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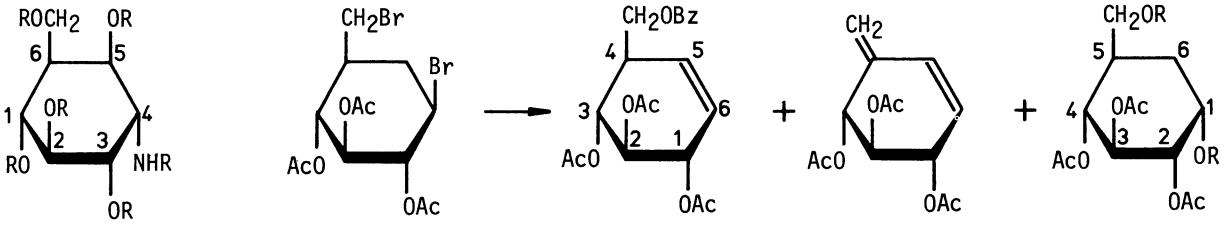
SYNTHESIS OF HEXA-N,O-ACETYL-DL-HYDROXYVALIDAMINE

Seiichiro OGAWA, Noritaka CHIDA, and Tetsuo SUAMI
Department of Applied Chemistry, Faculty of Engineering,
Keio University, Hiyoshi, Yokohama 223

DL-(1,3,4/2,5,6)-4-Amino-6-hydroxymethyl-1,2,3,5-cyclohexanetetrol (DL-hydroxyvalidamine) was first synthesized as the peracetate, which confirmed the proposed structure of the branched-chain aminocyclitol derived by hydrogenolysis of antibiotic validamycin B, followed by acid hydrolysis.

Hydrogenolysis of validamycin B,[1] an antibiotic, followed by acid hydrolysis, produces hydroxyvalidamine (1), validatol, and deoxyvalidatol.[2] The structure of 1 was tentatively assigned as 1D-(1,3,4/2,5,6)-4-amino-6-hydroxymethyl-1,2,3,5-cyclohexanetetrol,[3] on the basis of biogenetic analogy to validamine combined with ^{1}H NMR spectral data of the peracetyl derivative (2) of 1. In the present communication, we wish to report the first synthesis of racemic 2 by an unequivocal route, which also fully confirmed the proposed structure of 1.

Tri-O-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (3)[4] was used as the starting material. Treatment of 3 with 4 molar equiv. of sodium benzoate and 2 molar equiv. of lithium bromide in N,N-dimethylformamide (DMF) at 100°C for 20 h gave tri-O-acetyl-(1,3/2,4)-4-benzoyloxymethyl-5-cyclohexene-1,2,3-triol (4, mp 141–143°C, 36%) as the main product, together with smaller proportions of the known diolefin (5, ∿5%)[5] and the dibenzoate (6, syrup, ∿5%).[6] The structure of 4 was deduced by the ^{1}H NMR spectrum in which the signals for two olefinic protons appeared as a doublet of doublets (δ 5.66, J = 1.5 and 11 Hz, H-6) and a doublet of doublets of doublets (δ 5.82, J = 1.5, 2.5, and 11 Hz, H-5). Compound 6 was converted into penta-O-acetyl-(1,2,4/3,5)-5-hydroxymethyl-1,2,3,4-cylohexanetetrol (pseudo-α-glucopyranose) (7, mp 110–111°C) by deacylation (MeONa, MeOH, room temperature) followed by acetylation (Ac_2O, pyridine). The ^{1}H NMR spectrum showed five singlets (δ 1.99, 2.00, 2.03, 2.05, and 2.13) due to five acetoxyl



1 R = H
2 R = Ac

3

4

5

6 R = Bz
7 R = Ac

Fig. 1

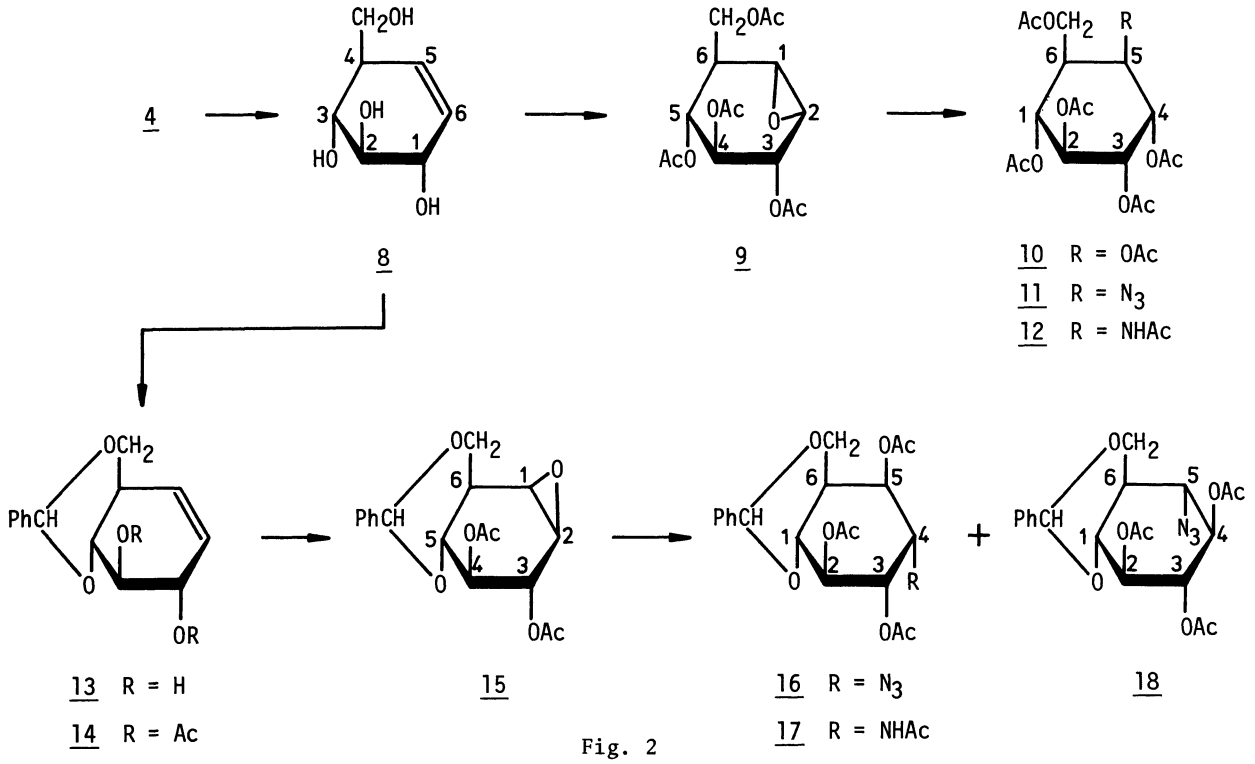


Fig. 2

groups. The presence of one axial acetoxyl group (δ 2.13)[7] at the C-1 position was supported by the appearance of a narrow quartet (δ 5.41, J = 3 Hz) attributable to equatorial H-1, being consistent with the structure assigned.

Epoxidation of 4 with m-chloroperbenzoic acid (mCPBA) in a stirred mixture of dichloroethane and phosphate buffer (1:1)[8] at 55°C for 4 d gave a 67% yield of a crystalline mixture of two stereoisomeric epoxides. Attempts to separate them either by chromatography or by fractional crystallization were unsuccessful. Therefore, the free tetrol (8) and some protected derivatives were prepared and subjected to the epoxidation reactions.[9]

Deacylation of 4 gave 8, mp 136–138°C, in 80% yield. Treatment of 8 with benzaldehyde dimethyl acetal (DMF, p-TsOH, 60°C, 20 mmHg, 1.5 h) gave the corresponding 3,7-O-benzylidene derivative (13, mp 158–160°C, 43%), which was further converted into the diacetate (14, mp 92–95°C, 75%). The ^{1}H NMR spectra of 13 and 14 were in agreement with the assigned structures (Fig. 2). As expected, epoxidation of 8 and 14 were found to proceed almost selectively to give rise to either of the corresponding isomeric epoxides, respectively. Thus, treatment of 8 with mCPBA (AcOH, room temperature, 17 h), followed by acetylation, gave the epoxy acetate (9, syrup, 78%), whose structure was tentatively assigned as tetra-O-acetyl-1,2-anhydro-(1,2,3,5/4,6)-6-hydroxymethyl-1,2,3,4,5-cyclohexanepentol. The ^{1}H NMR spectrum revealed the signals for two oxirane protons as a doublet (δ 3.20, J = 4 Hz) and a broad doublet of doublets (δ 3.44, J = 1.5 and 4 Hz), and that for the H-6 proton as a doublet of doublets of doublets (δ 2.50, J = 4.2, 4.7, and 9 Hz), supporting the structure proposed.[10] On the other hand, epoxidation of 14 (mCPBA, dichloroethane–phosphate buffer, 50°C, 66 h) gave a single epoxide (15, mp 179–182°C, 60%), the ^{1}H NMR spectrum of which showed the signals for two oxirane

protons as two doublets (J = 3.8 Hz) at δ 3.18 and 3.24, and those for the H-3 and H-4 as a doublet (J = 7.5 Hz) and a triplet (J = 7.5 Hz) at δ 5.17 and 5.26, respectively, being accord with the tentative structure shown in Fig. 2.

Hydrolysis of 9 (2-methoxyethanol, 1% sulfuric acid, reflux, 1.5 h), followed by acetylation, gave a peracetyl derivative of branched-chain cyclitol (10, mp 102–105°C, 70%). The ^{1}H NMR spectrum revealed the signals for six acetoxyl groups as five singlets at δ 1.96, 2.00, 2.01, 2.03, and 2.13 in the ratio of 1:1:1:1:2. The singlet appeared in the lowest field may be attributable to two axial acetoxyl groups, being consistent with the structure shown in Fig. 2. Hydrolysis seemed to proceed preferentially through diaxial opening of the epoxide ring.

Azidolysis of 9 (sodium azide, NH_4Cl, 90% aqueous 2-methoxyethanol, reflux, 2 h), followed by acetylation, gave a sole azido derivative (11, syrup, ∿100%): ^{1}H NMR δ=1.99 (6H, s), 2.03 (3H, s), 2.08 (3H, s), and 2.16 (3H, s) (OAc), 2.50 (1H, m, H-6), 3.95 (1H, broad t, J = 3 and 3.7 Hz, H-5), 4.10 (2H, d, J = 6.2 Hz, CH_2OAc), 4.96–5.38 (3H, m, H-1, H-2, and H-3), 5.42 (1H, dd, J = 2.3 and 3.7 Hz, H-4). The ^{1}H NMR spectral data, together with the proposed reaction mechanism involving the trans-diaxial opening of the epoxide with an azide ion, supported the structure assigned. Reduction of 11 was achieved by hydrogen sulfide [pyridine–water (1:1), room temperature, 2 h][11] to give, after acetylation, the corresponding peracetyl derivative of branched-chain aminocyclitol (12, mp 198–200°C, 58%). The similar treatment of 15 with sodium azide, followed by acetylation, gave, after chromatography on silica gel, two crystalline azido derivatives (16, mp 155–157°C, 55%) and (18, mp 160–162°C, 15%): ^{1}H NMR for 16, δ=2.04 (3H, s), 2.11 (3H, s), and 2.15 (3H, s) (OAc), 2.48 (1H, m, H-6), 3.70 (1H, t, J = 10.5 Hz, H-7ax), 3.96 (1H, dd, J = 9.8 and 10.5 Hz, H-1), 4.08 (1H, t, J = 3.3 Hz, H-4), 4.14 (1H, dd, J = 4.5 and 10.5 Hz, H-7eq), 4.94 (1H, t, J = 3 Hz, H-5), 5.22 (1H, dd, J = 3.3 and 9.8 Hz, H-3), 5.41 (1H, s, benzylic), 5.52 (1H, t, J = 9.8 Hz, H-2), 7.28–7.47 (5H, m, phenyl), and for 18, δ=2.04 (6H, s) and 2.10 (3H, s) (OAc), 3.28 (1H, broad dd, J = 9.3 and 12 Hz, H-5), 3.68 (2H, dd, J = 10.5 and 11.3 Hz, H-7ax and H-1), 4.41 (1H, dd, J = 4.8 and 11.3 Hz, H-7eq), 5.04–5.35 (3H, m, H-2, H-3, and H-4), 5.40 (1H, s, benzylic), 7.28–7.48 (5H, m, phenyl). The major product, 16, was expected to be formed by the trans-diaxial opening of the epoxide with an azide ion. The assigned structures of 16 and 18 shown in Fig. 2 were well supported by the ^{1}H NMR spectra. The similar reduction of 16 with hydrogen sulfide, followed by acetylation, gave the corresponding acetamide (17, mp 246–248°C, 80%): ^{1}H NMR δ=1.99 (3H, s), 2.02 (3H, s), 2.06 (3H, s), and 2.15 (3H, s) (NAc and OAc), 2.32 (1H, m, H-6), 3.72 (1H, t, J = 12 Hz, H-7ax), 4.00 (1H, dd, J = 9 and 10.5 Hz, H-1), 4.17 (1H, dd, J = 4.5 and 12 Hz, H-7eq), 4.47 (1H, dt, J = 3.2, 3.2, and 7.5 Hz, H-4), 5.17 (1H, dd, J = 2.6 and 3.2 Hz, H-5), 5.30 (1H, dd, J = 9 and 10.5 Hz, H-2), 5.40 (1H, dd, J = 3.2 and 10.5 Hz, H-3), 5.42 (1H, s, benzylic), 6.28 (1H, broad d, J = 7.5 Hz, NH), 7.28–7.46 (5H, m, phenyl). The spectral data confirmed the structure proposed. Hydrolytic removal of the O-benzylidene group of 17 (80% aqueous acetic acid, 80°C, 2 h), followed by acetylation, gave 2, mp 184–186°C (from ethanol–ether), in a 60% isolated yield: ^{1}H NMR δ=1.98 (3H, s), 2.00 (6H, s), 2.01 (3H, s), 2.04 (3H, s), and 2.13 (3H, s) (NAc and OAc), 2.42 (1H, m, H-6), 3.92 (1H, dd, J = 4.5 and 11 Hz) and 4.15 (1H, dd, J = 7.5 and 11 Hz) (CH_2OAc), 4.49 (1H,

broad dt, J = 3.8, 3.8, and 7.8 Hz, H-4), 5.00–5.35 (3H, m, H-1, H-2, and H-3), 5.40 (1H, t, J= 3.8 Hz, H-5), 6.16 (1H, broad d, J = 7.8 Hz, NH). This compound was identified with an authentic optically active sample except for optical activity by comparison of the ^{1}H NMR spectrum (100 MHz, Varian XL-100) with that reported by Horii and his coworkers.[2] Therefore, the present synthesis fully confirmed the assigned structure of (+)-hydroxyvalidamine (1) derived by hydrogenolysis of validamycin B.

References and Notes

1) T. Iwasa, E. Higashide, H. Yamamoto, and M. Shibata, J. Antibiot., 24, 107 (1971).
2) S. Horii, T. Iwasa, E. Mizuta, and Y. Kameda, J. Antibiot., 24, 61 (1971). Very recently, new antibiotic oligostatin C was proposed to have the branched-chain cyclitol structure correspond to hydroxyvalidamine in its molecule (S. Omoto, et al., 219th Scientific Meeting JARA, Tokyo, July 1980).
3) The nomenclature and numbering of cyclitols follow IUPAC and IUB tentative rules for cyclitol nomenclature [J. Biol. Chem., 243, 5809 (1968)].
4) S. Ogawa, K. Nakamoto, M. Takahara, Y. Tanno, N. Chida, and T. Suami, Bull. Chem. Soc. Jpn., 52, 1174 (1979).
5) S. Ogawa, T. Toyokuni, M. Omata, N. Chida, and T. Suami, Bull. Chem. Soc. Jpn., 53, 455 (1980).
6) All the compounds reported in this communication are racemic. The formulas depict only one of the respective enantiomers. Melting points were determined on Mitamura Riken micro hot stage and are uncorrected. Unless otherwise noted, ^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz) spectrometer in deuteriochloroform with reference to tetramethylsilane as an internal standard. All the new compounds gave satisfactory analytical data.
7) F. W. Lichtenthaler and P. Emig, Carbohydr. Res., 7, 121 (1968); F. W. Lichtenthaler, G. Bambach, and P. Emig, Chem. Ber., 102, 994 (1969).
8) M. Imuta and H. Ziffer, J. Org. Chem., 44, 1351 (1979).
9) It is known that in system containing the cyclohexene ring the C-3 substituent influences the direction of peracid epoxidation of the double bond. When the C-3 substituent is a hydroxyl group, the peracid attacks the double bond on the side cis to the hydroxyl substituent, which may be attributed to hydrogen bonding between the hydroxyl group and the attacking peracid. When the C-3 substituent is an acetoxyl group, epoxidation occurs preferentially trans to the C-3 substituent, probably due to steric hindrance: H. B. Henbest and R. A. L. Wilson, J. Chem. Soc., 1957, 1958.
10) In methyl 2,3-anhydropyranosides and their derivatives the coupling constant value of cis H-1 and H-2 protons is between 2.5–4.5 Hz, whereas that of the corresponding trans protons is close to zero: F. Sweet and R. K. Brown, Can. J. Chem., 46, 1481 (1968). The similar results have been observed in the derivatives of 1,2-anhydroinositols: T. Suami, S. Ogawa, S. Oki, and K. Ohashi, Bull. Chem. Soc. Jpn., 45, 2597 (1972).
11) T. Adachi, Y. Yamada, and I. Inoue, Synthesis, 1977, 45.

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