The Unsaturated Cyclitol Part of the New Antibiotics, the Validamycins

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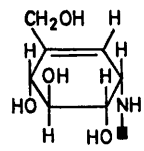
Summary Microbial degradation of validamycin A gave a new unsaturated aminocyclitol (**5**) with the 1*S*-configuration, establishing the structure (**1**) of the unsaturated cyclitol portion of validamycin A; the structure of epivalidamine (**6**), a new aminocyclitol derived from dihydrovalidamycin A was also elucidated.

VALIDAMYCINS A–F[1,2] are weakly basic, water-soluble antibiotics produced by *Streptomyces hygroscopicus* var. *limoneus* and all have the unsaturated aminocyclitol structure[3a] in their molecules.

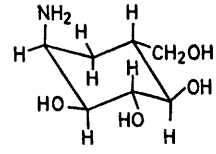
Previous studies[2b,3] of validamycin A, a main component of the validamycin complex have shown that: (i) acidic hydrolysis of validamycin A yields D-glucose and validoxylamine A, a weakly basic aglycone having the molecular formula $C_{14}H_{25}NO_8$, (ii) hydrogenolytic cleavage of validoxylamine A gives validamine (**2**), validatol (**3**), and deoxyvalidatol (**4**), (iii) hydrogenolytic cleavage of validamycin A gives β-D-glucopyranosylvalidamine, validatol, and deoxyvalidatol, (iv) the presence of the unsaturated cyclitol portion with the partial structure $HOCH_2–\overset{|}{C}=CH–$ is consistent with the n.m.r. spectrum of validoxylamine A, (v) the ring-methylene protons and the tertiary ring proton of validatol and deoxyvalidatol arise by catalytic hydrogenation.

We now describe the structural elucidation of the unsaturated aminocyclitol part of the validamycins.

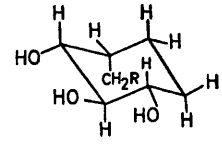
Validamycin A was added to a cell suspension of *Pseudomonas denitrificans* (pH 8) and the mixture incubated at 30°, with shaking. Validamycin A was biologically hydrolysed to D-glucose and validoxylamine A which gave further degradation products including validamine and a new unsaturated aminocyclitol, valienamine (**5**). By the same microbial degradation procedure, validamycin B[2] gave hydroxyvalidamine[3b] and valienamine, and dihydrovalidamycin A[4] gave validamine and a new aminocyclitol named epivalidamine (**6**), but no valienamine.



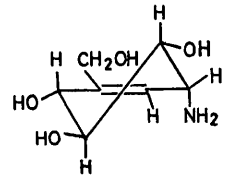
(1)



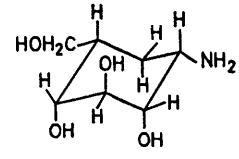
(2)



(3) R=OH
(4) R=H



(5)



(6)

Valienamine has the molecular formula $C_7H_{13}NO_4$ and contains one primary NH_2 (Van Slyke), one CH_2OH, and three secondary OH groups: monohydrochloride, $[\alpha]_D^{23}$ +68·6° (1N-HCl), penta-acetate, m.p. 95°, $C_{17}H_{23}NO_9$, $[\alpha]_D^{23}$ +30·2° ($CHCl_3$).

Because valienamine, validatol, and deoxyvalidatol are derived from the same part of the validamycins, the configuration of the one NH_2 and the three secondary OH

groups must be either *a'*, *e*, *e*, *e'* or *e'* *e*, *e*, *e'* in the half-chair conformation. The coupling constant, d, J 4·5 Hz, of the vinyl proton, δ 5·85 in $(CD_3)_2SO$; at 100 MHz with Me_4Si standard, of the penta-acetate shows that the configuration of the NH_2 group at C-1 is pseudo-axial.[5]

The absolute configuration, *S*, at C-1 was elucidated in relation to deoxyvalidatol whose absolute configuration is reported in the following communication.[4] Thus, the structure of valienamine is (**5**), with the *S*-configuration at C-1.

Epivalidamine has the molecular formula $C_7H_{15}NO_4$ and contains one primary NH_2 (Van Slyke), one CH_2OH, and three secondary OH groups, m.p. 210°, $[\alpha]_D^{22}$ +5·8° (H_2O). The n.m.r. data and the periodate oxidation experiments (three moles consumption in epivalidamine and two moles in *N*-acetylepivalidamine) indicated that epivalidamine was a stereoisomer of validamine (**2**), $[\alpha]_D^{21}$ +60·6° (H_2O).

The configuration of the three secondary OH groups must be vicinal *trans*, because epivalidamine, valienamine, validatol, and deoxyvalidatol are derived from the same part of the validamycins.

Periodate–permanganate oxidation of *N*-acetylepivalidamine, followed by acid hydrolysis gave L-(+)-aspartic acid. From this result and the absolute configuration of deoxyvalidatol,[4] the NH_2 group at C-1 must be *cis* to the OH group at C-2.

Epivalidamine and validamine must differ in the configuration of the CH_2OH group at C-5, because four of the five substituents at asymmetric carbon atoms have the same configurations. The CH_2OH group must therefore be *cis* to the OH group at C-4 and this configuration is reasonably explained by analogy with validatol and deoxyvalidatol. The *e,a,a,a,e* configuration of the substituent groups is consistent with the coupling constants of the ring-methine protons.

These results established the structure of epivalidamine as (**6**) with the *S*-configuration at C-1. The unsaturated cyclitol portion of the validamycins can thus be assigned structure (**1**).

We thank Drs. R. Takeda and A. Miyake for their encouragement and support of this work, and Drs. T. Yamano, J. Ueyanagi, M. Isono, and K. Mizuno for helpful discussions.

(*Received, 24th April* 1972; *Com.* 684.)

[1] (a) T. Iwasa, H. Yamamoto, and M. Shibata, *J. Antibiotics*, 1970, **23**, 595; (b) T. Iwasa, E. Higashide, H. Yamamoto, and M. Shibata, *ibid.*, 1971, **24**, 107; (c) T. Iwasa, E. Higashide, and M. Shibata, *ibid.*, p. 114.

[2] (a) T. Iwasa, Y. Kameda, M. Asai, S. Horii, and K. Mizuno, *J. Antibiotics*, 1971, **24**, 119; (b) S. Horii, Y. Kameda, and K. Kawahara, *ibid.*, 1972, **25**, 48.

[3] (a) S. Horii, T. Iwasa, and Y. Kameda, *J. Antibiotics*, 1971, **24**, 57; (b) S. Horii, T. Iwasa, E. Mizuta, and Y. Kameda, *ibid.*, p. 59; (c) K. Kamiya, Y. Wada, S. Horii, and M. Nishikawa, *ibid.*, p. 317.

[4] S. Horii and Y. Kameda, following communication.

[5] R. J. Abraham, H. Gottschalck, H. Paulsen, and W. A. Thomas, *J. Chem. Soc.*, 1965, 6268.