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SYNTHESIS OF β-D-GLUCOPYRANOSYLVALIDAMINE: 2-O-β-D-GLUCOPYRANOSYL-1L-(1,3,4/2,6)-4-AMINO-6-HYDROXYMETHYL-1,2,3-CYCLOHEXANETRIOL[1)]

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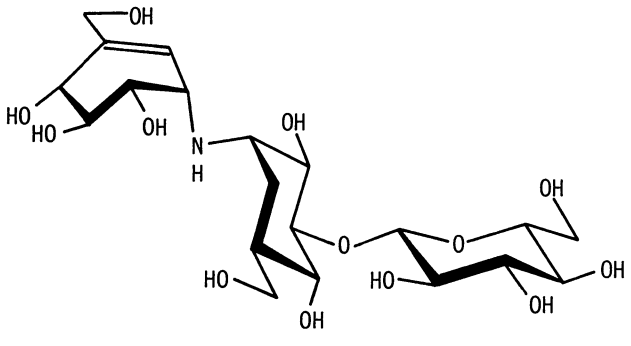
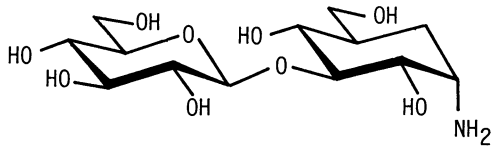
β-D-Glucopyranosylvalidamine (1a), the structure of which was assigned to the degradation product of validamycin A, was synthesized by condensation of a protected validamine (8) with acetobromoglucose, followed by deblocking. Unexpectedly, 1a was found not to be identical with an authentic sample derived from the antibiotic.

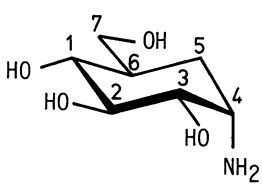
Validamycin A is a main component of the validamycin complex, which was isolated by Iwasa and his coworkers[2)] in 1970 from the broth of Streptomyces hygroscopicus var. limoneus. The structure was assigned by Horii and Kameda[3)] on the basis primarily of degradative studies (Scheme I). Thus, the hydrogenolysis of validamycin A produces β-D-glucopyranosylvalidamine (1a), validatol, and deoxyvalidatol.[4)] The structure of 1a was formulated as 2-O-β-D-glucopyranosyl-1L-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol,[5)] based on the results of the periodate oxidation of its N-acetyl derivative.[3)]



Validamycin A



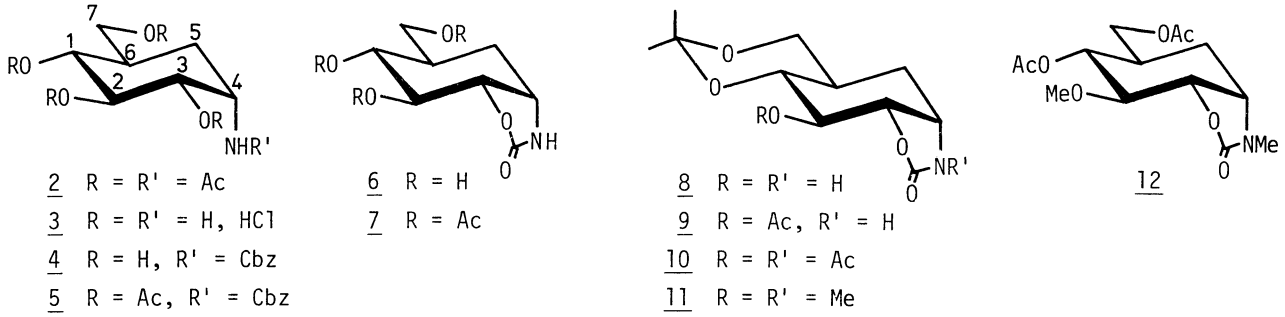
β-D-Glucopyranosylvalidamine (1a)



(+)-Validamine

Scheme I

In the present communication, as a part of study directed toward the total synthesis of validamycin A and its related substances, the synthesis of 1a was carried out by condensation of a properly protected DL-validamine with acetobromo-



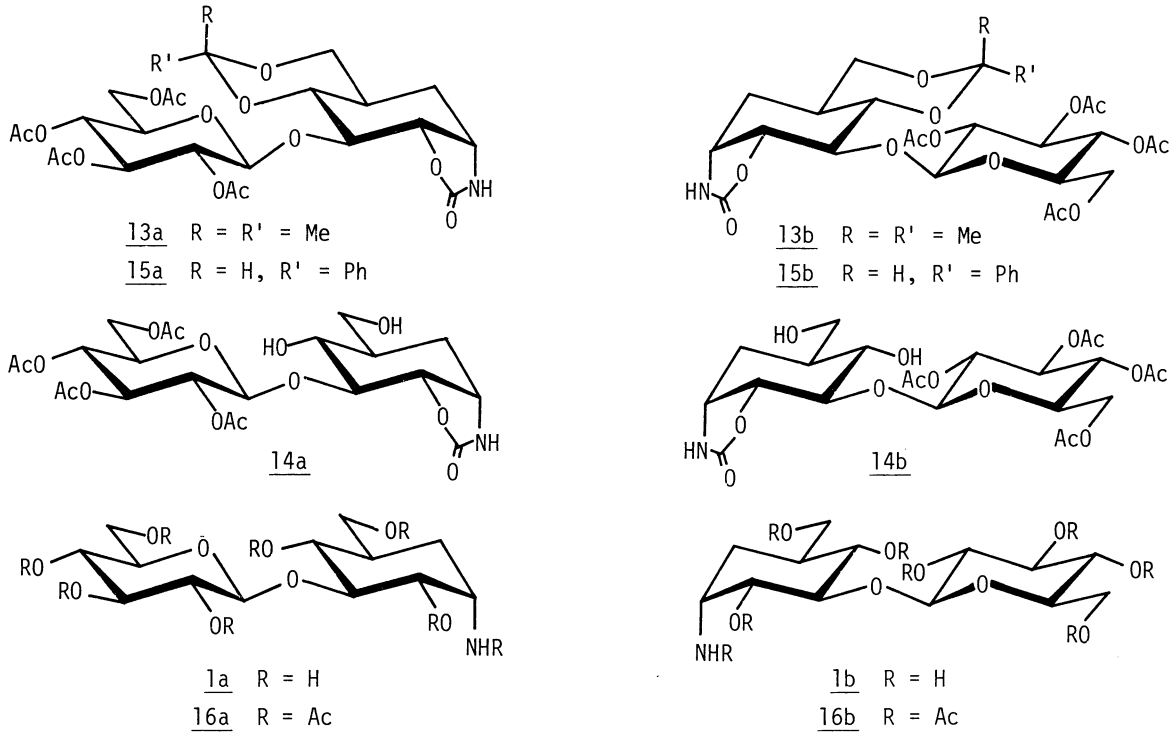
2 R = R' = Ac
3 R = R' = H, HCl
4 R = H, R' = Cbz
5 R = Ac, R' = Cbz

6 R = H
7 R = Ac

8 R = R' = H
9 R = Ac, R' = H
10 R = R' = Ac
11 R = R' = Me

12

Scheme II. Synthesis of Protected Validamine
(All the formulas depict only one of the respective racemates)



13a R = R' = Me
15a R = H, R' = Ph

13b R = R' = Me
15b R = H, R' = Ph

14a

14b

1a R = H
16a R = Ac

1b R = H
16b R = Ac

Scheme III. Synthesis of β-D-Glucopyranosylvalidamine (1a) and Its Diastereomer (1b)

glucose. The two diastereomeric β-D-glucopyranosides 1a and 1b thus obtained were hydrolyzed to give optically active validamines, which also constituted an optical resolution of racemic validamine.

Hydrolysis of penta-N,O-acetyl-DL-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (validamine) (2)[6] with boiling 6M hydrochloric acid gave the hydrochloride (3) as a syrup in quantitative yield. Treatment of 3 with benzyloxycarbonyl chloride in an alkaline solution gave crystalline N-benzyloxycarbonyl derivative (4), mp 148–150°C, which was further characterized as the tetra-O-acetyl derivative (5).[7] Compound 4 was then converted into the N,O-carbonyl derivative (6), mp 162–164°C, under the influence of 10% aqueous sodium hydroxide. The

structure of 6 was confirmed by the ^{1}H NMR spectrum of its tri-O-acetyl derivative (7), mp 133–134°C. Isopropylidenation of 6 with 2,2-dimethoxypropane in N,N-dimethylformamide (DMF) in the presence of p-toluenesulfonic acid gave the 1,7-O-isopropylidene derivative (8), mp 243–244°C, in 79% yield. The structure was supported by the ^{1}H NMR spectra of the corresponding O-acetyl (9), di-N,O-acetyl (10), and di-N,O-methyl derivatives (11). Removal of the isopropylidene group of 11, followed by acetylation, gave 1,7-di-O-acetyl-3,4-N,O-carbonyl-2,4-di-N,O-methyl-DL-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (12), mp 108–110°C, whose ^{1}H NMR spectrum was fully consistent with the assigned structure. Thus, there appeared two coupled doublets of doublets (J = 6 and 8 Hz) due to H-2 and H-3 at δ 3.36 and 4.50, respectively. Therefore, 8 was shown to be suitable for the synthesis of 1a.

Condensation of 8 with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide was conducted in a mixture of benzene and dioxane (2 : 1, v/v) in the presence of mercuric(II) cyanide and anhydrous calcium sulfate at 65°C for a week. As had been expected, formation of two new components was observed and they were clearly separated by chromatography on silica gel with 2-butanone–toluene (3 : 8, v/v) as an eluent, giving the protected β-D-glucopyranosides (13a), $[\alpha]_D$ +77.8°, and (13b), $[\alpha]_D$ -30.4°, as a syrup in 47 and 50% yields, respectively. They were shown to have four acetoxyl, one carbonyl, and one isopropylidene groups by the IR and ^{1}H NMR spectra, and their analytical data also supported the assigned structures. The β-configurations were proposed by the optical rotations and by the conditions employed for the condensation reaction. Treatment of 13a and 13b with 80% aqueous acetic acid at ambient temperature gave the corresponding dihydroxy compounds (14a), mp 180–182°C, $[\alpha]_D$ +73.4°, and (14b), mp 216–219°C, $[\alpha]_D$ -62.8°, in 44 and 76% yields, respectively. The presence of two hydroxyl groups at C-1 and C-7 was verified by their exclusive transformation into 1,7-O-benzylidene derivatives (15a), mp 240–242°C, $[\alpha]_D$ +56°, and (15b), mp 192–194°C, $[\alpha]_D$ -74°, in 74 and 66% yields, respectively, by treatment with 1,1-dimethoxy-1-phenylmethane in DMF in the presence of acid catalyst. The ^{1}H NMR spectra of 15a and 15b showed one-proton sharp singlets at δ 5.56 and 5.55, respectively, attributable to the benzylic proton. Removal of the acetyl and carbonyl groups was then carried out by treatment with boiling 10% aqueous barium hydroxide. The free bases (1a) and (1b) thus obtained as a homogeneous syrup were further characterized as the corresponding octa-N,O-acetyl derivatives (16a), $[\alpha]_D$ +9.5°, and (16b), $[\alpha]_D$ -41.7°. Acid

hydrolysis of 1a with boiling 6M hydrochloric acid gave D-glucose and validamine hydrochloride, detected by TLC on cellulose. They were acetylated in the usual way to give penta-O-acetyl-D-glucopyranose and penta-N,O-acetyl-(+)-validamine (2), $[\alpha]_D$ +60.2°, mp 146–148°C. The latter compound was identified with an authentic sample, $[\alpha]_D$ +61.6°, mp 147–149°C, prepared from (+)-validamine hydrochloride,[8,9] by comparison of their IR ($CHCl_3$) and ^1H NMR spectra, and chromatographic behavior. Penta-N,O-acetyl-(-)-validamine (2), $[\alpha]_D$ -59.8°, mp 147–149°C, was similarly obtained from 1b and identified with an authentic sample except for an optical rotation being opposite in sign. Therefore, the optical resolution of racemic validamine was accomplished by the above experiments.

Now, 1a should be the β-D-glucopyranoside, the structure of which was formerly assigned to the compound derived from validamycin A. Attempts were then made to compare 16a with an authentic sample,[8] however, unexpectedly, they were found to be completely different from each other, on the basis of ^1H and ^{13}C NMR spectra, and chromatographic behavior. Consequently, the present results were obviously incompatible with those suggested by Horii and Kameda.[2] We are on the way to get plausible evidence to determine the structure of the "β-D-glucopyranosylvalidamine."

References and Notes

1) Presented in part at The ACS/CSJ Chemical Congress: 1979, Honolulu, Hawaii, April 1979, Abstr. CARB 89.
2) T. Iwasa, H. Yamamoto, and M. Shibata, J. Antibiot., 23, 595 (1970).
3) S. Horii and Y. Kameda, J. Chem. Soc., Chem. Commun., 1972, 747.
4) S. Horii, T. Iwasa, and Y. Kameda, J. Antibiot., 24, 57 (1971).
5) The nomenclature and numbering of cyclitols used in this paper follow IUPAC and IUB tentative rules for cyclitol nomenclature [J. Biol. Chem., 243, 5809 (1968)].
6) S. Ogawa, K. Nakamoto, M. Takahara, Y. Tanno, N. Chida, and T. Suami, Bull. Chem. Soc. Jpn., 52, 1174 (1979), and references are cited in.
7) All the new compounds whose melting points and/or optical rotations were reported gave satisfactory analytical data. Unless otherwise stated, optical rotations were measured in chloroform at 20°C (c = ca. 1).
8) Authentic samples of (+)-validamine hydrochloride and β-D-glucopyranosyl-validamine were kindly supplied by Dr. Satoshi Horii.
9) The absolute configuration of (+)-validamine was established as depicted in the Scheme I by X-ray spectroscopic analysis of its hydrobromide [K. Kamiya, Y. Wada, S. Horii, and M. Nishikawa, J. Antibiot., 24, 317 (1971)].

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