Tetrahedron Letters,Vol.26,No.22,pp 2641-2644,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

NEW ANTHRACYCLINES SYNTHESIS : ELECTROCHEMICAL REDUCTION.RATE OF GLYCOSIDE ELIMINATION.

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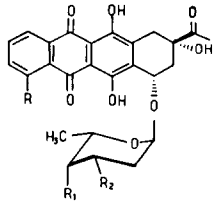
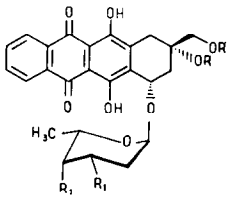
Summary : The synthesis of new 3'-deamino-3'-hydroxy-daunorubicin analogs is reported and the rate of glycoside elimination under electrochemical reduction in an aprotic medium is compared to known anthracyclines.

The anthracycline antibiotic daunomycin or daunorubicin 1 and its 14-OH derivative, adriamycin or doxorubicin are clinically useful drugs for the treatment of human cancer[1]. Nevertheless as their use is limited by a severe cumulative cardiotoxicity[2], the quest for improved anticancer drugs has led to numerous and various total syntheses of anthracycline analogs. Recently, 4-demethoxy anthracyclinones were selected as target molecules for synthesis since it has been established that 4-demethoxy-daunorubicin 2 (or idarubicin) is more potent and less toxic than the parent compound[3].

On the other hand, recent publications of D. Horton et al.[4,5] have shown that the presence of a 3'-amino group in anthracycline is not essential for manifestation of biological activity. Thus, 3'-deamino-3',4'-di-O-acetyl daunorubicin 3 and especially 3'-deamino-3'-hydroxy daunorubicin 4 exert anticancer activity and manifest much lower toxicity including cardiotoxicity than adriamycin.

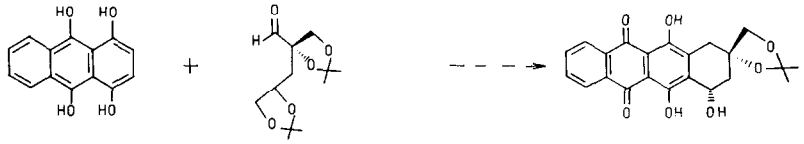


1 R = OCH_3 R_1 = OH R_2 = NH_2
2 R = H R_1 = OH R_2 = NH_2
3 R = OCH_3 R_1 = OAc R_2 = OAc
4 R = OCH_3 R_1 = OH R_2 = OH



5 R = $C(CH_3)_2$ R_1 = OAc
6 R = H R_1 = OAc
7 R = H R_1 = OH

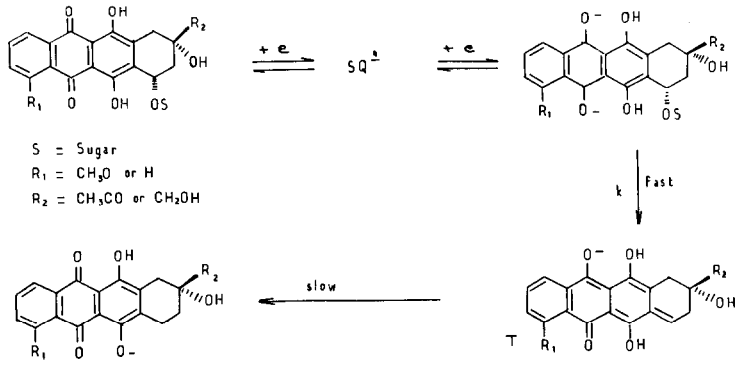
In a general program aimed toward the synthesis of anthracyclines, the optically active 4-demethoxy anthracyclinone 10 was synthesized in four steps from the aldehyde 9 (easily obtained in three steps from α-D-isosaccharino-1,4 lactone[6]) as chiral precursor of ring A and from leucoquinizarin 8 as represented on the following scheme[7].



8 9 10

To circumvent the potential cardiotoxicity and in connection with this program, we have now prepared a number of hitherto unknown anthracyclines and among them several 3'-deamino-3'-hydroxy daunorubicin analogs. Thus for example glycosylation of 10 with 3,4-di-O-acetyl-2,6-dideoxy-α-L-lyxo-hexopyranosyl chloride[8] was attempted under Koenigs-Knorr conditions (HgO, $HgBr_2$ and molecular Sieves 4A) giving after 24 h at 20°C, stereospecifically the α-L-glycoside 5 (m.p. 199-200° ; $|\alpha|_D^{20}$ + 105° ($CHCl_3$, c 0.04) in 85 % yield after chromatography on silica gel (toluene-acetone 95:5). The structure of 5 was unambigously established by 270 n.m.r. ^1H spectroscopy[9] and by DCI/NH_3 mass spectrometry. Selective hydrolysis of the acetal ring was performed by using HCl-MeOH 0.2 N at room temperature for 4 h. This led after chromatography on silica gel (CH_2Cl_2-MeOH 98:2) to 55 % of recovered starting material and to 45 % of 6 (m.p. 207-209° ; $|\alpha|_D^{20}$ + 91° ($CHCl_3$, c 0.05)[10]. Finally, the ester groups were removed by catalytic transesterification under smooth conditions at 0°C. After work-up as described by D. Horton et al[5], the fully deprotected glycoside 7[11] was obtained in 75 % yield (m.p. 224-227° ; $|\alpha|_D^{20}$ + 94° (MeOH, c 0.036).

The mechanism of the electrochemical reduction of 1 in an aprotic media has been analyzed in details in a previous paper[12]. The reversible addition of the first electron which occurs at ca -630 mV (s.c.e.) yields a stable semiquinone radical anion $SQ^{\cdot}$. The second electron addition produces a dianionic species which undergoes a rather fast first order reaction of glycoside elimination. The transitient quinone methide analog T which is endowed with alkylating properties[13] has been characterized by means of spectroelectrochemistry[12].



The electrochemical reduction of compounds 3, 4, 6 and 7 proceeds similarly to that of 1. From the electrochemical point of view, the mechanism of the second electron addition followed by glycoside elimination is a classical E.C. (electrochemical-chemical) mechanism which can be studied by means of cyclic voltammetry and the use of working curves given in the literature[14] enables us to determine the rate constant k :

Compound	1	3	4	6	7
$k(s^{-1})$	140 ± 30	750 ± 100	150 ± 25	250 ± 40	40 ± 10

As already shown by Malatesta et al[15] in the case of another series of anthracyclines, it appears that k depends upon both the natures of the aglycone (3 and 6 or 4 and 7) and sugar moities. Yet, it is not possible to propose a satisfactory explanation for the effect of the structure of the aglycone upon k. The comparison between 1 or 4 and 3 or 6 and 7 shows that the diacetyl sugar is a best leaving group than the dihydroxy or aminohydroxy sugar.

Studies to determine if there is any relationship between the rate of the glycoside elimination and the cytotoxicity of the drug are in progress.

Acknowledgement : We are grateful to Laboratories Hoechst (Paris) for financial support and to Research Laboratories of Behringwerke A.G.(D.3550 Marburg) for biological tests.

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9. Compound 5 : N.m.r. (270 MHz, $CDCl_3$) : δ 13.58 (1H, s) and 13.30 (1H, s) (OH chelated phenols) ; 8.28 (2H, m) and 7.80 (2H, m) (AA' and BB' syst., 4H aromat.) ; 5.58 (1H, d, J=3, J'<1Hz, 1'-H) ; 5.24 (1H, m, 3'-H) ; 5.20 (1H, broad s., W_H~ 5Hz, 1-H) ; 5.03 (1H, t, J=J'=5 Hz, 4'-H) ; 4.40 (1H, q, J=6.5 ; J'<1 Hz, 5'-H) ; 3.95 (1H, d) and 3.85 (1H, d) (AB syst. J= 9 Hz, 13-CH_2) ; 3.27 (1H, d) and 2.80 (1H, d)(AB syst., J= 19 Hz, 4-CH_2) ; 2.15 (3H, s) and 1.89 (3H, s)(2 OAc) ; 2.35-1.86 (4H, m, 2'-CH_2 and 2-CH_2) ; 1.48 (6H, s, CMe_2) ; 1,21 (3H, d, J= 6.5 Hz, 6'-CH_3). DCI/NH_3 : m/z 628 ($M+NH_4^+$), 396 (aglycone), 379 (aglyc.-OH), 232 (sugar), 215, 200 and 155.

10. Compound 6 : N.m.r. (270 MHz, $CDCl_3$) : cf. 5 except : δ 3.76 (1H, d) and 3.54 (1H, dd, ABX syst., J= 10 ; J'= 8 Hz, 13-CH_2), no signal at 1.48. DCI/NH_3 : m/z 588 ($M+NH_4^+$), 356 (aglycone), 232 (sugar) and 215, 155.

11. Compound 7 : N.m.r. (270 MHz, $CDCl_3$) : δ 13.60 (1H, s) and 13.30 (1H, s) (OH chelated phenols), 8.28 (2H, m) and 7.80 (2H, m) (AA' and BB' syst., 4H aromat.), 5.50 (1H, broad s, 1'-H), 5.26 (1H, broad s., W_H≅ 5 Hz, 1-H), 4.30 (1H) et 4.10 (1H) (m, 3'-H and 4'-H), 3.70 (1H, d) and 3.46 (1H, dd)(ABX syst., J= 10 ; J'= 8 Hz, 13-CH_2), 3.60 (1H, m, 5'-H), 3.16 (1H, d) and 2.52 (1H, d)(AB syst., J= 19 Hz, 4-CH_2) 2.34-1.74 (4H, m, 2-CH_2 and 2'-CH_2), 1.35 (3H, d, J = 6.5 Hz, 6'-CH_3).DCI/NH_3: m/z 504 ($M + NH_4^+$), 374, 356 (aglycone), 166, 148 (sugar), 130, 113 and 95.

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(Received in France 5 March 1985)