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THE TOTAL ABSOLUTE CONFIGURATION OF DAUNOMYCIN

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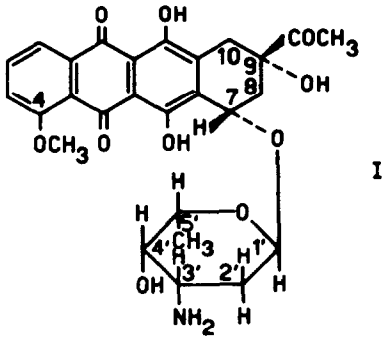
In the preceding paper [1] we have reported the structure of daunomycin, an antitumor antibiotic which has been proved active in acute leukemias and neuroblastoma in children.[2] The present report announces the total absolute configuration of daunomycin as represented in I, a consequence of arriving at specifications [3] for all six asymmetric centers, i.e. 7(S), 9(S), 1'(R), 3'(S), 4'(S), 5'(S).



I

Daunomycinone trimethylether [4] (IV) was treated with aluminum chloride in benzene to give 7-O-methyl-desmethyldaunomycinone (V), mp 215-217°, [b] $[\alpha]_D$ + 142° (chloroform), one OCH_3, same electronic spectrum in methanol as helminthosporin (1,4,5-trihydroxyanthraquinone chromophore); [c] tetraacetate (acetic anhydride and pyridine) $C_{29}H_{26}O_{18}$, mp 238-240°,

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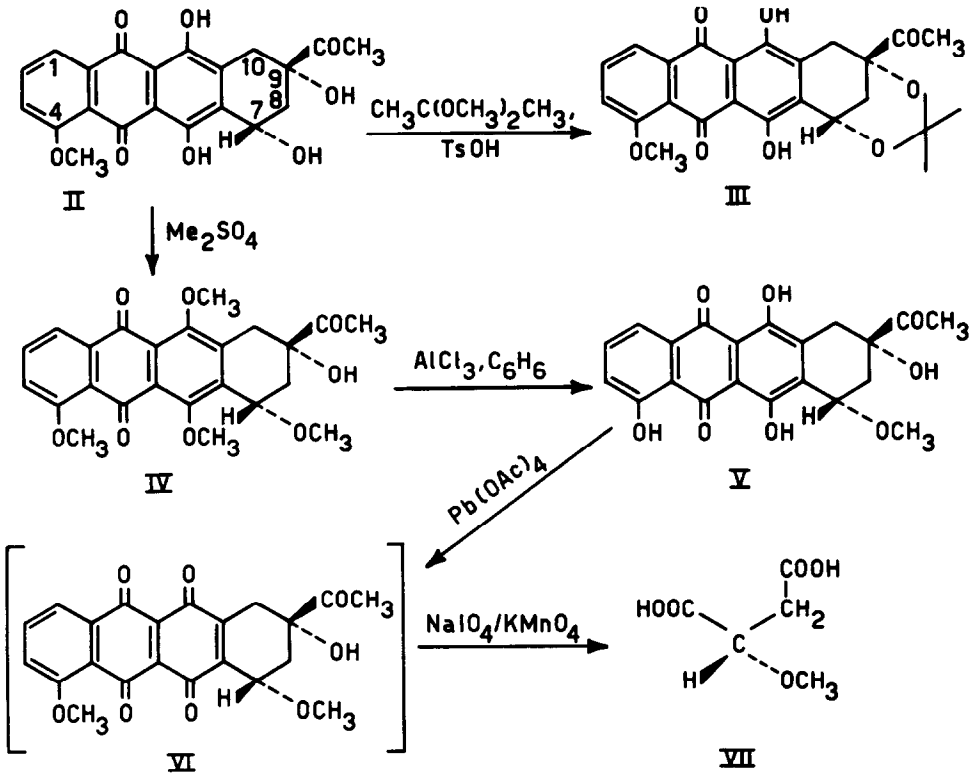
a) Centro del C.N.R. per la chimica delle sostanze organiche naturali.

b) See footnote 3 in ref. 4.

c) The 60 Mc nmr spectrum of V shows: aliphatic OCH_3 at δ 3.62; $COCH_3$ at 2.42; three strongly chelated hydroxyls at 13.50, 12.98, 12.22; aromatic H_1 (7.80), H_2 (7.67), H_3 (7.26), $J_{1,2} = J_{2,3} = 7.8$, $J_{1,3} = 1.8$ c.p.s.; one alcoholic hydroxyl at 5.02; CH_2-10, $\delta_{10A} = 3.17$, $\delta_{10B} = 2.95$, $J_{AB} = 19.2$, $^4J_{10A,8B} = 1$ c.p.s.; CH_2-8 and H-7 giving an ABX pattern: $\delta_{8A} = 1.94$, $\delta_{8B} = 2.42$, $\delta_7 = 4.85$ (H_X), $J_{AB} = 15.0$, $J_{AX} = 3.4$, $J_{BX} = 2.5$, $^4J_{8B,10A} = 1$.



$[\alpha]_D$ + 6° (chloroform). Oxidation of V with lead tetraacetate in acetic acid gave a yellow product which showed an electronic spectrum in chloroform typical of an anthradiquinone derivative (VI) and which readily was reconverted to V by reducing agents. [5] This product was recovered by freeze-drying the reaction mixture and, without isolation, subjected to further oxidation by means of the periodate-permanganate mixture [6] to give, after separation of the ether-soluble acid reaction products by preparative paper chromatography of the ammonium salts, S (-)-methoxysuccinic acid (VII), mp 89° (from benzene), $[\alpha]_D$ -56° (acetone), identified by direct comparison with a synthetic sample.[7] Accordingly, configuration (S) is established for C-7. On the other hand C-9 was configurationally related to C-7 by the formation of the isopropylidene derivative III, mp 224-226°, $[\alpha]_D$ + 220° (chloroform), diacetate $C_{28}H_{26}O_{10}$, mp 153-155°, $[\alpha]_D$ + 205° (chloroform), on treatment of daunomycinone (II) with 2,2-dimethoxypropane and p-toluensulfonic acid in dioxane. The cis configuration of the C-7 and C-9 hydroxyls allows definition of the absolute stereochemistry at C-9 as (S).

Our formulation of daunosamine as 3-amino-2,3,6-trideoxy-L-lyxohexose,[8] establishing the absolute configuration at C-3', C-4', C-5' as 3'(S), 4'(S), 5'(S), has been unequivocally supported by the stereospecific synthesis of derivatives of the D-enantiomer [9a] and of daunosamine itself.[9b] The configuration at C-1', i.e. the stereochemistry of the glycosidic linkage, is now deduced from the 100 Mc nmr spectrum of N-acetyldaunomycin (VIII), mp 180°, $[\alpha]_D$ + 228° (c 0.1, chloroform), prepared on treatment of dauno with acetic anhydride in acetone.

All the protons of VIII, assigned by decoupling experiments, are listed in fig. 1, together with the coupling constants values.[d] H-1' is a double doublet of 1.5 and 3.0-3.5 c.p.s. that collapses to a singlet on irradiation at δ 1.85 (CH_2-2', fig. 1a);[e] the sum of the coupling constant ($|J_{1'eq,\ 2'eq} + J_{1'eq,\ 2'ax}| = 5.0$-$5.5$ c.p.s.) excludes diaxial interaction, thus proving the equatorial orientation of the anomeric proton. H-3', overlapped by H-5' quartet, gives a broad absorption at δ 4.2 ; the width of 28 c.p.s., as measured in decoupling conditions of H-5', is reduced to 22 c.p.s. on irradiation of NH (fig. 1c and 1d [f]); it follows that H-3' must be axial.[g] H-4' is a broad signal because of coupling with the C-4' hydroxyl,[h] and sharpens on irradiation at δ 4.13 (fig. 1e); it becomes a double doublet (2.5 and ca 1 c.p.s.) after exchange with D_2O. H-5' is a double quartet with $J_{4',5'} = 1.0$-1.5 and $J_{Me,H-5'} = 6.5$ c.p.s. H-4' is deduced to be equatorial from the value of $J_{3',4'}$. The orientations of H-3' and H-4' dictate a 1C conformation, and consequently, together with equatorial H-1', the α-glycoside structure for VIII. The absolute stereochemistry at C-1' is therefore defined as (R).

The remaining aglycone protons, extra the methyl absorption, are: two strongly chelated phenolic hydroxyls (δ 13.86 and 13.13); one slightly hydrogen-bonded alcoholic hydroxyl (δ 4.41); H-7, a double doublet centered at δ 5.10, that sharpens on irradiation at δ 2.19 (fig. 1b); H-8A and H-8B, which are discovered at δ 2.09 and 2.29 on decoupling of H-7 (fig. 1f); CH_2-10, an AB quartet the half part of which at δ 3.21 shows a long-range coupling of ca 1 c.p.s. with one of the protons at C-8, as already found in daunomycinone trimethylether.[i]

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d) See footnote i) in ref. 1.
e) The two protons at C-2' show similar chemical shift; the center of the pattern is found at δ 1.85.
f) Recorded in different scale and in pyridine-d_5 solution.
g) See footnote 17 in ref. 8.
h) In DMSO-d_6 C-4' OH is a doublet of 6.0 c.p.s. at δ 4.63, whereas C-9 OH is a sharp singlet at δ 5.39.
i) See footnote 10 in ref. 4.

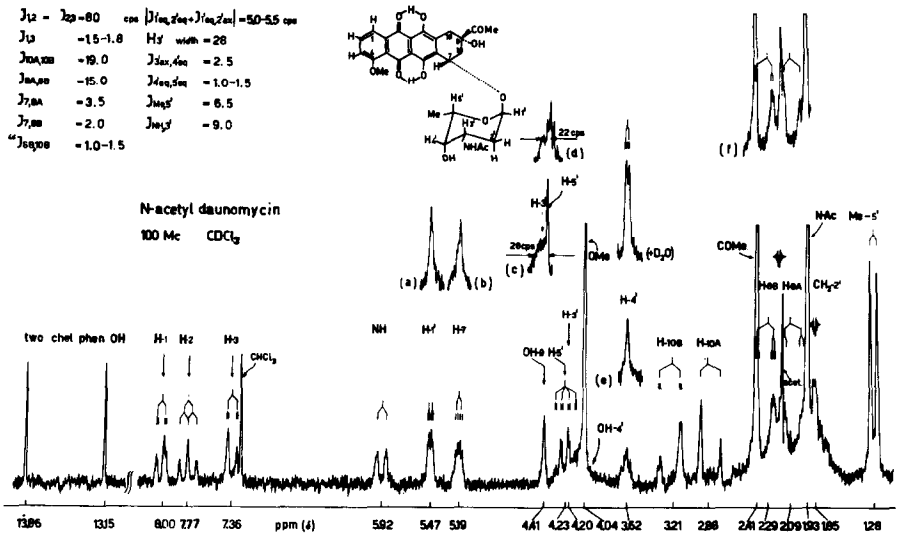

Figure 1. The nmr spectrum of N-acetyldaunomycin (VIII)

Studies concerning the conformation of the cyclohexene ring of the aglycone moiety are in progress.

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