, dd, J = 11Hz, J'= 6Hz)(CH_2OH), 3.18 (1H, dd, J = 14Hz, J'= 5Hz, H-4a), 2.89 (1H, dd, J = 14Hz, J'= 8Hz, H-4b), 2.53 (1H, br s , D_2O exch., CH_2OH).

14. (1S,3S)-5,12-dihydroxy-3-hydroxymethyl-1-methyl-3,4-dihydro-1H-anthra[2,3-c]pyran-6,11-dione (24) : $C_{19}H_{16}O_6$; ^{1}H n.m.r. ($CDCl_3$, TMS) δ ppm : 16.42 and 15.98 (2 x 1H, 2s, D_2O exch., OH-5, OH-12), 8.35 (2H, m, H-7, H-10), 7.82 (2H, m, H-8, H-9), 5.13 (q, J = 6Hz, H-1), 3.87 (1H, m, H-3), 3.73 (2H, m, CH_2OH), 2.91 (1H, dd, J = 17Hz, J'= 2Hz, H-4a), 2.60 (1H, dd, J = 17Hz, J'= 10Hz, H-4b), 2.15 (1H, br s , D_2O exch., CH_2OH), 1.58 (3H, d, J = 6Hz, CH_3).

15. (1R,3S)-5,12-dihydroxy-3-hydroxymethyl-1-methyl-3,4-dihydro-1H-anthra[2,3-c]pyran-6,11-dione (25) : $C_{19}H_{16}O_6$; ^{1}H n.m.r. ($CDCl_3$, TMS) δ ppm:16.20 and 16.07 (2 x 1H, 2s, D_2O exch., OH-5, OH-12), 8.35 (2H, m , H-7, H-10), 7.82 (2H, m, H-8, H-9), 5.27 (q, J = 7Hz, H-1), 4.11 (1H, m, H-3), 3.87 (1H, dd, J = 11Hz, J'= 2 Hz) and 3.71 (1H, dd, J = 11Hz, J'= 7Hz)(CH_2OH), 2.87 (1H, dd, J = 18Hz, J'= 4Hz, H-4a), 2.60 (1H, dd, J = 18Hz, J'= 11Hz, H-4b), 2.11 (1H, br s , D_2O exch., CH_2OH), 1.64 (3H, J = 7Hz, CH_3).

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