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Note

Synthesis of penta-*N,O*-acetyl-DL-validamine

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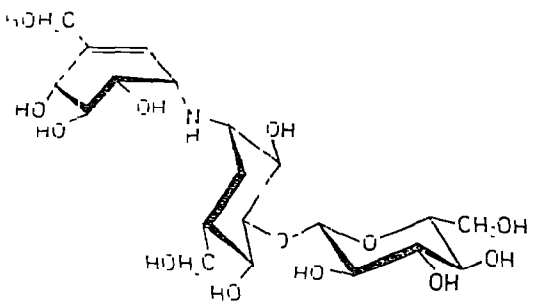
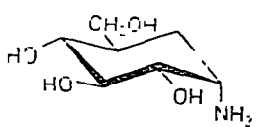
Validamine is a component of the validamycins, unique antibiotics that are produced by *Streptomyces hygroscopicus* var. *limoneus*[1–3]. Its structure has been established as 1*L*-(*1,3,4/2,6*)-4-amino-6-(hydroxymethyl)-1,2,3-cyclohexanetriol[4].

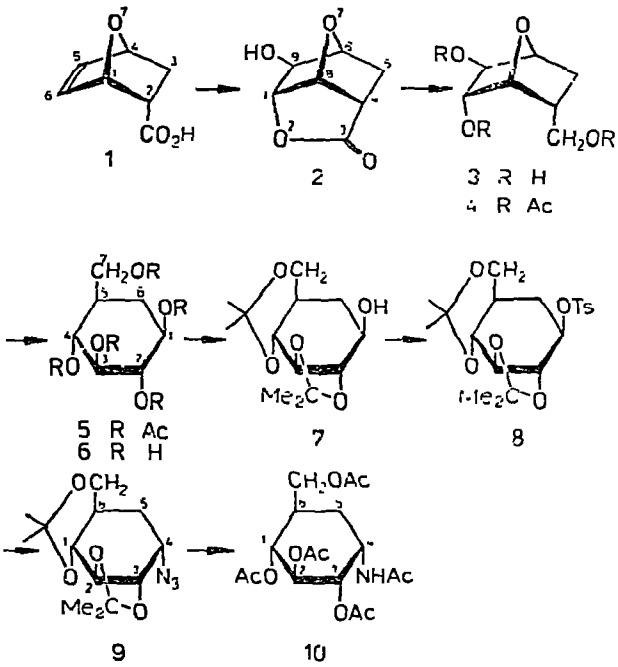


Validamycin A



Validamine

In the present note, we report a first synthesis of penta-*N,O*-acetyl-DL-validamine (**10**). Treatment of acrylic acid with furan in an atmosphere of nitrogen in the presence of hydroquinone as a polymerization inhibitor gave the known 7*endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid[5,6] (**1**). The *endo* configuration of **1** was confirmed by converting **1** into 7*endo*-oxabicyclo[2.2.1]heptane-2-carboxylic acid[6] in 92% yield



Oxidation of **1** with hydrogen peroxide in formic acid gave 9*exo*-hydroxy-2,7-dioxatricyclo[4.2.1.0^{1,8}]nonan-3-one[5] (**2**). Reduction of **2** with lithium aluminum hydride in tetrahydrofuran gave crude 5*exo*, 6*endo*-dihydroxy-2*endo*-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (**3**). Conventional acetylation of **3** afforded the tri-*O*-acetyl derivative (**4**) as a chromatographically homogeneous syrup. Compound **4** was heated in aqueous acetic acid containing conc. sulfuric acid. The product was acetylated, and purified by column chromatography to give penta-*O*-acetyl-DL-(*1,3,5/2,4*)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (**5**).

Opening of the 1,4-epoxide ring, followed by acetylation, might convert **4** into two diastereomers: compound **5** and penta-*O*-acetyl-DL-(*1,2/3,4,5*)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol[7]. The physical and spectral data observed for the product were completely different from those of the latter compound as described by McCasland and coworkers[7]. Therefore, the aforementioned configuration was assigned tentatively to **5**.

Deacetylation of **5** gave DL-(*1,3,5/2,4*)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (**6**) as a homogeneous syrup. Compound **6** was treated with 2,2-dimethoxypropane in *N,N*-dimethylformamide in the presence of *p*-toluenesulfonic acid to give a mixture of 2,3:4,7-di-*O*-isopropylidene-DL-(*1,3,5/2,4*)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (**7**) and its positional isomer, the DL-1,2:4,7-di-*O*-isopropylidene derivative, in the approximate ratio of 3:2. The mixture was tosylated in pyridine to give a crystalline mixture of the corresponding 1-sulfonate (**8**) and 3-sulfonate.

When the mixture of sulfonates was heated with sodium azide in *N,N*-dimethyl-

formamide, compound **8** was preferentially converted into 1,7:2,3-di-*O*-isopropylidene-DL-(*1,3,4/2,6*)-4-azido-6-(hydroxymethyl)-1,2,3-cyclohexanetriol (**9**). The unchanged 3-*p*-toluenesulfonate was recovered.

Catalytic hydrogenation of **9** in a hydrogen atmosphere in the presence of Raney nickel, followed by hydrolysis in 3M hydrochloric acid gave a crude hydrochloride salt. After treating the latter with Amberlite IRA-400(OH^-) resin, the resultant base was acetylated to give penta-*N,O*-acetyl-DL-validamine (**10**) as crystals. The ^{1}H-n.m.r. and i.r. spectra of **10** were superposable on those of an authentic sample[8].

EXPERIMENTAL

General methods. — Melting points were determined in capillary tubes and are uncorrected. Solutions were evaporated under diminished pressure. ^{1}H-n.m.r. spectra were recorded on a Varian A-60D spectrometer at 60 MHz in chloroform-*d*, unless otherwise noted, with tetramethylsilane as the internal standard, and the peak positions are given as δ values. I.r. spectra were recorded on a Hitachi-Perkin-Elmer 225 spectrometer. Acetylation was performed conventionally with acetic anhydride in pyridine. T.l.c. was performed on Wakogel B-10 (Wako Pure Chemical Co. Ltd.) plates. Silica gel (Wakogel C-300) was employed for column chromatography. Elemental analyses were performed by Mr. Saburo Nakada.

7endo-Oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**1**). — A mixture of acrylic acid (216 g, 3 mol) and furan (204 g, 3 mol) containing hydroquinone (0.3 g) was kept for 75 days under nitrogen. The resulting crystals were filtered off and recrystallized from ethyl acetate–ligroin to give 140 g (33%) of **1**. The filtrate gave another crop of crystals (50 g) after being kept for one month; total yield 45%; m.p. 97–100° (lit.[5] m.p. 98–99.5°). The ^{1}H-n.m.r. spectrum was superposable on that of an authentic sample reported by Nelson *et al.*[6] (*Anal.* Found: C, 59.79; H, 5.71)

Compound **1** (10 g) was hydrogenated in ethyl acetate (25 ml) over palladium black (0.1 g) for 30 min under hydrogen (3.4 kg/cm^2). The product was recrystallized from ethyl acetate–ligroin to give 9.3 g (92%) of *7endo*-oxabicyclo[2.2.1]heptane-2-carboxylic acid, m.p. 75–76°; lit.[6] m.p. 76–77°. The ^{1}H-n.m.r. spectrum was identical with that of an authentic sample reported by Nelson *et al.*[6] (*Anal.* Found: C, 59.00; H, 7.03).

9exo-Hydroxy-2,7-dioxatricyclo[4.2.1.0^{4,8}]nonan-3-one (**2**). — Compound **1** (20 g) was dissolved in 95% formic acid (38 ml), and 30% hydrogen peroxide (45 ml) was added gradually to the solution with vigorous stirring at 45°. After 5 min, the solution was steam-distilled to remove formic acid and then evaporated to give a crystalline residue. Recrystallization from aqueous ethanol gave 17 g (76%) of **2**, m.p. 112–113° (lit.[5] m.p. 115–116°): ν_{max}^{KBr} 3450 (OH) and 1790 cm^{-1} (lactone): ^{1}H-n.m.r. (D_2O): δ 2.03 (dd, 1, $J_{4,5endo}$ 3, J_{gem} 13.5 Hz, H-5*endo*), 2.31 (ddd, 1, $J_{4,5exo}$ 9.5, $J_{6,5exo}$ 4.5 Hz, H-5*exo*), 2.89 (dt, 1, $J_{4,8}$ 4.5 Hz, H-4), 4.05 (s, 1, H-9), 4.6–4.8 (m, 2, H-1 and 6), and 5.56 (dd, 1, $J_{1,8}$ 6 Hz, H-8). (*Anal.* Found: C, 53.88; H, 5.19).

5exo,6endo-Diacetoxy-2endo-(acetoxymethyl)-7-oxabicyclo[2.2.1]heptane (**4**). — To a stirred suspension of lithium aluminum hydride (0.51 g) in tetrahydrofuran (10 ml) was added a solution of **2** (2.1 g) in tetrahydrofuran (40 ml) with cooling by ice. The mixture was stirred for 15 min at 5° and then water (5 ml) was added. The resulting precipitate was filtered off and the filter cake was extracted in a Soxhlet extractor with tetrahydrofuran. The filtrate and extract were combined and evaporated to give *5exo,6endo*-dihydroxy-*2endo*-(hydroxymethyl)-7-oxabicyclo[2.2.1]heptane (**3**) as a syrup.

Compound **3** (1.8 g) was acetylated and the product was passed through a short column of alumina with chloroform. The eluate was evaporated to give **4** (2.6 g, 69%) as a syrup that showed only one spot at R_F 0.79 on t.l.c. in 2:1 (v/v) butanone–toluene; ^{1}H-n.m.r. data: δ 1.99 (s, 3, OAc), 2.03 (s, 3, OAc), 2.07 (s, 3, OAc), and 4.2–4.7 (m, 4, H-1, 4, 5, and 6).

Anal. Calc. for $C_{12}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.58; H, 6.18.

*Penta-O-acetyl-*DL-*(1,3,5/2,4)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol* (**5**). — Compound **4** (1.5 g) was heated in 80% aqueous acetic acid (375 ml) containing conc. sulfuric acid (4 ml) for 22 h under reflux. The solution was evaporated and the residue acetylated with acetic anhydride (140 ml). The product was fractionated on a column of silica gel with 1:10 (v/v) butanone–toluene as eluant. Fractions showing a single spot at R_F 0.18 on t.l.c. in the same solvent were combined and evaporated. The residue was recrystallized from ethanol to give **5** (4 g, 20%), m.p. 111–112°; ^{1}H-n.m.r. data: δ 1.99 (s, 3, OAc), 2.01 (s, 3, OAc), 2.02 (s, 6, 2 OAc), 2.05 (s, 3, OAc), 3.92–4.10 (m, 2, H-6 and 6'), and 4.85–5.23 (m, 4, H-1,2,3, and 4).

Anal. Calc. for $C_{17}H_{24}O_{10}$: C, 52.57; H, 6.23. Found: C, 52.71; H, 6.13.

*Mixture of 2,3:4,7-di-*O*-isopropylidene-1-*O*-tosyl-*DL*- (**8**) and 1,2:4,7-di-*O*-isopropylidene-3-*O*-tosyl-*DL*-(1,3,5/2,4)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol.* — Compound **5** (3.3 g) was dissolved in 0.3M methanolic sodium methoxide (30 ml). After 1 h at 70°, the solution was deionized with Amberlite IR-120(H^+) resin, and then evaporated to give DL-*(1,3,5/2,4)*-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol (**6**, 1.5 g, 97%) as a syrup. The product showed a single spot at R_t 0.75 on t.l.c. in 4:5:2 (v/v) butanol–ethanol–water.

Compound **6** (1.5 g) was treated with 2,2-dimethoxypropane (30 ml) in *N,N*-dimethylformamide (20 ml) in the presence of *p*-toluenesulfonic acid (5 mg) at 60°. After 3 h, the mixture was neutralized with solid sodium hydrogencarbonate and evaporated to give a crude syrup (2 g). T.l.c. indicated the formation of two new products [R_F 0.57 and 0.48 in the approximate ratio of 3:2 in 1:1 (v/v) butanone–toluene] that were assumed to be 2,3:4,7-di-*O*-isopropylidene-DL- (**7**) and -1,2:4,7-di-*O*-isopropylidene-DL-(*1,3,5/2,4*)-5-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol.

The mixture (2 g) was dissolved in pyridine (15 ml) and *p*-toluenesulfonyl chloride (3 g) was added to the solution. After 2 days, the mixture was poured into ice-water, and the resulting crystals were collected by filtration. Recrystallization from isopropyl alcohol gave a crystalline mixture (2.9 g, 90%) of **8** and the 3-*p*-toluenesulfonate. T.l.c. of the product showed two spots on t.l.c., at R_F 0.63 and 0.51,

in the approximate ratio of 3:2 in 1:4 (v/v) butanone–toluene. The product melted sharply at 146–147°.

Anal. Calc. for $C_{20}H_{28}O_7S$: C, 58.24; H, 6.84; S, 7.77. Found: C, 58.21; H, 6.82; S, 7.48.

*Penta-N,O-acetyl-*DL*-validamine* (**10**). — The preceding mixture of sulfonates (1.10 g) was heated with sodium azide (0.7 g) in *N,N*-dimethylformamide (55 ml) under reflux. After 2 h, the mixture was filtered and the filtrate was evaporated. T.l.c. indicated that the faster-moving sulfonate had disappeared and a new single product (R_F 0.59) had formed, whereas the slower-moving sulfonate remained at the same point in 1:4 (v/v) butanone–toluene. The residue was crystallized from isopropyl alcohol to give the unchanged 3-*p*-toluenesulfonate (0.12 g, 11%), m.p. 168–169°.

Anal. Calc. for $C_{20}H_{28}O_7S$: C, 58.24; H, 6.84; S, 7.77. Found: C, 57.98; H, 6.76; S, 7.71.

The mother liquor was evaporated to give 1,7:2,3-di-*O*-isopropylidene-DL-(*1,3,4/2,6*)-4-azido-6-(hydroxymethyl)-1,2,3-cyclohexanetriol (**9**, 0.51 g, 67%) as a crude syrup, ν_{max}^{KBr} 2140 cm^{-1} (N_3), which was shown by t.l.c. to contain a trace of the 3-sulfonate.

Compound **9** (0.4 g) in ethanol (50 ml) was hydrogenated (3.4 kg/cm^2 of hydrogen) over Raney nickel for 18 h. The product was heated in 3M hydrochloric acid (10 ml) for 1 h at 80° and the solution evaporated. The product was treated with Amberlite IRA-400(OH^-) resin and then acetylated for 2 days. The acetylation product was recrystallized repeatedly from ethanol to give **10** (153 mg, 28%) as crystals, m.p. 197–198°. The ^{1}H-n.m.r. and i.r. spectra (in $CHCl_3$) were superposable on those of an authentic sample derived from (+)-validamine hydrochloride that had kindly been supplied by Dr. Satoshi Horii.

Anal. Calc. for $C_{17}H_{25}NO_9$: C, 52.71; H, 6.51; N, 3.62. Found: C, 52.85; H, 6.59; N, 3.53.

REFERENCES

1 T. Iwasa, H. Yamamoto, and M. Shibata, *J. Antibiot.*, 23 (1970) 595–602.
2 T. Iwasa, Y. Kameda, M. Asai, S. Horii, and K. Mizuno, *J. Antibiot.*, 24 (1971) 119–123.
3 S. Horii, Y. Kameda, and K. Kawahara, *J. Antibiot.*, 25 (1972) 48–53.
4 S. Horii, T. Iwasa, E. Mizuta, and Y. Kameda, *J. Antibiot.*, 24 (1971) 59–63.
5 M. P. Kunstman, D. S. Tarbell, and R. L. Autrey, *J. Am. Chem. Soc.*, 84 (1962) 4115–4125.
6 W. L. Nelson and D. R. Allen, *J. Heterocycl. Chem.*, 9 (1972) 561–568.
7 G. E. McCasland, S. Furuta, and L. J. Durham, *J. Org. Chem.*, 33 (1968) 2841–2844.