Tetrahedron Letters,Vol.29,No.36,pp 4629-4630,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

5-DEOXYANTHRACYCLINES: NEW ANALOGUES OF DAUNOMYCIN AND ADRIAMYCIN

Donald W. Cameron*, (the late) Geoffrey I. Feutrill and Peter G. Griffiths
Department of Organic Chemistry, University of Melbourne, Parkville, Victoria 3052, Australia

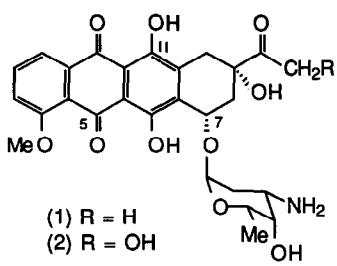
Abstract. Hydrogenation of daunomycin(1) and adriamycin(2) has afforded deoxygenation at position 5 with retention of the 7-glycoside. The resulting 5-deoxyanthracyclines (3), (4), (12), (13) represent a new family possessing high anticancer activity.

There is considerable current interest in deoxy derivatives of the commercial anthracyclines daunomycin(1) and adriamycin(2) as second-generation antitumor agents[1]. A direct approach to such systems might be anticipated by reduction of (1) or (2) but this has so far been impeded by preferential cleavage of the 7-glycosyloxy residue with consequent loss of water solubility[2].

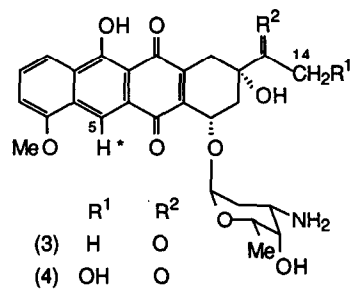
This paper develops conditions for deoxygenating (1) and (2) at position 5 with selective retention of the glycoside, so as to form new 5-deoxyanthracyclines (3), (4)[3]. This process is analogous to catalytic hydrogenation of a 5-methoxy-1,4-dihydroxy-9,10-anthraquinone to the corresponding anthrone followed by reoxidation to a 5-methoxy-9-hydroxy-1,4-anthraquinone[4].

Direct reduction of daunomycin derivatives has previously been observed to result in 5-deoxygenation but only subsequent to deoxygenation at position 7, cf formation of the 5,7-bisdeoxy product (5)[5,6]. In the present study hydrogenation of daunomycin (1) or daunomycinone (6) in several solvents over $Pd/BaSO_4$ was confirmed to proceed efficiently, first to 7-deoxydaunomycinone (7)[7] (97%) and then to (5)[5,6] (88%), m.p.231-233^0 [δ 2.38(14-Me); 8.50(H*); 13.77(ArOH)]. Hydrogenation of the phenylboronate (8) over the same catalyst was too slow to be useful.

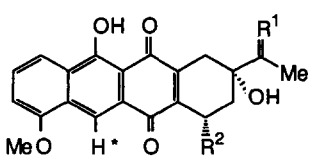
However hydrogenation of (8) over PtO_2 in ethyl acetate at room temperature and pressure, reoxidation of the crude product ($O_2/NaHCO_3$) and exchange of the boronate residue (2,4-pentanediol



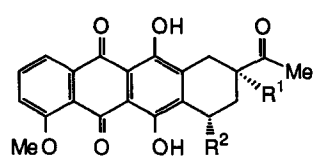
(1) R = H
(2) R = OH



	R^1	R^2
(3)	H	O
(4)	OH	O
(12)	H	H,OH
(13)	OH	H,OH



	R^1	R^2
(5)	O	H
(9)	O	OH
(10)	H,OH	OH
(11)	H,OH	H



	R^1	R^2
(6)	OH	OH
(7)	OH	H
(8)	-OBPhO-	

/HOAc) gave the new 5-deoxydaunomycinone (9) (45%), m.p.289-291^0 [δ 2.43(14-Me);8.54(H*); 13.74(ArOH)] and its 13-dihydro derivative (10)[8] (44%) [δ1.32,1.34(d,d,J7Hz,7Hz)(14-Me); 8.59(H*); 13.88(ArOH)]. The change of catalyst thus afforded preferential deoxygenation at position 5 over 7 for the first time, albeit accompanied by competitive reduction at position 13.

Retention of the 7-oxy substituent under these conditions is evidently associated not only with the catalyst but also the cyclic nature and/or bulk of the phenylboronate residue. Thus hydrogenation of daunomycinone (6) over PtO_2 gave only the 5,7-bisdeoxy product (5) and its 13-dihydro derivative (11)[8] [δ 1.31,1.34(d,d,J7Hz,7Hz)(14-Me); 8.54(H*); 13.88(ArOH)]. However daunomycin hydrochloride behaved like the phenylboronate (8). On hydrogenation [PtO_2 (20% w/w) in methanol containing chloroacetic acid], reoxidation of the crude product (O_2/$NaHCO_3$) and chromatography on silica gel it gave the new 5-deoxydaunomycin (3) isolated as its hydrochloride (57%), m.p.189-191^0 [δ 1.23(d,J7Hz)(6'-Me); 2.30(14-Me); 8.40(H*)] and its 13-dihydro derivative (12)[8] (25%) [δ 1.29(d,J7Hz)(6'-Me and 14-Me); 8.39(H*)]. Their structures were confirmed by acidic hydrolysis to the aglycones (9) and (10) respectively.

Hydrogenation of adriamycin hydrochloride (2) similarly gave the new 5-deoxadriamycin (4) isolated as its hydrochloride (59%), m.p.>200^0 (dec.) [δ 1.28(d,J7Hz)(6'-Me); 8.33(H*)] and its 13-dihydro derivative (13)[8] (21%) [δ 1.29(d,J7Hz)(6'-Me); 8.32(H*)]. Optimum yields of (12) (71%) and (13) (76%) resulted from increasing the ratio of catalyst to substrate (1:1).

The 5-deoxyanthracyclines (3), (4), (12), (13) represent a new modification of natural (1) and (2), derived by a simple, one-pot procedure. The products retain all stereochemical features of the parent compounds and most of the spatial ones. In preliminary testing they showed significant anticancer activity comparable with that of the parents. For example 5-deoxyadriamycin (4) (6.4mg/kg) gave T/C values of 234, 171, 235 against murine tumors P388, L1210 and B16 respectively in vivo.

All new compounds gave satisfactory analyses and spectroscopic data except for (10), (11) (exact mass). ^{1}H N.m.r. spectra of non-glycosides and glycosides were run in $CDCl_3$ and CD_3OD respectively. We thank Farmitalia Carlo Erba for gifts of (1) and (2) and the Cancer Institute, Melbourne for biological testing. This work was carried out during the tenure of a grant from the Anti-Cancer Council of Victoria.

References

1. F. Arcamone, Cancer Res., 1985, 45, 5595.
2. D.L. Kleyer and T.H. Koch, J. Am. Chem. Soc., 1984, 106, 2380.
3. Daunomycin numbering of tetracycles is retained for convenience of discussion, the quinonoid grouping in (3), (4) occupying a position tautomeric with its placement in (1), (2).
4. D.W. Cameron, G.I. Feutrill, C.L. Gibson and R.W. Read, Tetrahedron Lett., 1985, 26, 3887.
5. H. Berg, G. Horn and W. Ihn, J. Antibiotics, 1982, 35, 800; D. Tresselt, W. Ihn, G. Horn and H. Berg, Pharmazie, 1984, 39, 417; D.J. Brand and J. Fisher, J. Am. Chem. Soc., 1986, 108, 3088.
6. M.A.E. Sallam, R.L. Whistler and J.M. Cassady, Can. J. Chem.,1985, 63, 2697. [A hydrogenolysis product of daunomycinone (Pd/$BaSO_4$) tentatively assigned in that paper as 7,11-bisdeoxydaunomycinone has spectroscopic data which appear to be in better agreement with data for the 5,7-isomer (5) isolated in the present investigation].
7. F. Arcamone, G. Franceschi, P. Orezzi, S. Penco and R. Mondelli, Tetrahedron Lett., 1968, 3349.
8. Compounds (10), (11), (12), (13) were obtained as diastereoisomeric mixtures at C-13 as for other synthetic 13-dihydro anthracyclines [S. Penco, G. Cassinelli, A. Vigevani, P. Zini, G. Rivola and F. Arcamone, Gazz. Chim. Ital., 1985, 115, 195].

(Received in UK 6 July 1988)