THE STRUCTURE OF VINEOMYCIN B_2

Sir:

Vineomycins (A_1, A_2, B_1 and B_2) produced by *Streptomyces matensis* subsp. *vineus* are new antibiotics, active against Gram-positive bacteria and sarcoma 180 solid tumor on mice[1]. Recently, we reported the structure of vineomycin A_1,[2] as well as the identity of its aglycone with that of aquayamycin.[3] In the present paper, the structure of vineomycin B_2 determined on the basis of comparison with vineomycin A_1 is described.

Vineomycin B_2 (**1**), obtained as a yellow amorphous powder, mp 128~131°C, $[\alpha]_D^{26}$ +30.8° (*c* 0.5, $CHCl_3$), has a molecular formula, $C_{49}H_{58}O_{18}$, which was deduced from microanalysis,[1] FDMS: 973 (M^++K)* and the ^{13}C NMR data.

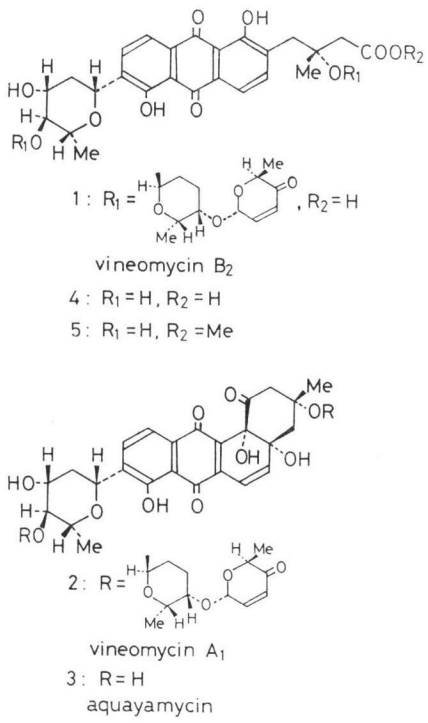
The ^1H and ^{13}C NMR spectra of **1** and vineomycin A_1 (**2**) suggested their close similarity in the structure. For example, though a few signals which overlap in the ^1H NMR spectrum of **2** are separated in that of **1**, no essential differences were observed in the region of δ_H 3.4~5.4 ppm. Since all signals in this region as well as olefinic proton signals (δ_H 6.06, d, J=10 Hz, δ_H 6.08, d, J=10 Hz, δ_H 6.85, dd, J=10 and 3 Hz and δ_H 6.86, dd, J=10 and 3 Hz) attributable to the protons of the sugar moieties and of the pyran ring of **2**, were discerned in the spectrum of **1** and since the enone systems of the sugar moieties of **2** were observed in the infrared spectrum (ν_{max}^{KBr} 1705 cm^{-1}, two carbonyl groups) of **1**, the sugar moieties and the pyran ring of **1** were supposed to be identical with those of **2**. In order to identify the sugar moieties of **1** with those of **2**, **1** and **2** were separately hydrogenated in the presence of 10% Pd-C in EtOH followed by methanolysis with 5% HCl-MeOH at 90°C, and the resulting methyl glycosides were analyzed by GC-MS.** Two peaks were observed on the GC traces for each product from **1** and **2**, and both of the retention times in each trace were identical. In addition, the mass spectra of the two peaks [more mobile *m/z*; 144 (M^+), 129 (M^+-15) and less mobile *m/z*; 131 (M^+-15), 115 (M^+-31)] were superimposed. Hence, the sugar moieties of **1** were concluded to be identical with those of **2**. The sequence of sugar moieties was implied to be identical with that of **2**, since the ^1H NMR data of anomeric protons of **1** and **2** were almost the same, *i.e.*, four anomeric protons (δ_H 5.20, d, J=3 Hz, δ_H 5.21, s, 2H and δ_H 5.27, d, J=3 Hz) in the spectrum of **1** and four ones (δ_H 5.23, s, 2H and δ_H 5.24, d, J=3 Hz, 2H) in that of **2**. Thus, the structural difference between **1** and **2** exists in the aglycone.

The UV-visible spectrum [λ_{max}^{EtOH} nm (log ε); 231 (4.62), 258 (4.53), 286 (3.85), 295 (3.89), 426 (4.05) and 444 (4.05)] of **1** suggested the presence of a 1,5- or 1,8-dihydroxy-9,10-anthraquinone skeleton.[4] The infrared absorption of two chelated quinone carbonyl groups at 1625 cm^{-1} and the signals of two hydrogen-bonded quinone carbonyl carbons at δ_C 187.7 (overlapped) in the ^{13}C NMR spectrum of **1** indicated the location of two hydroxyl groups at 1 and 5 positions. In addition, substitutions at the 2- or 4- and at the 6- or 8-positions of the anthraquinone skeleton were indicated by two AB type ^1H NMR systems (δ_H 7.86 and δ_H 7.74, J=8 Hz and δ_H 7.64 and δ_H 7.58, J=8 Hz). Although the above data did not allow assignment of the substituting groups, the locating position of the pyran ring was assigned to be at the vicinal position of one of hydroxyl groups with reference to the structure of **2**. Where the ^{13}C NMR spectra the aglycones of **1** and **2** are compared, new signals for a non-protonated sp^2 carbon (δ_C 134.9), a phenolic carbon (δ_C 161.5) and a carboxylic acid (δ_C 174.0) appeared in the spectrum of **1** in place of the signals for a carbonyl carbon and two oxygen-bearing non-protonated sp^3 carbons in that of **2**. The presence of a carboxylic acid in **1** was also supported by the infrared absorption (ν_{max}^{KBr} 3000~2500 cm^{-1}, broad and 1730 cm^{-1}). Two methylene signals (δ_C 38.6 and δ_C 44.4) and one oxygen-bearing non-protonated carbon signal (δ_C 77.2) were observed in the ^{13}C NMR of **1**, and these methylene protons (δ_H 2.64, d and δ_H 2.77, d, J=15 Hz and δ_H 3.16, s, 2H) did not couple to each other, whereas those in **2** showed a long-range W-type coupling. This suggests that these methylene groups are involved in a non-cyclic structure. By an acid treatment of aquayamycin (**3**), which yields a component identical with the aglycone of **2**, SEZAKI *et al.* obtained a 2,6-disubstituted 1,5-dihydroxy-9,10-anthraqui-

* The sample was applied with KI aqueous solution.

** Analytical conditions: GC; column: 1% ECNSS-M, 1 m, temp. 70°C (program rate; 6°C/minute), flow rate 25 ml/minute and MS; 70 eV.

Fig. 1. Structures of vineomycin B_2 (**1**) and A_1 (2), aquayamycin (**3**) and degradation products (**4** and **5**) from **3**.



none derivative (**4**) containing a carboxylic acid group.[3] All the spectroscopic data of the aglycone of **1** described above are completely compatible with **4**. To confirm the above assumptions, chemical comparison of the aglycones of **1** and **2** was undertaken. Thus, **1** and **2** were treated separately with 5 % HCl - MeOH at 90°C under the conditions used for aquayamycin methanolysis[3] and the chromophore were purified on each case by preparative tlc (benzene - MeOH, 5: 1). The ^{1}H NMR spectrum of the degradation product from **1** at 200 MHz was completely superimposed with that from **2**. Furthermore, the ^{1}H NMR spectrum of the former in DMSO-d_6 was completely consistent with the published data of the methanolysis product (**5**) from **3**.[3] Therefore, the structure of the aglycone part and hence the total structure of **1** were determined as shown in Fig. 1. Since the stereochemistry of **2** has been determined,[2,5] that of **1** can be elucidated as shown in Fig. 1.

It is interesting to note that the aglycone of **1** is identical to **4**, obtained by acid treatment of **3**, since **1** was proved to be a naturally occurring compound by tlc examination of the fermentation broth.* Biosynthetic studies of **1** and **2** are now in progress to determine the relationship between **1** and **2**.

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* *Streptomyces albogriseolus* subsp. No. 1894 producing **2** (P-1894B)[5] does not produce **1**, according to a private communication from Dr. T. Kishi, Takeda Pharmaceutical Co., to whom the authors are indebted.