Structure of the Antibiotic Validamycin A

By SATOSHI HORII* and YUKIHIKO KAMEDA

(*Microbiological Research Laboratories, Takeda Chemical Industries, Ltd., Higashiyodogawa-ku, Osaka, Japan*)

Summary The chemical structure of validamycin A, a new water-soluble weakly basic antibiotic, was shown to be (**1**).

VALIDAMYCIN A[1,2] is a main component of the validamycin complex which is used to control sheath blight in rice plants. The experimental evidence described in this communication, in addition to the information obtained in the previous studies[2,3] led to the assignment of (**1**) as the structure of validamycin A.

The suggested molecular formulae[2e] of validamycin A, $C_{20}H_{35}NO_{13}$ and validoxylamine A (**2**), $C_{14}H_{25}NO_8$ were consistent with molecular ions corresponding to the undeca-acetate (*m/e* 959) and the undeca-methyl ether (*m/e* 651) of validamycin A, and the octa-acetate (*m/e* 671) and the octa-trifluoroacetate (*m/e* 1103·192, calculated for $C_{30}H_{17}NO_{16}F_{24}$, 1103·204) of validoxylamine A.

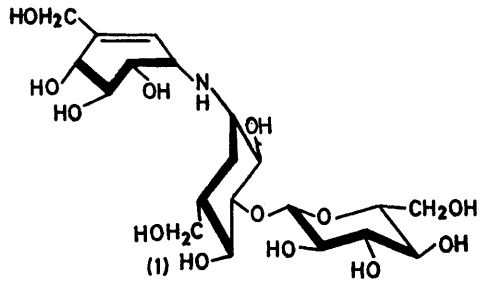
Catalytic reduction of validamycin A yields monodeoxydihydrovalidamycin A (**3**), $C_{20}H_{37}NO_{12}$,H_2O, pK'_a 7·4, $[\alpha]_D^{24}$ +37·9° (H_2O) and dihydrovalidamycin A (**4**), $C_{20}H_{37}NO_{13}$,H_2O, pK'_a 7·2, $[\alpha]_D^{32}$ +34·1 (H_2O) in addition to β-D-glucopyranosylvalidamine (**7**),[2c,d] validatol (**9**),[2c] and deoxyvalidatol (**10**).[2c]

Monodeoxydihydrovalidamycin A and dihydrovalidamycin A gave the crystalline deca-acetate of (**3**); $C_{40}H_{57}NO_{22}$, m.p. 186—188° (decomp.), $[\alpha]_D^{21}$ +28·6° ($CHCl_3$), M^+ 903 and the crystalline undeca-acetate of (**4**); $C_{42}H_{59}NO_{24}$, m.p. 184—186° (decomp.), $[\alpha]_D^{22}$ +28·1° ($CHCl_3$), M^+ 961, respectively.

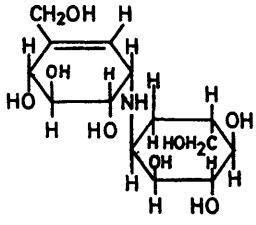
The formation of these catalytic reduction products is reasonably explained by the presence of the HO–CH_2–C(=)–CH–CH–NH– system in the validoxylamine A portion.

The coupling constant, q, *J* 4·5 and 9·0 Hz, of the AcO–C*H* ring proton on C-2, δ 4·87 in $CDCl_3$; at 100 MHz with Me_4Si standard, of triacetyldeoxyvalidatol indicates that the Me group at C-1 is *cis* to the vicinal OH group, because the configurations of three vicinal AcO–C*H* ring protons (δ 5·23, t, *J* 9·0 Hz on C-3, 4·87, m, on C-4) are all axial *trans*.

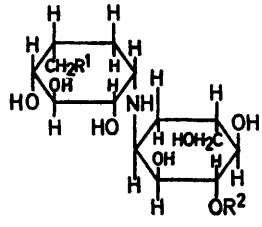
Periodate oxidation of deoxyvalidatol, followed by bromine oxidation gave *R*-(−)-2-methylglutaric acid, $[\alpha]_D^{22}$ −15·6° (EtOH), a compound of known absolute



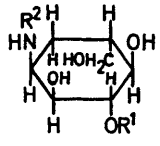
(1)

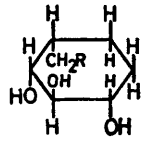


(2)



(3) R^1=H, R^2=Glc
(4) R^1=OH, R^2=Glc
(5) R^1=H, R^2=H
Glc = β-D-glucopyranosyl





(6) R^1=H, R^2=H
(7) R^1=Glc, R^2=H
(8) R^1=Glc, R^2=Ac
Glc = β-D-glucopyranosyl

(9) R=OH
(10) R=H

configuration.[4] Thus, the structure of deoxyvalidatol was clearly established as (**10**), with the 1*R*-configuration and validatol as (**9**), with the 1*S*-configuration. This result also established the absolute configuration of the unsaturated aminocyclitol moiety[3] in validoxylamine A.

Because the NH_2 group of validamine must be attached to the unsaturated cyclitol at the α-position of the allylic system as described above, the structure of validoxylamine A can be expressed by (**2**).

The n.m.r. spectrum of peracetylvalidoxylamine A is consistent with structure (**2**).

Acid hydrolysis of monodeoxydihydrovalidamycin A gave D-glucose and monodeoxydihydrovalidoxylamine A (**5**); $C_{14}H_{27}NO_7,H_2O$, pK'_a 7·4, $[\alpha]_D^{27}$ +61·9° (H_2O). The n.m.r. spectrum of the crystalline peracetate and the molecular ion at *m/e* 615 corresponding to the hepta-acetate, $C_{28}H_{41}NO_{14}$ are consistent with structure (**5**).

β-D-Glucopyranosylvalidamine (**7**)[2b] afforded the octa-acetate; $C_{29}H_{41}NO_{17}$, m.p. 117—119°, $[\alpha]_D^{27}$ +17·6° ($CHCl_3$), M^+ 675·234 (calculated for $C_{29}H_{41}NO_{17}$, M^+ 675·237). The octa-acetate was treated with ammoniacal methanol to give the *N*-acetate (**8**). Periodate oxidation (consumption of three moles) of the *N*-acetate, followed by acid hydrolysis gave validamine (**6**) as the hydrolysate. The isolation of validamine after periodate oxidation suggests the substitution at the C-3 position of validamine with D-glucose.

Therefore, the chemical structure of validamycin A was determined to be *N*-[(1*S*)-(1,4,6/5)-3-hydroxymethyl-4,5,6-trihydroxycyclohex-2-enyl][*O*-β-D-glucopyranosyl-(1→3)-(1*S*)-(1,2,4/3,5)-2,3,4-trihydroxy-5-hydroxymethylcyclohexyl]amine.

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