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# THE STRUCTURE OF DAUNOMYCIN

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We have previously reported structures for daunomycinone [1] and for daunosamine, [2] respectively the aglycone and the aminosugar moiety of daunomycin. We wish now to present evidence which affords decision between structures I and II for daunomycinone [b)] and establishes the position of the glycosidic linkage, thus completing the structure (except for stereochemical features) of the antibiotic.

Treatment of daunomycinone (I) with chromic anhydride in acetic acid gave III, [c) d)] $\lambda_{max}$ (methanol) 493,510,545 mμ. III was promptly converted by 2N sodium hydroxide to IV, $m/e$ 378 (M), conjugated ketone absorption at 1695 $cm^{-1}$; triacetate (acetic anhydride and pyridine) $C_{27}H_{20}O_{10}$, mp 270°. IV shows a visible spectrum in chloroform ($\lambda_{max}$ 491,525, 566 mμ) whose displacement towards longer wave lengths, when compared with the spectrum of bisanhydrodaunomycinone [1] ($\lambda_{max}$ 467,497,521,537 mμ), is in agreement with the presence of an additional peri hydroxyl group. [5]

Treatment of IV with either hydrogen bromide in boiling acetic acid or aluminum chloride in boiling 1,2-dichloroethane afforded V, $m/e$ 364 (M), $\lambda_{max}$ (relative intensities of the maxima and solvent) 486, 519, 588 mμ (1:2:2.2, chloroform); 580, 626 mμ (1:1.8, conc. sulfuric acid); 571, 613 mμ (1:1.3, dimethylformamide); 554, 596 mμ (1:1.3, piperidine); these spectra are of diagnostic value [5a] and suggest a 1,6,10,11-tetrahydroxy-5,12-

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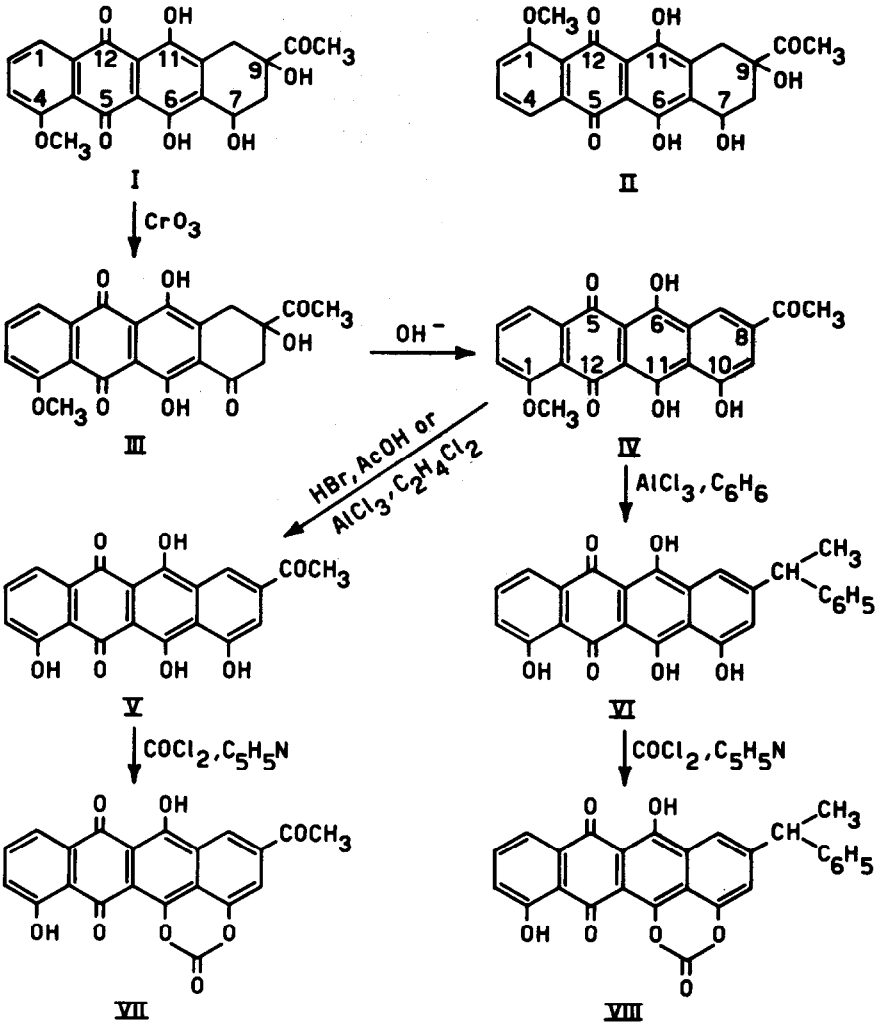
b) The numbering system adopted for the anthracyclinones (ref. 3) has been used for daunomycinone (I) and the other tetrahydronaphthacenequinones of this series. However, in the fully aromatic compounds, numbering begins from the carbon atom bearing the oxygen as indicated in IV (ref. 4).

c) See footnote (3) in ref. 1.

d) The 60 Mc nmr spectrum of III shows signals at $\delta$ 12.91, 14.28 (two strongly chelated hydroxyls), ca 4.0 (broad, one alcoholic hydroxyl), 2.44 ($COCH_3$), 4.05 ($OCH_3$), $\delta$ 7-8 (three aromatic H), 3.29 (broad singlet, $CH_2$-10), 2.76, 3.12 ($CH_2$-8, $J_{gem}$ = 16.0 c.p.s.)




-naphthacenedione chromophore. [e] On the other hand, when IV was refluxed with aluminum chloride in benzene, VI was obtained as the main reaction product (30% yield). The visible spectrum of VI in chloroform, dimethylformamide, and piperidine is identical to that of 1,6,10,11-tetrahydroxy-5,12-naphthacenedione; [5a] the infrared spectrum shows no ketone

e) The $\lambda_{max}$ show slight bathochromic shifts when compared with those given for the said chromophore, [5a] in agreement with the presence of the side chain conjugated ketone group.

absorption but a strong phenyl band at 700 $cm^{-1}$. The mass spectrum contains, inter alia, significant peaks at $m/e$ 426 (M), 411 (M - $CH_3$), 321 (M - $C_6H_5CHCH_3$), 104 ($C_6H_5CH{=}CH_2$). Acetylation of VI (acetic anhydride and pyridine) gave a tetraacetate $C_{34}H_{26}O_{10}$, [f] mp 218-220°, free quinone absorption at 1670 $cm^{-1}$. [g]

The pattern of hydroxylation of V and VI and consequently of I is definitely supported by the infrared spectra of the pericarbonates VII and VIII, prepared on treatment of resp. V and VI with phosgene and pyridine in chloroform, followed by hydrolysis of the chloroformyl groups with 0.5 N sodium bicarbonate. The 1670 $cm^{-1}$ free quinone absorption is absent in the spectra of both pericarbonates. [h]

The position of the glycosidic linkage at C-7 follows from nmr and chemical data. The 100 Mc spectrum [i] of daunomycin pentaacetate IX, mp 268-270°, $[\alpha]_D$ + 12° ($CHCl_3$), + 50° ($CH_3OH$), shows singlets at $\delta$ 2.49, 2.50 (two aromatic OAc), 2.14, 2.17, 2.19 (two aliphatic OAc and $COCH_3$), 1.88 (NAc), 3.97 (aromatic OMe), three aromatic protons interacting with ortho and meta couplings ($\delta_1$ = 7.71, $\delta_2$ = 7.64, $\delta_3$ = 7.25; $J_{1,2} = J_{2,3}$ = 8.0, $J_{1,3}$ = 1.3 c.p.s.), a slightly broadened singlet at 3.23 ($CH_2$-10), an ABX spectrum where H-8A at $\delta$ 2.17 is in part overlapped by the acetyl absorption, H-8B lies at $\delta$ 2.63, and $H_X$ = H-7 is a double doublet [j] at $\delta$ 5.07 ($J_{AB}$ = 16.0, $J_{AX}$ = 4.0, $J_{BX}$ = 2.0 c.p.s.); the sugar protons appear at $\delta$ 1.70-1.80 ($CH_2$-2'), 5.33 (NH, doublet, $J_{NH,H-3'}$ = 8.0 c.p.s.), 4.45 (H-3'), [k] 4.25 (H-5', quartet of doublets, $J_{Me,H-5'}$ = 6.5, $J_{4',5'}$ = 1.5-2.0 c.p.s.),

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f) The mass spectrum shows peaks at $m/e$ 594 (M), 552 (M-$CH_2CO$), 510 (M-2$CH_2CO$), 468 (M-3$CH_2CO$), 426 (M-4$CH_2CO$). In the 60 Mc nmr spectrum four acetyl groups appear at $\delta$ 2.38, 2.41, 2.43, and 2.50; ten aromatic protons at $\delta$ 7.0-8.0; a methyl doublet at $\delta$ 1.68 and the absorption of the $CHCH_3$ at $\delta$ 4.4 (J = 7.5).

g) Formation of VI from IV is in agreement with the known behavior of carbonyl compounds under conditions similar to those leading to VI (ref. 6a and 6b).

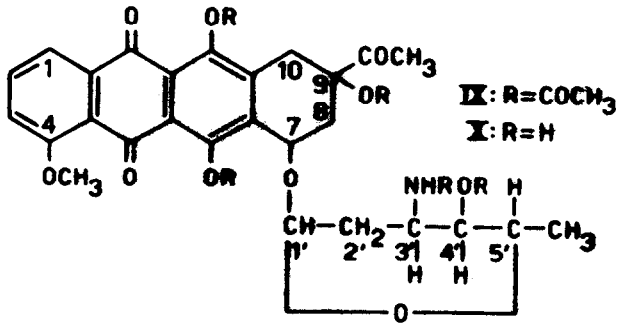
h) The free quinone band should obviously be present if daunomycinone had structure II, which would result in a 1,6,7,11 pattern of hydroxylation for compounds IV-VIII [5a]. VII shows bands at 1590-1620 (chelated quinone), 1690 (conjugated ketone) and 1810 $cm^{-1}$ (O-CO-O); in the spectrum of VIII no absorption is present between 1620 and 1800 $cm^{-1}$.

i) The nmr spectra were recorded with Varian HA-60 and HA-100 spectrometers; decoupling experiments were performed in "frequency sweep". The attributions of all the protons were possible with the aid of decoupling experiments and solvent shift. All chemical shifts are reported in $CDCl_3$, ppm ($\delta$) from tetramethylsilane as internal standard.

j) In $CDCl_3$ H-7 is very near to H-1' and H-4'; the fine structure of H-7 is however visible in benzene-$d_6$/DMSO-$d_6$, where H-7 appears at $\delta$ 5.10, and H-1', together with H-4', at $\delta$ 5.27 (width 1/2 = 6 c.p.s. that sharpens on irradiation of H-3', H-5', and $CH_2$-2').

k) Broad, partially overlapped by H-5'; the width (ca 26 c.p.s.) is reduced to ca 19 c.p.s. by decoupling the NH proton, and to ca 15 c.p.s. on irradiation at $\delta$ 1.75 ($CH_2$-2', center).

1.15 (C-5' $CH_3$, doublet, 6.5 c.p.s.), 5.10-5.12 (H-1' and H-4', W 1/2 = 8 c.p.s.). [l)] Comparison of the shifts of H-7 in IX in daunomycinone trimethylether (CHOMe, 4.92) [1] and in daunomycinone tetraacetate [1] (CHOAc, 6.42), reveals the type of substitution at C-7 (i. e. glycosidic oxygen instead of O-acetate). Catalytic hydrogenation of daunomycin with $Pd/BaSO_4$ in methanol gave 7-deoxydaunomycinone [1] and daunosamine, thus confirming the attachment of the aminosugar at C-7 and allowing to write structure X for the antibiotic.

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l) The chemical shifts of H-4' and H-5' indicate the pyranoside structure of the sugar moiety: see for comparison the shifts of the same protons in α-methyldaunosaminide-N,O-diacetate [2] and in N-acetyldaunomycin [F. Arcamone, G. Cassinelli, G. Franceschi, P. Orezzi, and R. Mondelli, Tetrahedron Letters

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