THE REVISED STRUCTURE OF VALIDAMYCIN A

Sir:

Validamycin A (**1**) is a main component of the validamycin complex which is produced by *Streptomyces hygroscopicus* var. *limoneus*[1]; its structure, formulated as **1a**, was established by HORII and KAMEDA.[2]

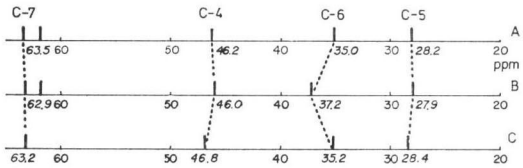
In the course of a study directed toward a total synthesis of **1**, β-D-glucopyranosylvalidamine, 2-O-β-D-glucopyranosyl-1L-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (**2a**),[3] was first synthesized by an unambiguous reaction sequence.[4] However, **2a** was different from an authentic sample (**2b**) derived by hydrogenolysis of **1**. Therefore, attempts were made to elucidate a correct structure of **2b** by synthesis of other positional isomers of the β-D-glucopyranosides.

A comparison of the ^{13}C NMR spectral data (Fig. 1) of the peracetyl derivatives of **2a**, **2b**, and (+)-validamine (**3**) suggested that a hydroxyl group on the C-1 of the validamine moiety might be substituted by a β-D-glucopyranosyl group in **2b**, since an appreciable down-field shift was observed in the chemical shift of C-6 in the spectrum of the octa-N,O-acetyl derivative of **2b**, relative to the spectra of **2a** and **3**.

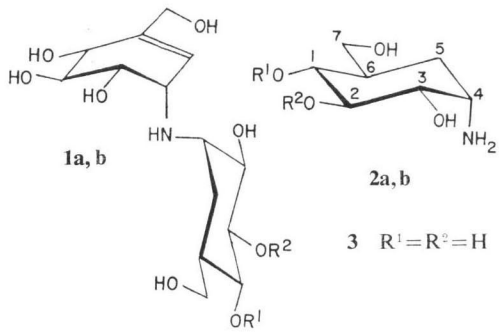
The synthesis of the 1-O-β-D-glucopyranoside of (+)-validamine was carried out by condensing a racemic partially blocked precursor of validamine, 7-O-benzoyl-2,3-O-isopropylidene-DL-(1,3,4/2,6)-4-azido-6-hydroxymethyl-1,2,3-cyclohexanetriol (**8**), with acetobromoglucose. Compound **8** was prepared from the readily available tri-O-acetyl-DL-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (**4**)[5] in the following way (**4**→**8**): O-deacylation by acid hydrolysis, acetonation with 2,2-dimethoxypropane in DMF in the presence of *p*-toluenesulfonic acid, preferential substitution of the C-7 bromine atom by treatment with sodium benzoate, and azidolysis in DMSO. The 1,2-O and 2,3-O positional isomers, formed by isopropylidenation, were easily separated by fractional crystallization after the introduction of a benzoyloxyl group. The structure of **8**, mp 105~108°C, was confirmed by the ^1H NMR spectra of the corresponding O-acetyl and O-methyl derivatives.

Fig. 1. Partial carbon-13 chemical shifts of peracetyl derivatives of **2a** (A), **2b** (B), and **3** (C) in $CDCl_3$[8].

a) In parts per million downfield from tetramethylsilane.



Scheme 1.

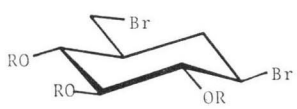


a: R^1=H
R^2=β-D-Glucopyranosyl
b: R^1=β-D-Glucopyranosyl
R^2=H

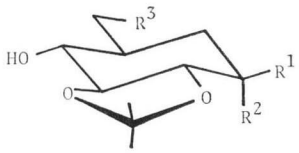
Condensation of **8** with acetobromoglucose in dry benzene in the presence of mercuric (II) cyanide and anhydrous calcium sulfate at 70°C for 2 days gave two condensation proudcts **9**(+) and **9**(−), which were successively O-deisopropylidenated to give, after fractionation on a silica gel column, crystalline dihydroxy compounds **10**(+), mp 182~183.5°C, $[\alpha]_D^{24}$ +27°, and **10**(−), mp 158~161°C, $[\alpha]_D^{23}$ −16°, in 18 and 13% isolated yields, respectively.* On removal of the protective groups, followed by hydrogenation in the presence of 5% palladium on carbon and hydrochloric acid, **10**(+) gave the corresponding amine hydrochloride, which was fully characterized as the octa-N,O-acetyl derivative,** $[\alpha]_D^{23}$ +16° (lit.[2] $[\alpha]_D$ +17.6°). This compound was identified with the help of an authentic sample*** by comparison of their respective ^1H and ^{13}C NMR, and IR spectra, and chromatographic behavior in several solvent systems.

* The optical rotations were measured in chloroform (*c ca.* 1).

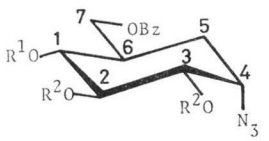
Scheme 2. Formulas depict only one isomer of the respective racemates.



4 R=Ac
5 R=H



6 R^1=Br, R^2=H, R^3=Br
7 R^1=Br, R^2=H, R^3=OBz
8 R^1=H, R^2=N_3, R^3=OBz



9(+), (−) R^1=Tetra-O-acetyl-β-D-glucopyranosyl R^2, R^2=Me_2C
10(+), (−) R^1=Tetra-O-acetyl-β-D-glucopyranosyl R^2=H

Consequently, on the basis of the present synthetic study, "β-D-glucopyranosylvalidamine" was assigned as 1-O-β-D-glucopyranosyl-1L-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (**2b**). Accordingly the structure of validamycin A should be revised to **1b** depicted in Scheme 1.

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** The octa-N,O-acetyl derivative of **2b** isolated as an amorphous solid melted at 114~118°C (lit.[2] 117~119°C) and the melt, on continuous heating, solidified at 150~160°C to give needles, which melted again sharply at 187~189°C. The same melting and crystallization behavior was observed for an authentic sample.

*** An authentic sample was kindly supplied by Dr. Satoshi Horii.

References

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