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STEREOSPECIFIC EPOXIDATION OF ANTHRACYCLINONES A ROUTE TO 8(R)-METHOXYDAUNOMYCINONE

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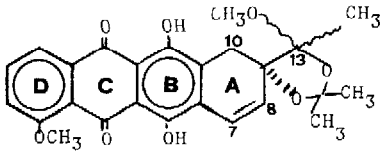
Abstract - Stereoselective epoxidation of 1, the 7,8-unsaturated derivative of daunomycinone, followed by trans opening of the epoxide 2, afforded 8(R)-methoxydaunomycinone 6a, its configuration at C-8 was determined by chemical correlations and PMR studies

As part of our continuing investigation into the synthesis of new derivatives of the antitumouranthracyclines daunorubicin and doxorubicin modified at ring A,[1] we wish to report the synthesis and stereochemistry of 8(R)-methoxydaunomycinone 6a Among the anthracyclinones, the only reported compound substituted at C-8 is the aglycone of steffimycin A and B, bearing in such position a methoxyl group,[2] whose configuration, however, was not determined

Unsaturated daunomycinone derivative 1[3,4] is a useful chiral intermediate for the introduction of a methoxyl group at C-8 of daunomycinone (see scheme) The epoxy derivative 2a mp 166-170°C (dec) obtained almost quantitatively from 1 with m-chloroperbenzoic acid ($CHCl_3$, R T) was converted (KI, $PhCH_2Br$ DMF-Me_2CO, 60°C for 3 hrs) in 70% yield after chromatography into dibenzyl ether 2b mp 88-89°C [5]

Opening of the oxirane ring by treatment of 2b with methanol and a catalytic amount of p-toluenesulfonic acid gave only two products (9 1 ratio) of which 3a was the main one, mp 102-104°C.[6] The minor product 4a, mp 117-120°C, differed from 3a only in the stereochemistry at C-13 In fact both products gave only 5a upon mild acidic treatment (aq 80% TFA, 0°C, 5 min). Compounds 3b, mp 105-107°C, and 4b, mp 205-207°C, obtained from 2a (MeOH, p-toluenesulfonic acid, 5 hrs at R T, 80% yield after chromatography) in 6 1 ratio, as well as the corresponding acetates 3c (Ac_2O, pyridine, R T, 16 hrs), mp 225°C, and 4c, mp 260°C, were useful in the determination of the S configuration at C-13 in compounds 3a,c. In fact the $CH_3C(O\underline{CH_3})$ signal shifted from 3.43 to 3.26 δ in converting 3b into 3c, whereas a similar change was not observed for the pair of compounds 4b (3.34 δ) and 4c (3.35 δ) This interpretation was corroborated by the chemical shift difference between H-10eq and H-10ax, which was larger in 4a c ($\Delta\delta$ = 0.4) than in 3a,c ($\Delta\delta$ = 0 1)

Methylation of the hydroxyl group of 3a, (MeI and NaH, THF, 55°C for 6 hrs), gave 3d, mp 105-107°C, PMR in a . δ 3.37 (s, CH_3O-8), 4 00 (d, J = 2 Hz, H-8) Finally, treatment of 3d with TFA containing a tiny amount of water at R T for 24 hrs, afforded 6a, 7a, and 9, separated by silicagel column chromatography. Compounds 6a and 7a differed in the stereochemistry at C-7 indeed by catalytic benzylic hydrogenolysis (5% $Pd/BaSO_4$, 1 atm, R T) both gave 8 as unique product.



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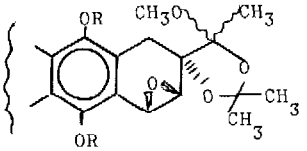
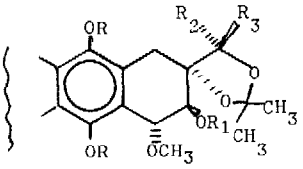
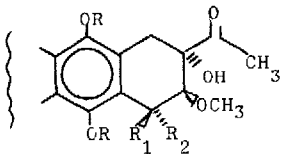


2 a R = H
b R = CH_2Ph



3 a R=CH_2Ph, R_1=H, R_2=CH_3, R_3=OCH_3
b R=R_1=H, R_2=CH_3, R_3=OCH_3
c R=R_1=$COCH_3$, R_2=CH_3, R_3=OCH_3
d R=CH_2Ph, R_1=R_2=CH_3, R_3=OCH_3

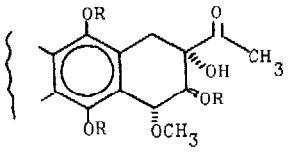
4 a R-CH_2Ph, R_1=H, R_2=OCH_3, R_3=CH_3
b R=R_1=H, R_2=OCH_3, R_3= CH_3
c R=R_1=$COCH_3$, R_2=OCH_3, R_3=CH_3



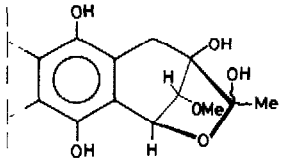
6 a R=H, R_1=H; R_2=OH
b R=$COCH_3$, R_1=H; R_2=$OCOCH_3$

7 a R=H, R_1=OH, R_2=H
b R=$COCH_3$, R_1=$OCOCH_3$, R_2=H

8 R=R_1=R_2=H



5 a R = H
b R = $COCH_3$



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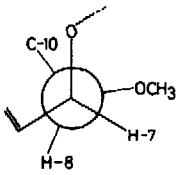

Compound 6a, mp 238°C, $[\alpha]_D$ +147° (c 0 107, $CHCl_3$), PMR 1 a. δ 3 04 (d, J = 17 Hz, H-10ax), 3 28 (d, J = 17 Hz, H-10eq), 3 51 (s, CH_3O-8), 3 71 (d, J = 3 Hz, H-8), 5 15 (d, J = 3 Hz, H-7), by acidic treatment with 2,2-dimethoxypropane afforded the 7,9-isopropylidene derivative, mp 206-207°C, PMR 1.a δ 0 96, 1.30 (two s, $C(CH_3)_2$), 2.27 (s, $COCH_3$), 4.14 (d, J = 4 Hz, H-8), 5.30 (d, J = 4 Hz, H-7), thus showing the cis diaxial relationship of OH-7 and OH-9 The value of $J_{H-7,\,H-8}$ did not allow to distinguish between H-7eq, H-8eq and H-7eq, H-8ax. However the formation of small amounts of 9 from 7a, via internal acetalyzation between OH-7 and the C-13 carbonyl group, allowed to establish the orientation of H-8 in 7a In fact, in 9, PMR 1.a. δ 1 31 (bs, $C(OH)\underline{CH_3}$), 5.60 (d, J = 2.5 Hz, H-7), the formation of the five membered ring induces a change of conformation of ring A and a deformation of the dihedral angle between H-7 and H-8 as compared with that in the unstrained isopropylidene derivative of 6a, thus causing the observed change of $J_{H-7,H-8}$ from 4.0 to 2 5 Hz, which can be justified only by assigning H-8 to the α axial position (see Newman projection of 9). This is in agreement with a H-7ax, H-8eq relationship in the parent compound 7a. The above interpretation is supported by the values of $J_{H-7,H-8}$ in the acetyl derivatives 6b, mp 265°C, and 7b, mp 205°C ($J_{H-7eq,\,H-8eq}$ - 1 6 Hz and $J_{H-7ax,\,H-8eq}$ = 4.5 Hz, respectively)

Since the configuration of the chiral centre at C-8 is directly related to the stereochemistry of epoxide 2a, this is β with respect to the plane of ring A, and since 2 is the unique product, the epoxidation reaction of 1 is stereoselective. Moreover, the similarity of CD curves of 5a and 6a with those of daunomycinone[7,8] and other anthracyclinones[8,9] allows to establish the S configuration at C-7 in 5a, thus revealing that in our conditions the oxirane ring of 2b undergoes exclusively a trans opening reaction.

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References and Notes

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2) R.C. Kelly, I. Schetter, J.M. Koert, F.A. MacKellar, and P.F. Wiley, J. Org. Chem., 42, 3591 (1977).

3) F Arcamone, and G Franceschi, unpublished results Compound 1 was obtained as a mixture of epimers at C-13 in 28% yield after chromatography by treatment of daunomycinone with 2,2-dimethoxypropa e and p-toluenesulfonic acid in anhydrous $CHCl_3$; mp 290-295°C (dec); λ_{max} ($CHCl_3$) 385, 507, and 542 nm, PMR 1 a δ 1 25-1 52 (four s, $C(CH_3)_2$, $C(OCH_3)\underline{CH_3}$), 3 27, 3 36 (two s, $C(CH_3)O\underline{CH_3}$), 6 26, 6 32 (two d, J = 10 Hz, H-8), 7 10, 7.16 (two d, J = 10 Hz, H-7), 12 97, 13 00, 13 37, and 13 50 (four s, OH-6 and OH-11)

4) All compounds gave mass, IR, and PMR ($CDCl_3$) spectra consistent with the assigned structures Yields are unoptimized and mp uncorrected

5) PMR of 2b 1 a. δ 1 38, 1 53 (two s, $C(CH_3)_2$, $C(OCH_3)\underline{CH_3}$), 3 32 (s, $C(CH_3)O\underline{CH_3}$), 3 98 (s, CH_3O-4, H-8), 4.37 (d J = 4 5 Hz, H-7). However, in the PMR spectrum of 2a, either before benzylation or when reobtained upon hydrogenolysis (5% $Pd/BaSO_4$, 1 atm, R T) of 2b, the signals of $C(CH_3)O\underline{CH_3}$ (3 32 and 3.36 δ) and of H-7 (4.54 and 4 59 δ) were splitted, indicating the presence of two C-13 epimers in 1 1 ratio

6) PMR of 3a 1.a. δ 1.26, 1.40, 1 46 (three s, $C(\underline{CH_3})_2$, $C(OCH_3)\underline{CH_3}$), 2 82 (d, J = 16 Hz, H-10ax), 3 24 (d, J = 16 Hz, H-10eq), 3 32 (s, $C(CH_3)O\underline{CH_3}$), 3 37 (s, CH_3O-7), 4.52 (d, J = 3 5 Hz, H-8), 4 80 (d, J = 3 5 Hz, H-7)

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