THIOVALIDAMINE DERIVATIVES OF *manno*- AND *gluco*-TYPE: REMOTE ACTIVATION AND ANCHIMERIC ASSISTANCE

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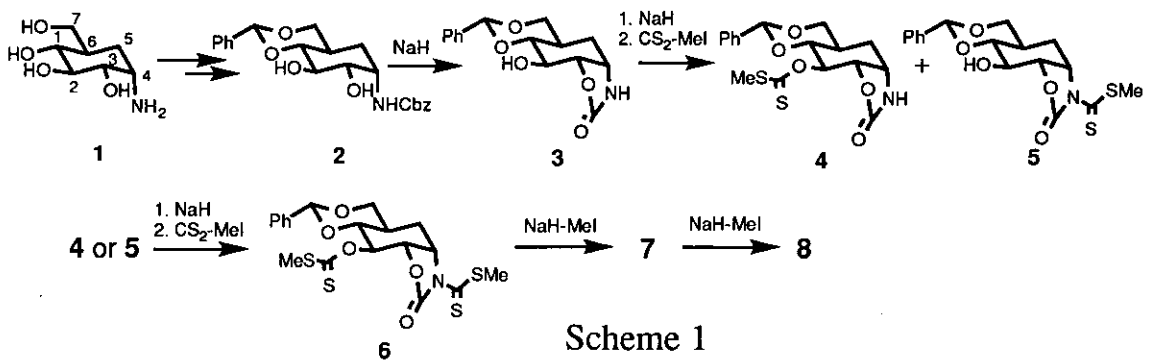
Abstract – The oxazolidone (**3**) derived from validamine (**1**) was dithiocarbonylated, on treatment with NaH followed by CS_2-MeI, to the *N,O*-dicarbodithioate (**6**). On treatment with NaH-MeI, this afforded the *manno*-type thiovalidamine derivative (**7**) and then the *gluco*-type thiovalidamine derivative (**8**) following the pathway shown in Scheme 2: an activation at a C=S group by methylation, transferring this activation to a remote position accompanied with decarboxylation, and cyclization of the neighboring group to the transferred position (C-3).

Validamine (**1**), one of the sugar component of validamycin, is attracting attentions by its physiological actions such as glucosidase inhibitory activity.[1] Thiovalidamine, in which one of the hydroxyl groups in validamine is substituted by a thiol group, is also an attractive compound, but has no precedent. In this paper, we show a facile synthesis of two thiovalidamine derivatives. The principal part of this synthetic method is constituted by a series of successive reactions on a cyclitol ring, in which an activation at a remote position initiates the reaction and the following reactions are assisted by anchimeric participation of a

neighboring group.

1,7-*O*-Benzylidene-*N*-carbobenzyloxy derivative (**2**)[1] of validamine smoothly gave the oxazolidone derivative (**3**) on treatment with NaH. Both **2** and **3** afforded, on further treatment with NaH followed by CS_2-MeI at room temperature in THF, four compounds, **4** (colorless needles, mp 202-203°C), **5** (yellow oil), **6** (yellow prisms, mp 162-165°C), and **7** (pale yellow prisms, mp 162-164°C), whose yields and ratios were dependent on the reaction conditions. Compounds (**4**) and (**5**) were the mono-carbodithioates of *O* and *N*, respectively, since they had the same molecular formula (M^+, *m/z* 381) and had SMe and C=S groups in the ^{1}H- and ^{13}C-nmr spectra. The H-2 signals appeared at δ 6.44 in **4** and at δ 3.87 in **5**, revealing that **4** is the *O*-carbodithioate and **5** is the *N*-carbodithioate. Further treatment of either **4** or **5** with the same reagents gave the same *O, N*-dicarbodithioate which was identical with compound (**6**), whose structure was confirmed by its formula ($C_{19}H_{21}NO_5S_4$) and the spectral data (two SMe and two C=S groups).[2]



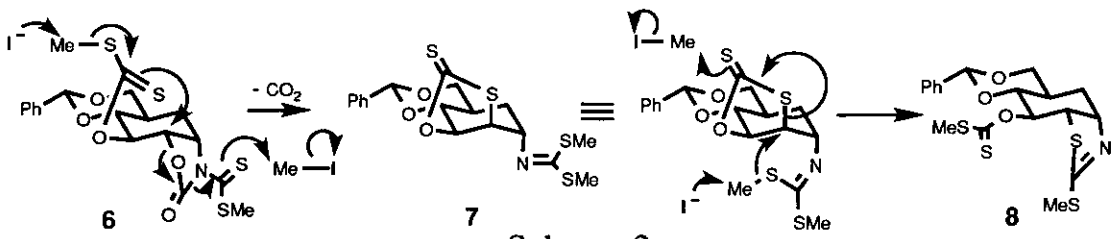
Scheme 1

Compound (**7**) was analyzed as $C_{18}H_{21}NO_3S_4$ and exhibited two SMe groups in the ^{1}H-nmr spectrum, but the absorption of an oxazolidone in the ir spectrum was lacking. Its unique structure was established by a single crystal X-ray analysis. In accord with this structure, treatment of compound (**6**) with NaH-MeI afforded compound (**7**) in a good yield. The ^{13}C-nmr spectrum of **7** showed signals of C=S and C=N at δ 209.6 and 161.7, respectively.

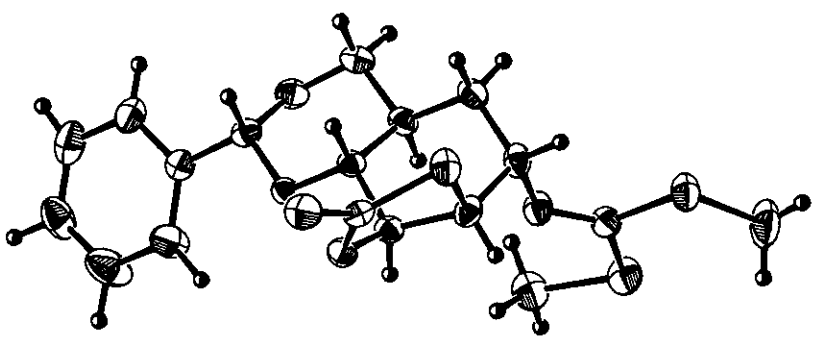
On further treatment with NaH-MeI in THF, compound (**7**) isomerized into a different compound (**8**) (colorless prisms, mp 198-199°C) in 84% yield, which showed two SMe peaks together with the H-2 signal at δ 6.14 in the ^{1}H-nmr spectrum. The ^{13}C-nmr signals at δ 167.3 and 217.2 indicated the presence of C=N and C=S, respectively. Since the coupling pattern of the cyclitol ring moiety of **8** was very similar to that of **3**, the structure of **8** was assigned as

depicted in Scheme 2.

The above transformations are explained as shown in Scheme 2, which suggests an interesting remote activation and anchimeric participation. For compound (**7**), the thiocarbonyl group in the *N*-carbodithioate of **6** is initially activated by an *S*-methylation on the C=S group. Then, the strong electron withdrawing effect of $\rangle C{=}\overset{+}{S}\text{-}Me$ is transferred to the remote position (C-3) through the oxazolidone ring accompanying decarboxylation, where the neighboring C=S group cyclizes with liberating a methyl group, thus affording the thiovalidamine derivative of *manno*-type (**7**).[3] For compound (**8**), the reverse process may have been taken place. An activation of C=S in the *O*-carbodithioate of **7** followed by substitution at C-3 by one of the SMe groups again liberating a methyl group reformed thiovalidamine derivative of *gluco*-type (**8**).[3]



Scheme 2



ORTEP Drawing of Compound (**7**)

EXPERIMENTAL

The Oxazolidone Derivative (3)

The 1,7-*O*-benzylidene-*N*-Cbz derivative(**2**)(2 g, 5.0 mmol) and NaH (60% oil dispersion, 782 mg, 6.5 mol eq) in THF (80 ml) were stirred for 1 h under reflux. The cooled mixture was neutralized with AcOH, THF was evaporated *in vacuo*, and the resulting solution was passed

through a Diaion HP-20 column. Elution of the column with MeOH gave **3** (1.27 g, 87%). It was dimorphic when crystallized from AcOEt, colorless plates of mp 189-192°C and colorless prisms of mp 214-215°C. Ir (KBr): 1773, 1682 cm^{-1}. ^{1}H-Nmr (500 MHz, acetone-d_6) δ: 1.46 (1H, ddd, *J*=4.6, 12.8, 17.4 Hz, H-5a), 1.87 (1H, ddd, *J*=1.8, 3.6, 17.4 Hz, H-5e), 2.04 (1H, m, H-6), 3.48 (1H, t, *J*=10.1 Hz, H-1), 3.65 (1H, t, *J*=11.3 Hz, H-7a), 3.79 (1H, ddd, *J*=1.0, 7.3, 10.1 Hz, H-2), 4.15 (1H, dd, *J*=4.6, 11.3 Hz, H-7e), 4.23 (1H, m, H-4), 4.42 (1H, t, *J*=7.3 Hz, H-3), 4.80 (1H, br s, NH or OH), 5.59 (1H, s, PhCH), 6.45 (1H, s, OH or NH), 7.34-7.51 (5H, m, Ph-H). Ei-Ms *m/z* : 291 (M^+, 67%). *Anal.* Calcd for $C_{15}H_{17}NO_5$: C, 61.85; H, 5.88; N, 4.81. Found: C, 61.82; H, 5.90; N, 4.77.

Reaction of the Diol (2) with NaH-CS_2-MeI

(1) A mixture of **2** (100 mg, 0.25 mmol), NaH (60% oil dispersion, 66 mg, 6.5 mol eq), and imidazole (3 mg, 0.2 mol eq) in THF (15 ml) was heated under reflux for 30 min, then CS_2 (2 ml, excess) was added. After stirring the mixture at room temperature for 5 min, MeI (2 ml, excess) was added and the whole was stirred for further 30 min at the same temperature. The mixture was neutralized with AcOH, concentrated to dryness, and the residue was extracted with AcOEt. The extract was washed with saturated solution of $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. Chromatography of the residue gave **6** (32 mg, 32%) and **7** (39 mg, 36%) from the hexane-AcOEt (2:1) eluate and **4** (30 mg, 32%) from the AcOEt eluate.

(2) Another run (treatment with NaH for 5 min at room temperature, then the same as above) gave **5** (19%), **6** (25%), and **7** (53%).

Reaction of the Oxazolidone (3) with NaH-CS_2-MeI

(1) Treatment of **3** (500 mg) as described above gave **6** (138 mg, 17%), **7** (149 mg, 20%), **4** (56 mg, 12%), and **5** (56 mg, 12%) together with a recovery of **3** (49 mg, 10%).

(2) Treatment of **3** (84 mg) as described (2) for the diol (**2**) gave **6** (49 mg, 36%), **7** (5 mg, 4%), and **4** (23 mg, 29%).

Compound (**4**): Colorless needles from acetone, mp 202-203°C. Ir ($CHCl_3$): 1774 cm^{-1}. ^{1}H-Nmr (500 MHz, $CDCl_3$) δ: 1.38 (1H, ddd, *J*=3.9, 13.2, 15.1 Hz, H-5a), 1.61 (1H, m, H-6), 1.84-1.89 (1H, m, H-5e), 2.59 (3H, s, SMe), 3.62 (1H, t, *J*=11.2 Hz, H-7a), 3.69 (1H, t, *J*=10.3 Hz, H-1), 4.24 (1H, dd, *J*=4.9, 11.2 Hz, H-7e), 4.31 (1H, m, H-4), 4.71 (1H, t, *J*=7.3 Hz, H-3), 5.51 (1H, s, PhCH), 5.55 (1H, br s, NH), 6.44 (1H, dd, *J*=7.3, 10.3 Hz, H-2), 7.31-7.45 (5H, m, Ph-H). Ei-

Ms *m/z* : 381 (M^+, 6%).

Compound (**5**): Yellow oil. Ir ($CHCl_3$): 1773 cm^{-1}. ^{1}H-Nmr (500 MHz, $CDCl_3$) δ: 1.34 (1H, ddd, *J*=5.4, 13.2, 16.1 Hz, H-5a), 1.79-1.82 (1H, m, H-6), 2.60 (3H, s, SMe), 2.67 (1H, ddd, *J*=2.0, 3.9, 16.1 Hz, H-5e), 3.41 (1H, t, *J*=9.3 Hz, H-1), 3.46 (1H, t, *J*=11.2 Hz, H-7a), 3.87 (1H, dd, *J*=6.4, 9.3 Hz, H-2), 4.09 (1H, dd, *J*=4.4, 11.2 Hz, H-7e), 4.60 (1H, dd, *J*=6.4, 7.8 Hz, H-3), 4.95 (1H, ddd, *J*=2.0, 5.4, 7.8 Hz, H-4), 5.47 (1H, s, PhCH), 7.29-7.41 (5H, m, Ph-H). Ei-Ms *m/z*: 381 (M^+, 81%).

Compound (**6**): Yellow prisms from AcOEt-hexane, mp 162-165°C. Ir ($CHCl_3$): 1771 cm^{-1}. ^{1}H-Nmr (500 MHz, $CDCl_3$) δ: 1.56-1.68 (1H, m, H-5e), 1.60 (1H, ddd, *J*=6.8, 13.6, 15.6 Hz, H-5a), 2.29-2.39 (1H, m, H-6), 2.53, 2.57 (each 3H, s, SMe), 3.58 (1H, t, *J*=11.2 Hz, H-7a), 3.94 (1H, dd, *J*=6.4, 11.2 Hz, H-1), 4.23 (1H, dd, *J*=4.4, 11.2 Hz, H-7e), 4.94 (1H, dd, *J*=2.9, 7.3 Hz, H-3), 5.35 (1H, br t, *J*=6.4 Hz, H-4), 5.55 (1H, s, PhCH), 6.20 (1H, dd, *J*=2.9, 6.4 Hz, H-2), 7.34-7.46 (5H, m, Ph-H). Ei-Ms *m/z* : 471 (M^+, 2%). *Anal.* Calcd for $C_{19}H_{21}NO_5S_4$: C, 48.41; H, 4.49; N, 2.97. Found: C, 48.50; H, 4.58; N, 2.97.

Compound (**7**): Pale yellow prisms from AcOEt-hexane, mp 162-164°C. ^{1}H-Nmr (500 MHz, $CDCl_3$) δ: 1.55 (1H, br td, *J*=3.8, 13.7 Hz, H-5e), 1.72 (1H, ddd, *J*=3.7, 12.8, 13.7 Hz, H-5a), 2.47 (1H, m, H-6), 2.36, 2.59 (each 3H, s, SMe), 3.68 (1H, t, *J*=11.0 Hz, H-7a), 4.21 (3H, m, H-1,4,7e), 4.45 (1H, dd, *J*=2.8, 7.3 Hz, H-3), 5.34 (1H, dd, *J*=7.3, 8.3 Hz, H-2), 5.63 (1H, s, PhCH), 7.33-7.54 (5H, m, Ph-H). ^{1}H-Nmr (500 MHz, benzene-d_6) δ: 1.00 (1H, dtd, *J*=1.0, 3.9, 13.7 Hz, H-5e), 1.16 (1H, ddd, *J*=3.9, 12.2, 13.7 Hz, H-5a), 1.88, 2.04 (each 3H, s, SMe), 2.11-2.20 (1H, m, H-6), 3.02 (1H, t, *J*=10.7 Hz, H-7a), 3.60 (1H, dd, *J*=3.9, 6.6 Hz, H-3), 3.71 (1H, dd, *J*=4.4, 10.7 Hz, H-7e), 3.83 (1H, dd, *J*=8.3, 10.3 Hz, H-1), 3.90 (1H, td, *J*=3.9, 12.2 Hz, H-4), 4.91 (1H, dd, *J*=6.6, 8.3 Hz, H-2), 5.21 (1H, s, PhCH), 7.11-7.65 (5H, m, Ph-H). Ei-Ms *m/z* : 427 (M^+, 12%). *Anal.* Calcd for $C_{18}H_{21}NO_3S_4$: C, 50.59; H, 4.95; N, 3.28. Found: C, 50.80; H, 5.01; N, 3.31. Crystal data: Orthorhombic, *a*=10.960 Å, *b*=21.329 Å, *c*=8.76 Å. Space group, $P2_12_12_1$. *Z*=4. *R*=0.03. The other parameters are available on request to the authors.

Transformations of Compound (4) and Compound (5) to Compound (6)

Compounds (**4**) and (**5**) (each 13 mg) were separately treated with NaH-CS_2-MeI as described above in (1), and the product was monitored by tlc. Compound (**4**) changed to **6** after 0.5 h and then to a mixture of **6** and **7** after 1 h. Compound (**5**) changed to a mixture of **6**

and **7** after 3.5 h of the reaction.

Reaction of Compound (6) with NaH-MeI

A mixture of **6** (5 mg, 11 μmol), NaH (60% oil dispersion, 4 mg, 6.5 mol eq), and MeI (0.2 ml, excess) in THF (1 ml) was stirred at room temperature with periodical monitoring by tlc. After 2 h, the spot of **6** disappeared and a new spot identical with that of **7** appeared. Work-up of the product as described above gave compound (**7**) (3 mg, 66%).

Reaction of Compound (7) with NaH-MeI

A mixture of **7** (50 mg, 120 μmol), NaH (60% oil dispersion, 34 mg, 6.5 mol eq), and imidazole (1 mg, 0.2 mol eq) in THF (15 ml) was stirred under reflux for 0.5 h, then CS_2 (2 ml, excess) was added. After stirring the mixture at room temperature for 5 min, MeI (2 ml, excess) was added and the mixture was stirred for further 15 h at the same temperature. The mixture was neutralized with AcOH and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ solution, brine, dried, and concentrated. Chromatography of the residue afforded compound (**8**) (42 mg, 84%) from the benzene-AcOEt eluate with a recovery of **7** (6 mg, 12%). Treatment of **7** (6 mg, 14 μmol) with NaH (60% oil dispersion, 5 mg, 6.5 mol eq, room temperature, 35 min) in THF (5 ml) followed by MeI (0.1 ml, excess, room temperature, 2 h) showed that the conversion of **7** to **8** proceeded without CS_2 and completed within 2 h. Compound (**8**) formed colorless prisms from AcOEt, mp 198-199°C. ^{1}H-Nmr (500 MHz, $CDCl_3$) δ: 1.97-2.10 (2H, m, H-5), 2.25-2.34 (1H, m, H-6), 2.52, 2.61 (each 3H, s, SMe), 3.72 (1H, t, *J*=11.2 Hz, H-7a), 4.16-4.21 (2H, m, H-3,4), 4.27 (1H, dd, *J*=5.9, 12.2 Hz, H-1), 4.35 (1H, dd, *J*=4.9, 11.2 Hz, H-7e), 5.54 (1H, s, PhCH), 6.14 (1H, t, *J*=5.9 Hz, H-2), 7.34-7.47 (5H, m, Ph-H). ^{1}H-Nmr (500 MHz, benzene-d_6) δ: 1.40 (1H, ddd, *J*=8.3, 9.8, 13.2 Hz, H-5a), 1.50 (1H, ddd, *J*=9.3, 10.7, 13.2 Hz, H-5e), 1.60-1.70 (1H, m, H-6), 2.09, 2.14 (each 3H, s, SMe), 2.96 (1H, t, *J*=11.2 Hz, H-7a), 3.62 (1H, dd, *J*=5.9, 14.7 Hz, H-3), 3.76 (1H, dd, *J*=4.9, 11.2 Hz, H-7e), 3.81 (1H, dd, *J*=5.9, 12.2 Hz, H-1), 4.03 (1H, ddd, *J*=8.3, 10.7. 14.7 Hz, H-4), 5.16 (1H, s, PhCH), 6.24 (1H, t, *J*=5.9 Hz, H-2), 7.06-7.59 (5H, m, Ph-H). Ei-Ms *m/z* : 427 (M^+, 8%). *Anal.* Calcd for $C_{18}H_{21}NO_3S_4$: C, 50.59; H, 4.95; N, 3.28. Found: C, 50.48; H, 5.08; N, 3.23.

^{13}C-Nmr Data

	3	4	5	6	7	8
C1	81.7	79.0	80.8	80.6	79.3	80.6
C2	75.1	81.8	74.4	80.0	89.8	80.5
C3	83.8	78.6	78.8	75.8	54.9	57.7
C4	53.3	52.5	58.5	58.0	55.8	70.9
C5	26.3	25.8	24.6	26.4	26.6	27.3
C6	32.4	31.0	30.9	30.5	31.4	30.8
C7	71.4	70.3	70.4	70.8	70.6	70.9
PhC<u>H</u>	102.3	101.1	101.9	101.8	101.6	101.4
C=O	160.5	158.8	152.2	150.9		
C=S		215.7	204.6	202.3	209.6	217.2
				214.9		
C=N					161.7	167.3
SMe		19.5	20.7	19.7	14.6	14.6
				20.7	14.3	19.2

REFERENCES AND NOTES

1. S. Horii, H. Fukase, T. Matsuo, Y. Kameda, N. Asano, and K. Matsui, *J. Med. Chem.*, 1986, **29**, 1038.
2. The ^{1}H-nmr spectrum suggested that this compound is markedly distorted from the typical chair conformation.
3. The terms, *gluco* and *manno*, are used on analogy of the corresponding carbohydrate series.

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