CONVERSION OF DIHYDRO-1,4-OXATHIIN-3-CARBOXAMIDE TO THE ISOMERIC DIHYDRO-1,4-OXATHIIN-2-CARBOXAMIDE

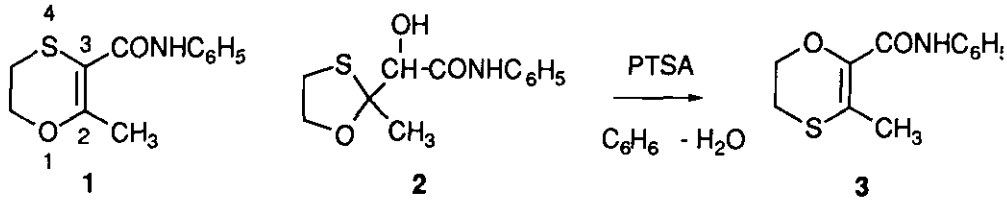
Hoh-Gyu Hahn,* Kee-Hyuk Chang, and Wha Suk Lee

Organic Chemistry Lab, Korea Institute of Science and Technology, P. O. Box 131, Cheongryang, 130-650, Seoul, Korea

Abstract --- The preparation of isomeric dihydro-1,4-oxathiin (**3**) from the dihydro-1,4-oxathiin (**1**) *via* dichloro-1,4-oxathiane (**4**) is described. Chlorination of **1** followed by treatment of the resulting dichloride (**4**) with aqueous acetone gave dihydroxy-1,4-oxathiin (**5**). The solvolysis to produce intermediate chlorohydrin (**11**) was favored relative to elimination reaction to give exomethylene compound (**8**). Dehydration of **5** followed by reduction afforded α-hydroxy-1,3-oxathiolane (**2**) which is a key compound to prepare the isomeric dihydro-1,4-oxathiin (**3**). The reason for more facile displacement of chlorine at C-2 in comparison with that at C-3 in **4** was also discussed.

INTRODUCTION

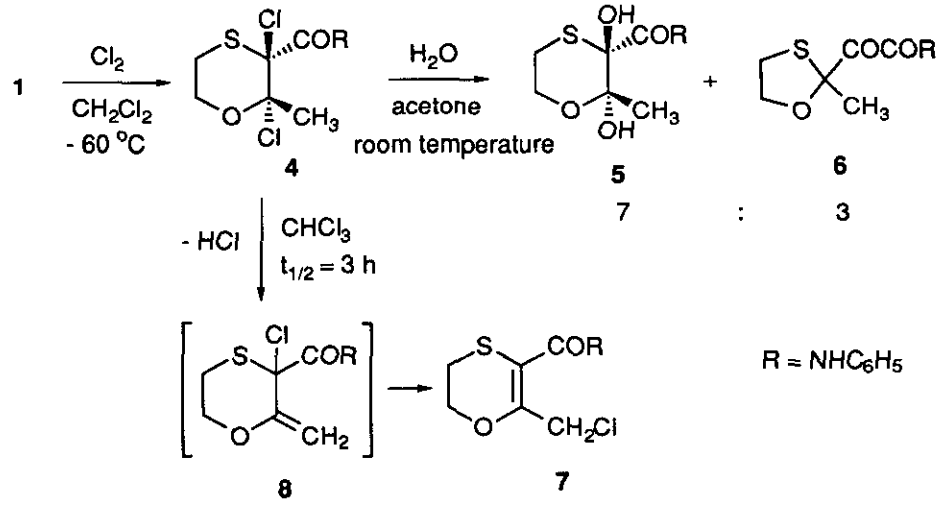
5,6-Dihydro-*N*-phenyl-1,4-oxathiin-3-carboxamide (**1**) is a well-known systemic fungicide used for seed treatment.[1] We previouly prepared the isomer of **1** with O and S transposed by the acid catalyzed rearrangement of α-hydroxy-1,3-oxathiolane (**2**).[2] We now report the conversion of the dihydro-1,4-oxathiin (**1**) to the isomeric dihydro-1,4-oxathiin (**3**).



1 **2** **3**

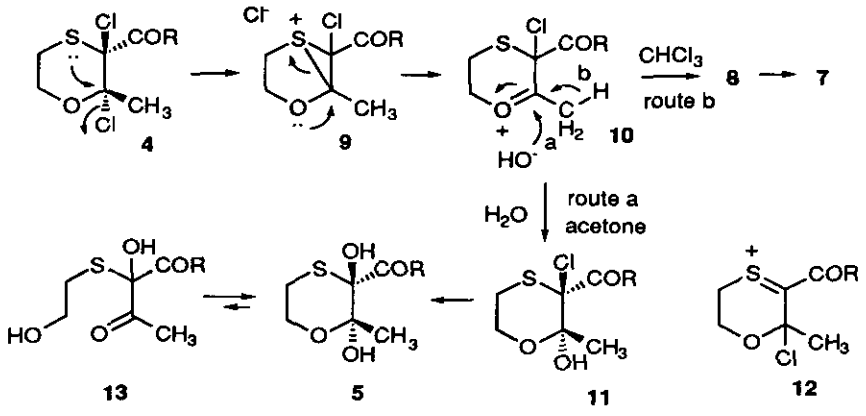
RESULTS AND DISCUSSION

The starting dihydro-1,4-oxathiin (**1**) was obtained by the previous method.[3] Chlorination of **1** was carried out in a methylene chloride solution at -60 °C to ambient temperature to give dichloro-1,4-oxathiane (**4**).[4] As shown in Scheme 1, treatment of **4** with aquous acetone at room temperature gave a 7:3 mixture of dihydroxy-1,4-oxathiane (**5**) and 1,3-oxathiolane (**6**) in high yields (92%), while **4** was gradually ($t_{1/2}$ = 3 h) converted to chloromethyl compound (**7**) *via* exomethylene derivative (**8**) in a chloroform solution at room temperature as reported previously.[2]



Scheme 1

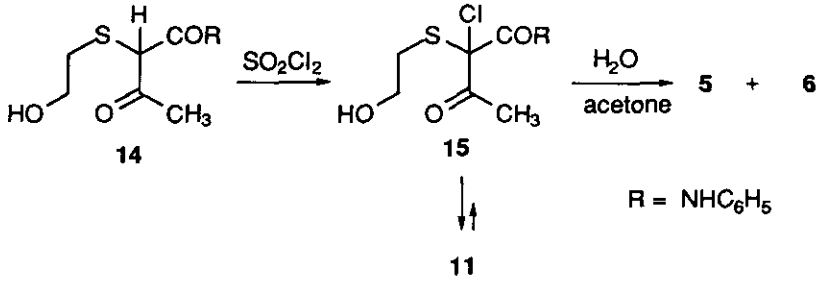
It appeared likely that the unexpected 1,3-oxathiolane (**6**) came from dihydroxy-1,4-oxathiane (**5**) by the acid catalyzed dehydration, which will be discussed later. The sulfur in **4** is postulated to attack the anomeric carbon of the halo ether to give a thiiranium ion (**9**) which would open to more stable oxonium ion (**10**) (Scheme 2). A possible intermediate chlorohydrin (**11**) was formed by the attack of hydroxide ion from the less hindered direction at C-2 position of **10**. In an aqueous acetone solution, solvolysis to produce **11** (route a) was favored relative to elimination reaction to give exomethylene compound (**8**) (route b). Thus, aqueous acetone rendered the solvolysis reaction more effective. Likewise, the second hydroxy group would be introduced at C-3 in **11** to form **5** in which bulky carboxanilide group is in equatorial position.



R = NHC_6H_5

Scheme 2

The reason for more facile displacement of chlorine atom by the hydroxyl group at C-2 in comparison with that at C-3 in **4** is attributable to at least three factors. First, C-2 chlorine atom is easily displaced by the neighboring group participation of sulfur[6] to form **9**. Second, C-2 carbon is anomeric.[7] Third, the formation of thiiranium ion (**12**) would not readily be formed due to the neighboring carbonyl group. The dihydro-1,4-oxathiane (**5**) was a white crystalline solid as a 3:7 mixture of α-hydroxy ketone (**13**) and 2,3-diol (**5**) in equilibrium respectively, as shown by ^1H nmr spectrum. Thus, the chemical shifts of methyl protons showed singlet at δ 1.46 ppm for **5**, and δ 2.63 ppm for **13**. The hydroxy protons appeared as a singlet at δ 4.39 ppm (tertiary OH) and as a triplet at δ 4.75 ppm (primary OH) in **13**, and as two singlets at δ 2.22 and 5.85 ppm in **5**, of which hydrogens were exchanged with deuterium by addition of deuterium oxide. The elemental analysis fitted the empirical formula $C_{12}H_{15}NO_4S$. The intermediate chlorohydrin (**11**) was also obtained by an independent synthesis (Scheme 3).

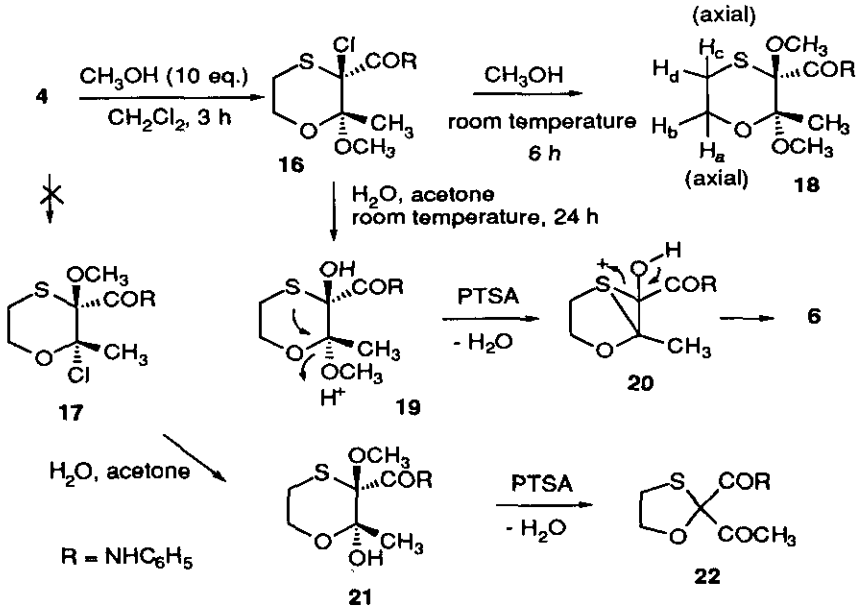


R = NHC_6H_5

Scheme 3

Thus, reaction of β-hydroxy sulfide (**14**) obtained from known method[8] with sulfuryl chloride gave a mixture of α-chloride (**15**) (major) and its tautomer the chlorohydrin (**11**) (minor) in equilibrium as shown by ^{1}H nmr spectrum. As expected, **15** was transformed to a 1:1 mixture of dihydroxy-1,4-oxathiane (**5**) and 1,3-oxathiolane (**6**) in aqueous acetone solution.

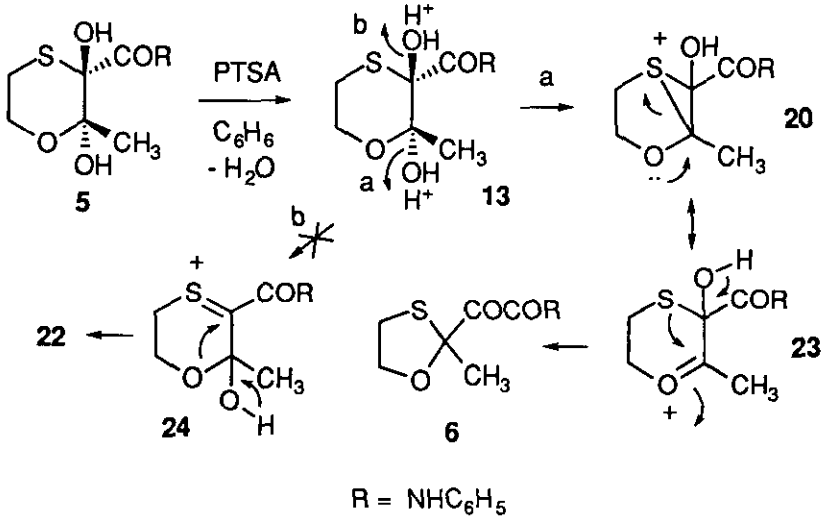
In order to confirm the reaction pathway, dichloro-1,4-oxathiane (**4**) was allowed to react with excess methanol (10 equivalents) in a methylene chloride solution at room temperature (Scheme 4). When the reaction was quenched after 3 h, 3-chloro-2-methoxy-1,4-oxathiane (**16**) was produced rather than **17**. Stirring of **16** in a methanol solution at room temperature for 6 h gave dimethoxy-1,4-oxathiane (**18**),[9] whereas the same reaction in an aqueous acetone solution for 24 h afforded 3-hydroxy-2-methoxy-1,4-oxathiane (**19**). The structures of compounds (**18**) and (**19**) were proven by ^{1}H nmr spectroscopy and elemental analysis. Thus, in the ^{1}H nmr spectra, the C-2 and C-3 methoxy protons in **18** showed singlets at δ 3.37 and 3.62 ppm respectively, while the methoxy and hydroxy protons in **19** showed respective singlets at δ 3.50 ppm and at δ 5.16 ppm. The four protons at C-5 and C-6 in **18** showed an ABCD spin system. The chemical shifts δ 4.11 for H_a(axial), 3.87 for H_b(equatorial), 3.01 for H_c(axial), 2.26 for H_d(equatorial), and coupling constants (geminal and vicinal) of the methylene protons, J_{ab} = 11.8 Hz, J_{ac} = 12.5 Hz, J_{ad} = 2.3 Hz, J_{bc} = 3.5 Hz, J_{bd} = 2.1 Hz, and J_{cd} = 13.6 Hz were in agreement with the structure of the dimethoxy-1,4-oxathiane (**18**) (see Scheme 4).



Scheme 4

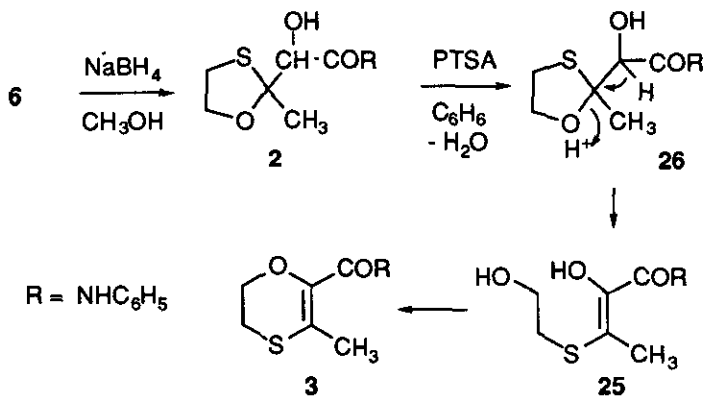
The ^{13}C nmr of **18** had the right number of signals for a single compound. We proposed the conformation of **18** in which the bulky carboxanilide group is in equatorial position. The elemental analysis of **18** fitted the empirical formula $C_{14}H_{19}NO_4S$. Further proof of the structure of **19** was given by its conversion to 1,3-oxathiolane (**6**) probably *via* **20** under the acid catalyzed dehydration. This results demonstrated the structure of 3-hydroxy-2-methoxy-1,4-oxathiane (**19**) rather than 2-hydroxy-3-methoxy-1,4-oxathiane (**21**) which might produce **22**.

As shown in Scheme 5, dehydration of **5** in benzene solution in the presence of acid catalyst (*p*-toluenesulfonic acid monohydrate, PTSA) gave 1,3-oxathiolane (**6**)[9] *via* the plausible intermediate thiiranium ion (**20**) by protonation on hydroxy group at C-2. For the similar reasons as discussed above regarding neighboring group participation of sulfur, anomeric carbon and relative carbocation stability due to neigboring carbonyl group, oxonium ion (**23**) (route a) may be formed in preference to **24** (route b). As a result, rearrangement of **23** gave 1,3-oxathiolane (**6**).



Scheme 5

Reduction of 1,3-oxathiolane (**6**) with sodium borohydride gave a key intermediate α-hydroxy-1,3-oxathiolane (**2**) in the preparation of isomeric dihydro-1,4-oxathiin (**3**) (Scheme 6). Thus, acid catalyzed dehydration of **2** gave **3** in high yields *via* possible intermediate (**25**) by the ring opening of protonated 1,3-oxathiolane (**26**) as reported previously.[2] It is interesting that dichloro-1,4-oxathiane (**4**) could be converted at will either to chloromethyl compound (**7**) or to 1,3-oxathiolane (**6**) by choice of reaction conditions.



Scheme 6

EXPERIMENTALS

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. The ir spectra were recorded on an Analect FX 6160 spectrophotometer. All ^{1}H and ^{13}C nmr spectra were recorded on either a Varian EM 360 at 60 MHz, or Varian Gemini 300 spectrometer at 300 and 78.5 MHz, respectively, with tetramethylsilane as an internal standard and are reported in δ units. Mass spectra were recorded on a JEOL JMS-DA 303 mass spectrometer, equipped with JMA-DA 5000 data system. Elemental analyses of new compounds were performed by a Perkin Elmer 240 DS analyzer. All chromatographic isolations were accomplished by Kieselgel GF 254 (230-400 mesh) silica gel.

Preparation of 2,3-dihydroxy-2-methyl-*N*-phenyl-1,4-oxathiane-3-carboxamide (5). A solution of dihydro-1,4-oxathiin (**1**) (5.4 g, 23 mmol) in methylene chloride (100 ml) at -60 °C under a dry ice-acetone bath was treated with chlorine (1.63 g, 23 mmol) for 5 min 50 seconds. The reaction mixture was stirred for 10 min at the same temperature. The solvent was removed under reduced pressure to give 2,3-dichloro-1,4-oxathiane (**4**) as a colorless oily residue. A solution of **4** in acetone (80 ml) was treated with a water (30 ml) for 4 h at room temperature. A saturated sodium bicarbonate solution was added to the reaction mixture until it reaches neutral. The reaction mixture was evaporated under the reduced pressure, and then extracted with chloroform. The organic layer was dried ($MgSO_4$), concentrated to afford a pale yellow oily residue. This was separated by the flash chromatography on silica gel with a mixture of benzene:ethyl acetate = 7:3 as an eluent to give 2,3-dihydroxy-1,4-oxathiane (**5**) (3.92 g, 65%) (R_f =0.2) and 2-methyl-1,3-oxathiolane-*N*-phenyl-2-ketocarboxamide (**6**) (1.61 g, 27%)(R_f=0.5).

For **5**: crystallized from ether; mp 104-107 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.46 (s, 2.1H, 2-CH_3)^a, 2.22 (t, 0.3H, J=5.7 Hz, OH(primary))^b, 2.63 (s, 0.9H, CH_3)^b, 2.38-2.44 and 3.32-3.43 (m, 1.4H, SCH_2)^a, 2.71-2.87 (m, 0.6H, SCH_2)^b, 3.75 (doublet of triplet, 0.6H, J=5.7Hz, J=5.8Hz, OCH_2)^b, 3.92-3.98 and 4.20-4.51 (m, 1.4H, OCH_2)^a, 4.39 and 4,75 (2s, 1.4H, 2-OH and 3-OH)^a, 5.85 (s, 0.3H, *tert*-OH)^b, 7.16-7.60 (m, 5H, ArH), 8.87 (br s, 0.7H, NH)^a, 8.79 (br s, 0.3H, NH)^b; ir (KBr) 1660, 1660, 3350 cm^{-1}. *Anal.* Cacld for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.61; N, 5.20. Found C, 53.3; H, 5.64; N, 5.15.

a/b = dihydroxy-1,4-oxathiane (**5**)/ α-hydroxy ketone (**13**) = 7/3.

Preparation of 2-methyl-1,3-oxathiolane-*N*-phenyl-2-ketocarboxamide (6).[9] A solution of dihydroxy-1,4-oxathiane (**5**) (0.21 g, 8 mmol) and PTSA (7 mg) in benzene (20 ml) was refluxed for 3 h with a Dean-Stark water trap. The reaction mixture was washed with saturated sodium bicarbonate solution, water, and then dried ($MgSO_4$). The solvent was removed to give **6** as a light brown solid residue (0.15 g, 77%), which was recrystallized from ethyl acetate and petroleum ether to give **6**. mp 130-131 °C ; ^{1}H nmr (60 MHz, $CDCl_3$) δ 2.12 (s, 3H, 2-CH_3), 2.93-3.15 (m, 2H, SCH_2), 3.80-4.58 (m, 2H, OCH_2), 7.15-7.80 (m, 5H, ArH), 8.90 (br s, 1H, NH); ir (KBr) 3340, 1710, 1690 cm^{-1}. *Anal.* Cacld for $C_{12}H_{13}NO_4S$: C, 57.35; H, 5.21; N, 5.57. Found C, 56.96; H, 5.18; N, 5.58.

Preparation of α-hydroxy-1,3-oxathiolane-2-methyl-*N*-phenyl-2-acetamide (2). A solution of 1,3-oxathiolane (**6**) (0.11 g, 0.4 mmol) in methanol (10 ml) cooled in ice bath was treated with sodium borohydride (27 mg, 0.66 mmol) for 5 min. The reaction mixture was poured into ice water (40 ml), extracted with methylene chloride. The organic layer was washed with water, and then dried ($MgSO_4$). The solvent was evaporated to give **2** as a white solid residue (79 mg, 64%). This was a 2:1 diasteromeric mixture by the ^{1}H nmr spectrum. mp 122-128 °C; ^{1}H nmr ($CDCl_3$)(60 MHz) δ 1.65^a and 1.75^b (2s, 3H, 2-CH_3), 3.00-3.24 (m, 2H, SCH_2), 3.90-4.03 (m, 1H, OH), 4.18-4.49 (m, 3H, OCH_2 and methine CH), 7.15-7.70 (m, 5H, ArH), 8.50 (br s, 1H, NH); ir (KBr) 1660, 3250 cm^{-1}. *Anal.* Cacld for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found C, 57.10; H, 6.02; N, 5.58. a/b = 2/1

Preparation of 5,6-dihydro-3-methyl-*N*-phenyl-1,4-oxathiin-2-carboxamide (3). A solution of α-hydroxy-1,3-oxathiolane (**2**) (0.18 g, 0.7 mmol) and PTSA (6 mg) in toluene (20 ml) was refluxed for 30h with a Dean-Stark water trap. The reaction mixture was washed with cold water, and then dried ($MgSO_4$). The solvent was removed to give an oily residue, which was a 9:1 mixture of isomeric dihydro-1,4-oxathiin (**3**) and dihydro-1,4-oxathiin (**1**) by the ^{1}H nmr spectrum. Flash chromatography on silica gel with a benzene as

an eluent gave isomeric dihydro-1,4-oxathiin (**3**) (110 mg)(R_f=0.6) and dihydro-1,4-oxathiin (**1**) (12 mg)(R_f= 0.5). mp 82.5-84 °C (recrystallized from benzene and petroleum ether); ^{1}H nmr (60 MHz)($CDCl_3$) δ 2.42 (s, 3H, CH_3), 3.02-3.18 (m, 2H, 5-CH_2), 4.25-4.40 (m, 2H, 6-CH_2), 7.03-7.80 (m, 5H, ArH), 8.47 (br s, 1H, NH); ir (KBr) 3300 (NH), 1650 (C=O) cm $^{-1}$; mass spectrum (70 eV), m/z (relative intensity) 235 (54.1, M^+), 143 (100, M^+ - $C_6H_5NH_2$), 115 (10.7, M^+ - C_6H_5NHCO). *Anal.* Cacld for $C_{12}H_{13}O_2NS$: C, 61.3; H, 5.57; N, 5.95; S, 13.6. Found: C, 61.2; H, 5.45; N, 6.07; S, 13.4.

Preparation of 2,3-dimethoxy-2-methyl-*N*-phenyl-1,4-oxathiane-3-carboxamide (18).[9] To a solution of dihydro-1,4-oxathiin (**4**) (2.35 g, 0.01 mol) in methylene chloride (50 ml) at -60 °C was added dropwise a solution of chlorine (0.71 g, 0.01 mol) dissolved in methylene chloride (22.7 ml) for 5 min. After the reaction mixture was stirred for 10 min, a methanol (4.0 ml) was added dropwise for 4 min at the same temperature. The cooling bath was removed, and stirring was continued for 3 h at room temperature. The reaction mixture was washed with saturated sodium bicarbonate solution, water, and then dried ($MgSO_4$). The solvent was removed to give a light yellow oily residue (3.02 g), which was 3-chloro-2-methoxy-1,4-oxathiane (**16**) by ^{1}H nmr spectrum. The solution of **16** (0.5 g, 1.6 mmol) in methanol (5 ml) was stirred for 6 h at room temperature. The reaction mixture was dissolved in methylene chloride, washed with water, and then dried ($MgSO_4$). The solvent was removed to afford **18** as a light yellow oily residue (0.4 g, 85%). Crystallization from ether gave white needles (0.1 g).

For **16**: obtained as a 8:2 diastereomeric mixture; a light yellow oil; ^{1}H nmr (60 MHz) ($CDCl_3$) δ 1.53[a] and 1.73[b] (2s, 3H, 2-CH_3), 2.12-3.18 (m, 2H, SCH_2), 3.43 and 3.50 (s, 6H, OCH_3), 3.60-4.70 (m, 2H, OCH_2), 7.18-7.73 (m, 5H, ArH), 8.76[a] and 9.03[b] (2br s, 1H, NH). a/b = 8/2

For **18**: mp 121-123 °C; ^{1}H nmr (300 MHz) ($CDCl_3$) δ 1.43 (2s, 3H, 2-CH_3), 2.26 (m, Jad = 2.3 Hz, Jbd = 2.1 Hz, Jcd = 13.6 Hz, 1H, 5-CH(equatorial)), 3.01 (m, Jac = 12.5 Hz, Jbc = 3.5 Hz, 1H, 5-CH (axial)), 3.37 (s, 3H, 2-OCH_3), 3.62 (s, 3H, 3-OCH_3), 3.87 (m, Jab = 11.8 Hz, 1H, 6-CH(equatorial)), 4.11 (m, 1H, 6-CH(axial)), 7.09-7.53 (m, 5H, ArH), 8.12 (br s, 1H, NH); ^{13}C nmr ($CDCl_3$) δ 19.38, 24.64, 49.45, 53.50, 61.21, 90.23, 98.83, 166.27; ir (KBr) 1600, 1680, 3370 cm^{-1}. *Anal.* Cacld for $C_{14}H_{19}NO_4S$: C, 56.5; H, 6.44; N, 4.58. Found: C, 56.6; H, 6.42; N, 4.58.

Preparation of 3-hydroxy-2-methoxy-2-methyl-*N*-phenyl-1,4-oxathiane-3-carboxamide (19). A solution of 3-chloro-2-methoxy-1,4-oxathiane (**16**) (0.5 g, 1.6 mmol) obtained from the above experiment dissolved in acetone (5 ml) was treated with water (1 ml) for 24 h at room temperature. The solvent was removed to give

an oily residue, which was dissolved in methylene chloride. The reaction mixture was washed with water, and then dried ($MgSO_4$). The solvent was removed to afford **19** as a light yellow oily residue (0.34 g, 76%). Crystallization from ethyl acetate and cyclohexane gave **19** as white needles (0.11 g). mp 118-120 °C; ^{1}H nmr (300 MHz) ($CDCl_3$) δ 1.35[a] and 1.42[b] (2s, 3H, 2-CH_3), 2.34-2.40 and 3.45-3.55 (2m, 2H, SCH_2), 3.50 (s, 3H, OCH_3), 5.16 (s, 1H, OH), 7.13-7.53 (m, 5H, ArH), 8.93 (br s, 1H, NH); ir (KBr) 1600, 1680, 3320, 3350 cm^{-1}. a/b = 7:3

Independent Synthesis of 2,3-dihydroxy-2-methyl-*N*-phenyl-1,4-oxathiane-3-carboxamide (5). To a suspended solution of α-chloroacetoacetanilide[3] (2.75 g, 13 mmol) in benzene (30 ml) was added sequentially triethylamine (2.0 ml, 14.3 mmol) and 2-mercaptoethanol (0.96 ml, 13.6 mmol) under a cold water bath. The reaction mixture was stirred for 2 h at room temperature. The white solid was filtered off and the mother liquid was washed with water, and then dried ($MgSO_4$). The solvent was removed to give 2-(2-hydroxyethylthio)-3-oxo-*N*-phenylbutanamide (**14**) as a light yellow solid (3.25 g). To a solution of this solid (3.25 g) in benzene (30 ml) was added dropwise sulfuryl chloride (1.1 ml, 13.4 mmol) for 5 min at room temperature. After the reaction mixture was stirred for 2 h, the solvent was removed under the reduced pressure to afford **15** as light yellow solids (3.3 g, 94.3%). A solution of **15** in acetone (60 ml) was treated with water (30 ml) for 1 h at room temperature. The reaction mixture was evaporated to give a yellow oily residure, which was dissolved in methylene chloride. The organic layer was washed with water, and then dried ($MgSO_4$) to afford a yellow oily residure (2.7g) as a 1:1 mixture of **5** and **6** by ^{1}H nmr spectrum. Flash chromatography on silica gel with a mixture of benzene:ethyl acetate = 7:3 as an eluent gave **5** (1.24 g) and **6** (1.13 g). The nmr spectra of these compounds were identical with those of the compounds obtained by the previous methods.

Reaction of 3-hydroxy-2-methoxy-1,4-oxathiane (19) in the presence of PTSA. A solution of **19** (50 mg, 0.176 mmol) and PTSA (1.6 mg) in chloroform (10 ml) was refluxed for 2 h. The reaction mixture was washed with water and then dried ($MgSO_4$). The solvent was removed to give **6** (34 mg, 77%) as a light yellow solid. This compound had identical ^{1}H nmr spectrum and mp with an authetic sample obtained by the previous methods.

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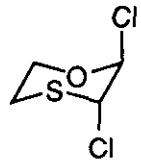
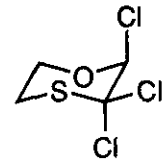
4. Concerning the sterochemistry of the dichloro-1,4-oxathiane (**4**), the two chlorine atoms are assinged in *trans* relationship in which the chlorines are axial on the basis of the similarity of the structures to those of previously reported[5] *trans*-2,3-dichloro-1,4-oxathiane and 2,3,3-trichloro-1,4-oxathiane.





trans-2,3-dichloro-1,4-oxathiane 2,3,3-trichloro-1,4-oxathiane

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