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ADRIAMYCIN (14-HYDROXYDAUNOMYCIN), A NOVEL ANTITUMOR ANTIBIOTIC

F. Arcamone, G. Franceschi, S. Penco

Istituto Ricerche Farmitalia, Milan, Italy and

A. Selva

Istituto di Chimica del Politecnico, Milan, Italy [a)]

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We report herein the structural elucidation of adriamycin, an antitumor antibiotic which has been compared favourably with clinically useful daunomycin in the experimental chemotherapy studies. [1,2]

Adriamycin, $C_{27}H_{29}O_{11}N$, must have the same anthraquinone chromophore and glycoside structure as does daunomycin, [3] on the basic of spectroscopic data and of formation, on acid hydrolysis, of a red aglycone, adriamycinone, and of the aminosugar, daunosamine. [1] Adriamycinone, $C_{21}H_{18}O_9$, m.p. 223-224°, $[\alpha]_D^{23}$ + 188° (c 0.1, dioxane), one OCH_3, hydroxyl (3440 cm^{-1}), carbonyl (1727 cm^{-1}), and chelated quinone (1615 cm^{-1}) absorptions in the infrared, shows ultraviolet and visible spectra superimposable on those displayed by the parent glycoside and by daunomycinone (I), [3] thus indicating the same type of substitution of the anthraquinone system as in I. Upon acetylation with acetic anhydride and pyridine, adriamycinone gives a pentaacetate $C_{31}H_{28}O_{14}$, m/e 624 (M), m.p. 166°, $[\alpha]_D^{23}$ - 94° (c 0.1, $CHCl_3$), phenolic (1775 cm^{-1}) and alcoholic (1740 cm^{-1}) acetate bands, no hydroxyl absorption in the infrared. When treated with hydrogen bromide in acetic acid, adriamycinone gives a product whose visible spectrum (λ_{max} 467, 497, 521, 537 mμ in $CHCl_3$) is identical to that shown by bisanhydrodaunomycinone. This indicates the presence of two (and only two) hydroxyls on the aliphatic ring of the anthracyclinone system in adriamycinone. [b)] The fifth hydroxyl should therefore be placed on the acetyl side chain as in II.

Comparison of the mass spectra of daunomycinone and adriamycinone shows a similar fragmentation pattern (scheme 1), strongly supporting structure II for the latter compound. The 60 Mc n.m.r. spectrum ($CDCl_3$) of adriamycinone pentaacetate shows five sharp

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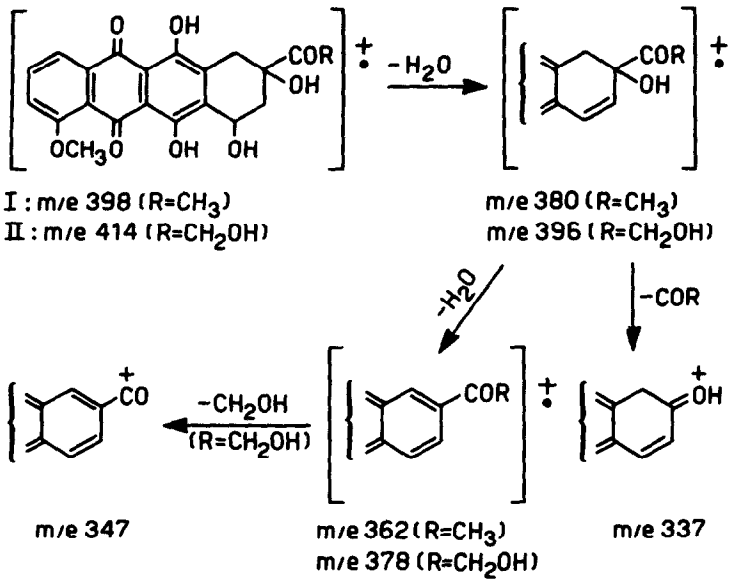
a) Centro del C.N.R. per lo studio delle sostanze organiche naturali.

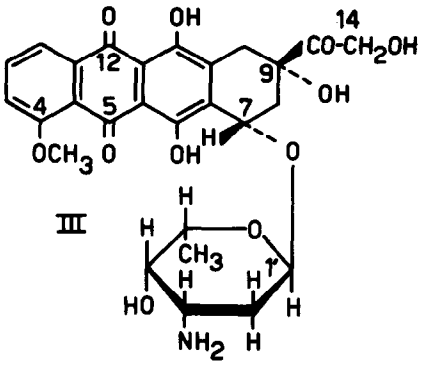
b) An additional hydroxyl group on the said ring would be revealed by a substantially different visible spectrum of the dehydration product [see (3), and references cited therein].

Scheme 1

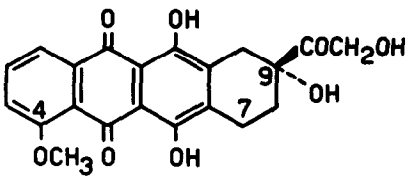


singlets at δ 2.01 (6 H, two aliphatic OAc), 2.13 (3 H, aliphatic OAc), 2.40 (3 H, aromatic OAc), 2.48 (3 H, aromatic OAc), 3.95 (3 H, aromatic OCH_3). Four protons in the range 1.8 - 3.7 δ are attributed to CH_2-8 and CH_2-10. A quartet centered at δ 4.83 (2 H, $J_{gem.}$ = 16.5 c.p.s.) is consistent with the presence of the $COC\underline{H}_2OAc$ group. A double doublet at δ 6.35 (1 H, $J_{H-7,H-8_A} \sim 5$, $J_{H-7,H-8_B} \sim 1.5$ c.p.s.) indicates the C-7 benzylic $C\underline{H}OAc$. Three aromatic protons appear as a complex multiplet at δ 7-8.

Hydrogenolysis of adriamycin (III) with $Pd/BaSO_4$ in methanol gives daunosamine and 7-deoxyadriamycinone (IV), $C_{21}H_{18}O_8$, m.p. 253-255°, m/e 398 (M), 380 (M-H_2O), 349 (M-H_2O-CH_2OH), 339 (M-$COCH_2OH$), carbonyl (1727 cm^{-1}) and chelated quinone (1615 cm^{-1}) bands, tetraacetate (acetic anhydride and pyridine) $C_{29}H_{26}O_{12}$, m/e 566 (M), m.p. 186-188°, $[\alpha]_D^{23}$ - 6° (c 0.1 dioxane). The 60 Mc n.m.r. spectrum ($CDCl_3$) of this tetraacetate shows, inter alia, two aliphatic OAc at δ 2.05 and 2.18, the CH_2-14 quartet at δ 4.88, and the absence of the C-7 benzylic $C\underline{H}OAc$ signal described above. The structure of IV proves the position of the glycosidic linkage at C-7 as in III.



III



IV

C.D. curves have been employed for establishing stereochemical relationships among anthracycline derivatives.[4] The stereochemistry at C-7 and C-9 in adriamycin is proved to be identical [i.e. 7(S), 9(S)] to that of daunomycin[5] by comparison of their C. D. curves, clearly demonstrating the same configuration at the said centers. The absolute configuration at C-1' in III is deduced to be (R), i.e. α-glycoside, from the identity of the optical rotations of adriamycin and daunomycin,[6] and of adriamycinone and daunomycinone,[6] suggesting the same optical contribution of the daunosamine moiety in the two glycosides. This is in agreement with general observations on the stereochemistry of the glycosidic linkage of a given carbohydrate inside a restricted class of natural glycosides, as in Klyne's rule and its extensions,[7] and it is also supported by biogenetic arguments.[8]

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