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Pummerer Reaction of Thienamycin-Type Cyclic Vinylogous Sulfide and Sulfoxide

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The Pummerer reaction of the thienamycin-type cyclic vinylogous sulfide (**4**) and sulfoxide (**5**) was studied. When the sulfide (**4**) was treated with *tert*-BuOCl and MeOH in the presence of Ag₂O, an additive-type Pummerer reaction took place to produce **17** instead of the normal rearranged product (**6**). The sulfoxide (**5**), on treatment with Ac₂O, (CF₃CO)₂O, and 2,4,6-collidine, underwent an intramolecular additive-type Pummerer reaction to give the bicyclic compound (**19**) as a main product. In the reaction of the alkoxysulfonium salt (**25**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Pummerer-type rearrangement took place, giving the methoxy compound (**6**) in poor yield.

Keywords—thienamycin; Pummerer reaction (additive type); cyclic vinylogous sulfide; cyclic vinylogous sulfoxide; alkoxysulfonium salt; thienamycin model compound; acetoxysulfonium salt

It has been reported that thienamycin¹⁾ (**1**) and related 1-carbapenem antibiotics are metabolized by renal dehydropeptidase-1 (DHP-1),²⁾ and so are poorly recovered in urine. Recently, a group at Merck³⁾ found that alkyl substitution at the S- α -position of the cysteamine side chain of thienamycin resulted in excellent resistance to DHP-1. However, the antimicrobial activities, particularly the antipseudomonal activities of the alkylated derivatives, were found to be weaker than those of thienamycin.

Cefoxitin (**3**),⁴⁾ the first semi-synthetic cephamycin derivative, possesses satisfactory antimicrobial activity while having the desirable characteristic of high resistance to β -lactamase as a result of the steric effect of the 7- α -methoxy group. These results suggested that the methoxy group is a favorable substituent,⁴⁾ and so we designed the S- α -methoxy thienamycin derivative (**2**) (see Chart 1), expecting high antimicrobial activity as well as considerable stability to DHP-1. Introduction of a methoxy group into the cysteamine side chain of thienamycin using the Pummerer reaction⁵⁾ was planned, but the Pummerer reaction of thienamycin-type cyclic vinylogous sulfide has not been well investigated. To elucidate the reactivity in this system, the Pummerer reaction of a thienamycin model compound was investigated.

As a model compound of thienamycin, we designed a compound (**4**) having the cyclic β -thio-substituted α,β -unsaturated carboxylate segment of thienamycin. Preparation of the model compound (**4**) is shown in Chart 2. The amino acid ester (**10**), prepared according to the method of Graf,⁶⁾ was treated with methyl bromoacetate and triethylamine in *N,N*-dimethylformamide (DMF) to give **11** in 57% yield, followed by acetylation of **11** with acetyl chloride and triethylamine to give the amide (**12**) in 87% yield. Dieckmann condensation of the amide (**12**) using *tert*-BuOK as a base in toluene, according to the method of Rapoport *et al.*,⁷⁾ gave the cyclic β -keto ester (**13**) in 53% yield as a single isomer. Finally, the β -keto ester (**13**) was converted to the model compound (**4**) in fairly good yield by use of the procedure of Shinkai *et al.*⁸⁾

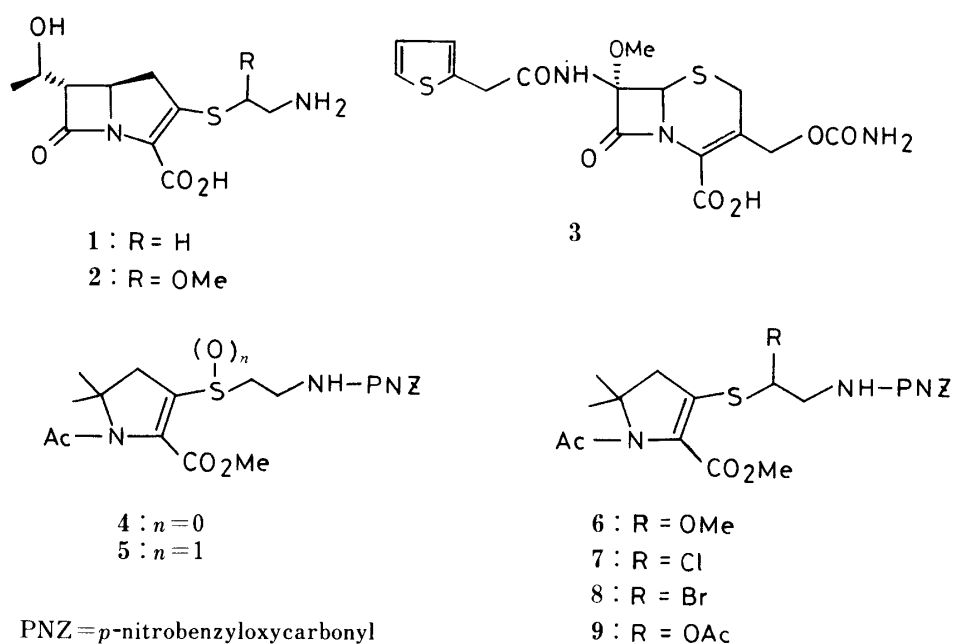


Chart 1

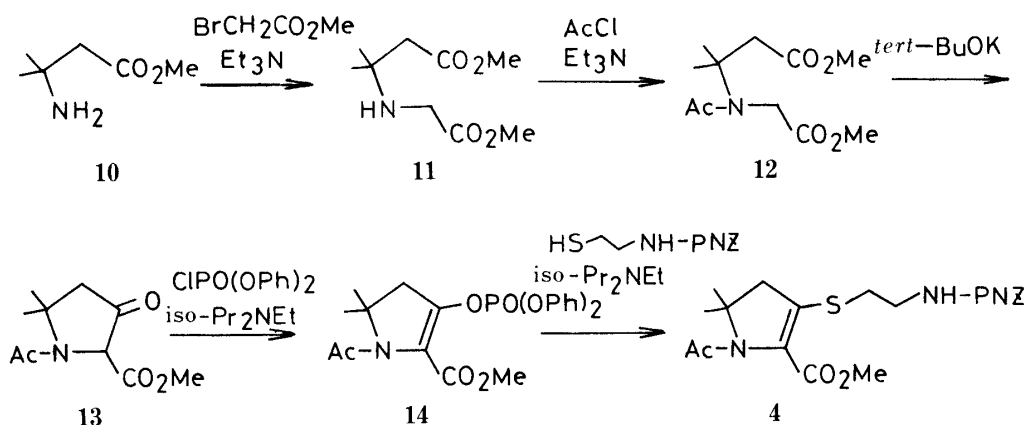


Chart 2

When **4** was treated with *tert*-BuOCl⁹⁾ and MeOH in the presence of Ag₂O in CH₂Cl₂, the expected compound (**6**) was not obtained even in a trace amount, but the pyrroline derivative (**17**) was isolated in 89% yield. The structure of **17** was established from the nuclear magnetic resonance (NMR) spectrum, infrared (IR) spectrum, and mass spectrum (MS). The NMR spectrum of **17** showed the presence of two singlets at δ 3.24 assigned to the methoxy group and δ 5.86 due to the olefinic proton; its IR spectrum displayed an absorption band at 1750 cm⁻¹ corresponding to the saturated ester. Compound **17** was presumed to have been formed by the additive-type Pummerer reaction¹⁰⁾ of the vinylogous sulfonium chloride (**15**),¹¹⁾ followed by the conversion of the resulting intermediate (**16**) to the stable pyrroline derivative (**17**) (Chart 3).

Then we tried to isolate the α -halosulfides (**7** and **8**). When **4** was treated with *tert*-BuOCl in CH₂Cl₂, the hydroxy compound (**18**) was isolated in 68% yield along with the sulfoxide (**5**) in 8% yield. The NMR spectrum¹²⁾ of **18** showed the presence of two singlets at δ 5.28 and 5.90 assigned to the olefinic proton and the IR spectrum displayed absorption bands at 1740 and 1720 cm⁻¹ corresponding to the α -hydroxy ester. Compound **18** was presumed to have

been formed by the attack of $\text{OH}^{-13)}$ as a nucleophile instead of MeO^- on the intermediate (15) (Chart 3). Employment of a halogenating reagent such as *N*-chlorosuccinimide or Br_2 instead of *tert*-BuOCl gave similar results.

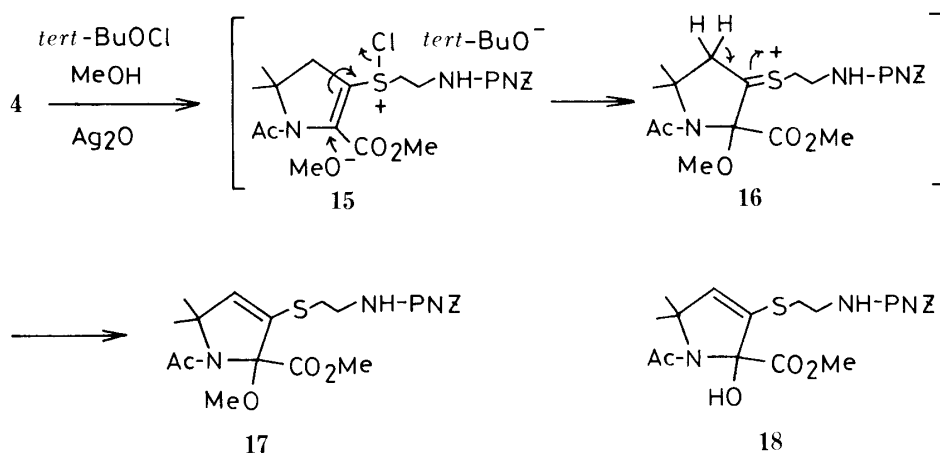


Chart 3

Next we investigated the Pummerer reaction of the sulfoxide (5). Oxidation of 4 with *m*-chloroperoxybenzoic acid (MCPBA) in CH_2Cl_2 gave the sulfoxide (5) in 76% yield. In the reaction of 5 with acetic anhydride (Ac_2O),¹⁴⁾ the starting material was recovered even under drastic reaction conditions. On the other hand, treatment of 5 with Ac_2O , $(\text{CF}_3\text{CO})_2\text{O}$ and 2,4,6-collidine¹⁵⁾ gave the bicyclic compound (19), the pyrrole compound (20), and 18 in 54%, 15%, and 5% yields, respectively, instead of the acetoxy compound (9). When the sulfoxide (5)

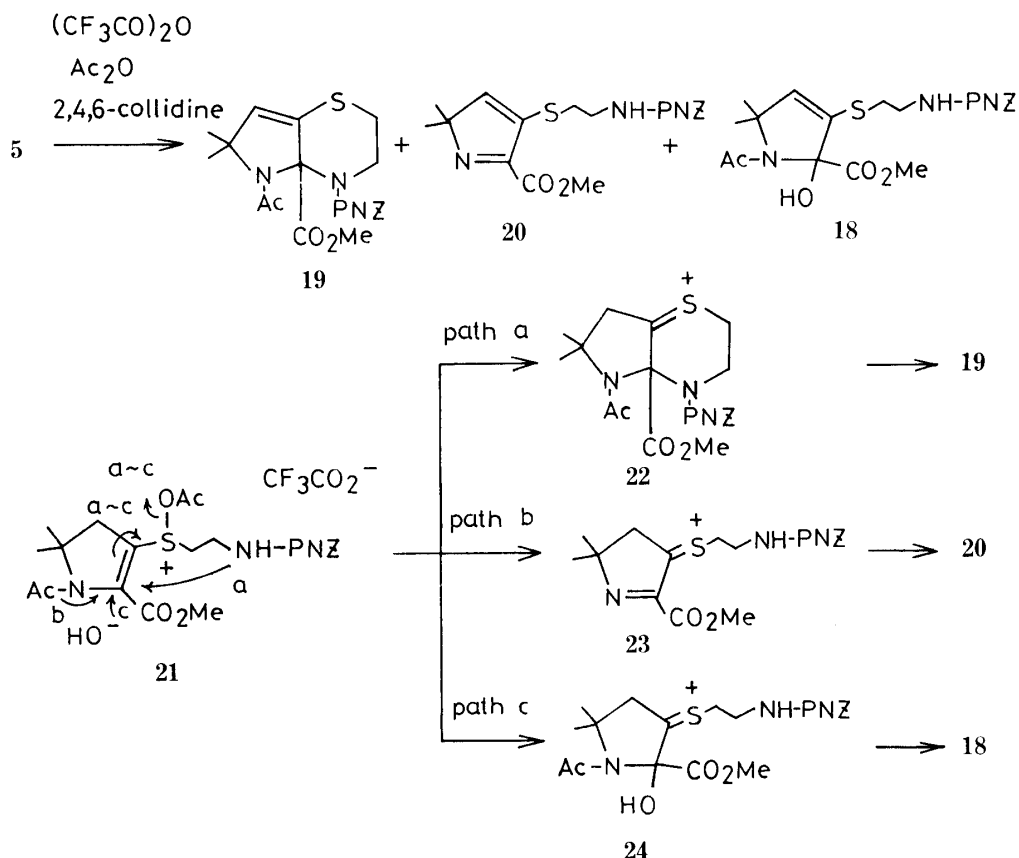


Chart 4

was treated with $(\text{CF}_3\text{CO})_2\text{O}$ and 2,4,6-collidine, **19**, **20**, and **18** were obtained in 27%, 33%, and 25% yields, respectively. The structures of these compounds were supported by the NMR, IR, and MS. The NMR spectrum of **19** showed the presence of a singlet at δ 6.06 assigned to the olefinic proton and the disappearance of signals attributed to the C_4 -methylene protons and NH. Formation of this compound (**19**) can probably be accounted for by the intramolecular additive-type Pummerer reaction¹⁶⁾ of the vinylogous acetoxysulfonium salt (**21**),¹¹⁾ followed by the migration of the double bond of the resulting intermediate (**22**) (Chart 4, pathway a). The NMR spectrum of **20** showed the presence of a singlet at δ 7.00 attributed to the aromatic proton and the disappearance of the signal due to the acetyl group. A reasonable pathway for the formation of this compound (**20**) would be *via* the intermediate (**23**), followed by the migration of the double bond (Chart 4, pathway b). Compound **18** was presumed to have been formed by the attack of $\text{OH}^{-13)}$ on the intermediate (**21**) (Chart 4, pathway c).

Then, the Pummerer reaction of alkoxysulfonium salt (**25**)¹⁷⁾ was investigated. Treatment of the sulfoxide (**5**) with MeI and AgBF_4 ^{17a)} in nitromethane gave a mixture of the alkoxysulfonium salt (**25**) and the starting material (**5**) in the ratio of *ca.* 7 : 3¹⁸⁾ as judged from the NMR spectrum. When the mixture was treated (without further purification) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the desired methoxy compound (**6**), the sulfide (**4**), and the sulfoxide (**5**) were obtained in 3%,¹⁹⁾ 26%,¹⁹⁾ and 47%¹⁹⁾ yields from **25**, respectively. The NMR spectrum of **6** showed the presence of a singlet at δ 3.43 assigned to the methoxy group, an AB-quartet at δ 2.60 and 2.92 attributed to the C_4 -methylene protons, and a double-doublet at δ 4.44 due to the methine proton of $\text{S}-\text{CH}-\text{OCH}_3$. It has been reported²⁰⁾ that the reaction of alkoxysulfonium salts with nucleophiles gave a variety of products, depending on the nature of the nucleophile and the substrate. Kobayashi and co-workers have reported²¹⁾ that reaction of an alkoxysulfonium salt with tertiary amines proceeds *via* three pathways. In the reaction of the alkoxysulfonium salt (**25**) with DBU, a Pummerer-type reaction leading to the formation of the methoxy compound (**6**) was found to be a minor pathway.

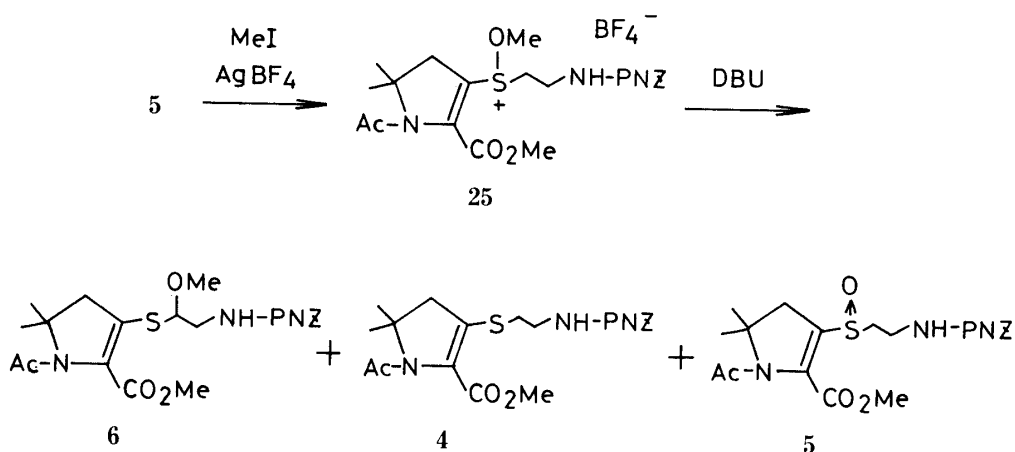


Chart 5

In summary, an inter- or intramolecular additive-type Pummerer reaction was predominant in the case of the thienamycin-type cyclic vinylogous sulfide and sulfoxide. In the reaction of the alkoxysulfonium salt (**25**) with a base, Pummerer-type reaction took place, giving the methoxy compound (**6**), but the yield was poor. These investigations indicated that the preparation of the S- α -methoxy thienamycin derivative (**2**)²²⁾ might be difficult using the Pummerer reaction.

Experimental

Melting points were determined on a Yanagimoto melting point apparatus, and are uncorrected. IR spectra were recorded on a Hitachi 260-30 infrared spectrophotometer. Proton nuclear magnetic resonance ($^1\text{H-NMR}$) spectra were obtained on a Hitachi R-40 (90 MHz) using tetramethylsilane as an internal standard. Mass spectra were recorded on JEOL JMS-01SG-2 and JMS-D300 mass spectrometers. Preparative thin-layer chromatography (preparative TLC) was performed by using Merck Silica gel 60 F_{254} plates.

Methyl 3-Methoxycarbonylmethylamino-3-methylbutyrate (11)—Methyl bromoacetate (37.5 g, 0.23 mol) was added to an ice-cooled solution of **10** (30.5 g, 0.23 mol) and triethylamine (23.5 g, 0.23 mol) in DMF (170 ml), and the mixture was stirred at room temperature for 17 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was taken up in CHCl_3 and brine, and the separated CHCl_3 layer was dried over Na_2SO_4 and concentrated. Distillation of the residue gave **11** (26.9 g, 57%), bp 93–94 °C (3 mmHg). $^1\text{H-NMR}$ (CDCl_3) δ : 1.20 (6H, s, $2 \times \text{CH}_3$), 2.46 (2H, s, $\text{C-CH}_2\text{-CO}_2$), 3.45 (2H, s, $\text{N-CH}_2\text{-CO}_2$), 3.71 (3H, s, CO_2CH_3), 3.76 (3H, s, CO_2CH_3).

Methyl 3-(*N*-Acetyl-*N*-methoxycarbonylmethylamino)-3-methylbutyrate (12)—Acetyl chloride (10.6 g, 0.14 mol) was added dropwise to an ice-cooled solution of **11** (27.4 g, 0.14 mol) and triethylamine (13.6 g, 0.14 mol) in CH_2Cl_2 (250 ml). The mixture was stirred for 5 h at room temperature, then triethylamine (2.7 g, 0.03 mol) and acetyl chloride (2.1 g, 0.03 mol) were added, and stirring was continued for 12 h. The reaction mixture was washed successively with 5% NaHCO_3 , water, 0.5 N HCl and water, dried over Na_2SO_4 and concentrated to afford **12** (28.7 g, 87%) as an oil, which was used for the next reaction without further purification. $^1\text{H-NMR}$ (CDCl_3) δ : 1.53 (6H, s, $2 \times \text{CH}_3$), 2.08 (3H, s, $\text{CH}_3\text{CO-}$), 3.16 (2H, s, $-\text{CH}_2\text{-CO}_2$), 3.68 (3H, s, CO_2CH_3), 3.83 (3H, s, CO_2CH_3), 4.23 (2H, s, $\text{N-CH}_2\text{-CO}_2$).

Methyl 1-Acetyl-5,5-dimethyl-3-oxopyrrolidine-2-carboxylate (13)—A solution of **12** (760 mg, 3.1 mmol) in toluene (2 ml) was added to a suspension of *tert*-BuOK (492 mg, 4.4 mmol) in toluene (10 ml) at 0–5 °C under nitrogen. After being stirred for 1 h at the same temperature, the reaction mixture was allowed to warm to room temperature and stirring was continued for an additional 3 h. Ice-water and AcOH (0.4 ml) were added to the reaction mixture under ice-cooling, and the aqueous layer was adjusted to pH 4.0 with AcOH. The separated organic layer was washed with water, dried over Na_2SO_4 and concentrated. The residue crystallized on standing at room temperature. Trituration of the crystals with isopropyl ether gave **13** (350 mg, 53%) as colorless crystals, mp 90–93 °C. IR (KBr): 1760, 1740, 1620 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.66 (3H, s, CH_3), 1.72 (3H, s, CH_3), 1.94 (2H, brs, $\text{CH}_3\text{CO-}$), 2.28 (1H, brs, $\text{CH}_3\text{CO-}$), 2.67 (2H, brs, $\text{C}_4\text{-H}_2$), 3.85 (3H, s, CO_2CH_3), 4.72 (2/3H, s, $\text{C}_2\text{-H}$), 4.6–4.9 (1/3H, br, enol). FD-MS m/e : 213 (M^+). Anal. Calcd for $\text{C}_{10}\text{H}_{15}\text{NO}_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.43; H, 7.06; N, 6.60.

1-Acetyl-2-methoxycarbonyl-5,5-dimethyl-3-diphenoxylphosphoryloxy-2-pyrroline (14)—Diisopropylethylamine (4.36 g, 33.8 mmol) and diphenyl phosphorochloridate (9.06 g, 33.8 mmol) were added to a solution of **13** (3.60 g, 16.9 mmol) in CH_3CN (80 ml). The reaction mixture was stirred for 17 h at room temperature, and concentrated *in vacuo*. The residue was chromatographed on silica gel (150 g) using benzene– CHCl_3 (1:1) to give **14** (7.70 g, quant.) as a pale yellow oil. IR (neat): 1740, 1650 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.55 (6H, s, $2 \times \text{CH}_3$), 2.01 (3H, s, $\text{CH}_3\text{CO-}$), 2.86 (1H, s, $\text{C}_4\text{-H}$), 2.89 (1H, s, $\text{C}_4\text{-H}$), 3.73 (3H, s, CO_2CH_3), 7.2–7.5 (10H, m, aromatic-H).

1-Acetyl-2-methoxycarbonyl-5,5-dimethyl-3-(*p*-nitrobenzyloxycarbonylaminoethylthio)-2-pyrroline (4)—A solution of **14** (3.83 g, 8.6 mmol), 2-(*p*-nitrobenzyloxycarbonylamino)ethanethiol²³⁾ (3.50 g, 13.8 mmol), and diisopropylethylamine (1.55 g, 12.0 mmol) in DMF (80 ml) was stirred for 24 h under nitrogen. The reaction mixture was concentrated and the residue was taken up in CHCl_3 and water. The separated CHCl_3 layer was dried over Na_2SO_4 and concentrated to give colorless crystals, which were triturated with Et_2O and recrystallized from benzene to afford **4** (2.76 g, 71%) as colorless crystals, mp 133 °C. IR (KBr): 3340, 1705, 1625 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.56 (6H, s, $2 \times \text{CH}_3$), 2.06 (3H, s, $\text{CH}_3\text{CO-}$), 2.73 (2H, s, $\text{C}_4\text{-H}_2$), 2.81 (2H, t, $J=6\text{ Hz}$, S-CH_2), 3.39 (2H, q, $J=6\text{ Hz}$, N-CH_2), 3.86 (3H, s, CO_2CH_3), 5.22 (2H, s, $\text{NCO}_2\text{CH}_2\text{Ar}$), 5.65 (1H, brs, NH), 7.53 (2H, d, $J=9\text{ Hz}$, aromatic-H), 8.24 (2H, d, $J=9\text{ Hz}$, aromatic-H). Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_7\text{S}$: C, 53.21; H, 5.58; N, 9.31. Found: C, 53.20; H, 5.41; N, 9.32.

Reaction of 4 with *tert*-BuOCl, MeOH, and Ag_2O —A solution of *tert*-BuOCl (24 mg, 0.22 mmol) in CH_2Cl_2 (1 ml) was added to a mixture of **4** (90 mg, 0.2 mmol), MeOH (32 mg, 1.0 mmol), and Ag_2O (34 mg, 0.15 mmol) in CH_2Cl_2 (2 ml) under ice-cooling. The mixture was stirred for 1 h at the same temperature, then the insoluble materials were filtered and washed with CH_2Cl_2 . The combined filtrate and washings were concentrated to give 1-acetyl-2-methoxy-2-methoxycarbonyl-5,5-dimethyl-3-(*p*-nitrobenzyloxycarbonylaminoethylthio)-3-pyrroline (**17**) (85 mg, 89%) as a colorless oil. IR (CHCl_3): 3455, 1750, 1730, 1660 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.62 (6H, s, $2 \times \text{CH}_3$), 2.00 (3H, s, $\text{CH}_3\text{CO-}$), 2.98 (2H, t, $J=6\text{ Hz}$, S-CH_2), 3.24 (3H, s, OCH_3), 3.48 (2H, q, $J=6\text{ Hz}$, N-CH_2), 3.85 (3H, s, CO_2CH_3), 5.24 (2H, s, $\text{NCO}_2\text{CH}_2\text{Ar}$), 5.3 (1H, brs, NH), 5.86 (1H, s, $\text{C}_4\text{-H}$), 7.55 (2H, d, $J=9\text{ Hz}$, aromatic-H), 8.27 (2H, d, $J=9\text{ Hz}$, aromatic-H). FD-MS m/e : 481 (M^+).

Reaction of 4 with *tert*-BuOCl—A mixture of **4** (90 mg, 0.2 mmol) and *tert*-BuOCl (21 mg, 0.2 mmol) in CH_2Cl_2 (4 ml) was stirred under ice-cooling for 0.5 h. The reaction mixture was concentrated and the residue was fractionated by preparative TLC using AcOEt. The more mobile fraction afforded 1-acetyl-2-hydroxy-2-methoxycarbonyl-5,5-dimethyl-3-(*p*-nitrobenzyloxycarbonylaminoethylthio)-3-pyrroline (**18**) (63 mg, 68%) as an oil.

IR (neat): 1740, 1720, 1640 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.61 (6H, s, $2 \times \text{CH}_3$), 2.02 (1H, s, $\text{CH}_3\text{CO-}$), 2.22 (2H, s, $\text{CH}_3\text{CO-}$), 2.7—3.3 (2H, m, S- CH_2), 3.3—3.6 (2H, m, N- CH_2), 3.80 (2H, s, CO_2CH_3), 3.87 (1H, s, CO_2CH_3), 5.22 (2H, s, $\text{NCO}_2\text{CH}_2\text{Ar}$), 5.61 (1H, br s, NH), 5.83 (2/3H, s, olefinic-H), 5.90 (1/3H, s, olefinic-H), 7.55 (2H, d, $J=9$ Hz, aromatic-H), 8.25 (2H, d, $J=9$ Hz, aromatic-H). FD-MS m/e : 467 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_8\text{S} \cdot 1/2\text{H}_2\text{O}$: C, 50.34; H, 5.38; N, 8.48. Found: C, 50.41; H, 5.50; N, 8.82. The less mobile fraction gave **5** (8 mg, 8%), whose NMR spectrum was identical with that of an authentic sample.

1-Acetyl-2-methoxycarbonyl-5,5-dimethyl-3-[2-(*p*-nitrobenzyloxycarbonylamino)ethylsulfanyl]-2-pyrroline (5**)**—A solution of 85% MCPBA (203 mg, 1.0 mmol) in CH_2Cl_2 (5 ml) was added to a stirred solution of **4** (451 mg, 1.0 mmol) in CH_2Cl_2 (20 ml) under ice-cooling. The resulting solution was stirred for 1 h at the same temperature, and then washed with 5% NaHCO_3 and water, dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel (10 g) with AcOEt to give **5** (355 mg, 76%) as a colorless solid, mp 103—104 $^\circ\text{C}$. IR (KBr): 3250, 1740, 1725, 1665 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.59 (3H, s, CH_3), 1.67 (3H, s, CH_3), 2.17 (3H, s, $\text{CH}_3\text{CO-}$), 2.90 and 3.00 (2H, ABq, $J=17$ Hz, $\text{C}_4\text{-H}_2$), 3.1—3.3 (2H, m, SO CH_2), 3.5—3.8 (2H, m, N- CH_2), 3.88 (3H, s, CO_2CH_3), 5.24 (2H, s, $\text{NCO}_2\text{CH}_2\text{Ar}$), 5.85 (1H, br s, NH), 7.56 (2H, d, $J=9$ Hz, aromatic-H), 8.27 (2H, d, $J=9$ Hz, aromatic-H). FD-MS m/e : 467 (M^+). Anal. Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_8\text{S}$: C, 51.38; H, 5.39; N, 8.99. Found: C, 51.00; H, 5.19; N, 8.89.

Reaction of **5 with Ac_2O , $(\text{CF}_3\text{CO})_2\text{O}$, and 2,4,6-Collidine**—A solution of $(\text{CF}_3\text{CO})_2\text{O}$ (63 mg, 0.3 mmol) and Ac_2O (0.2 ml) was stirred for 3 h at room temperature. To this solution was added **5** (93 mg, 0.2 mmol), and then 2,4,6-collidine (48 mg, 0.4 mmol) was added after 2 min. After being stirred for 45 min at room temperature, the reaction mixture was diluted with benzene, washed with 0.5N HCl, water, 5% NaHCO_3 and water, dried over Na_2SO_4 and concentrated. The residue was fractionated by preparative TLC using benzene–AcOEt (1:1). The following three products were isolated in order of increasing *R_f*. Compound **18** (5 mg, 5%). 2-Methoxycarbonyl-5,5-dimethyl-3-(*p*-nitrobenzyloxycarbonylaminoethylthio)-5*H*-pyrrole (**20**) (12 mg, 15%) as an oil. IR (neat): 1730 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.41 (6H, s, $2 \times \text{CH}_3$), 3.01 (2H, t, $J=6$ Hz, S- CH_2), 3.54 (2H, q, $J=6$ Hz, N- CH_2), 3.96 (3H, s, CO_2CH_3), 5.24 (2H, s, $\text{NCO}_2\text{CH}_2\text{Ar}$), 5.35 (1H, br s, NH), 7.00 (1H, s, aromatic-H), 7.55 (2H, d, $J=9$ Hz, aromatic-H), 8.26 (2H, d, $J=9$ Hz, aromatic-H). High-resolution MS m/e : M^+ Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}_6\text{S}$: 407.1149. Found: 407.1132. 5-Acetyl-4a-methoxycarbonyl-6,6-dimethyl-4-(*p*-nitrobenzyloxycarbonyl)-2,3,4,4a,5,6-hexahydropyrrolo[3,2-*b*][1,4]thiazine (**19**) (49 mg, 54%) as an oil. IR (CHCl_3): 1740, 1715, 1655 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.54 (3H, s, CH_3), 1.61 (3H, s, CH_3), 2.06 (3H, s, $\text{CH}_3\text{CO-}$), 2.8 (2H, m, S- CH_2), 3.80 (3H, s, CO_2CH_3), 4.1 (2H, m, N- CH_2), 5.26 (2H, s, $\text{NCO}_2\text{CH}_2\text{Ar}$), 6.06 (1H, s, olefinic-H), 7.54 (2H, d, $J=9$ Hz, aromatic-H), 8.26 (2H, d, $J=9$ Hz, aromatic-H). FD-MS m/e : 449 (M^+).

Reaction of **5 with $(\text{CF}_3\text{CO})_2\text{O}$ and 2,4,6-Collidine**—A stirred solution of **5** (93 mg, 0.2 mmol) in CH_2Cl_2 (1 ml) was treated with $(\text{CF}_3\text{CO})_2\text{O}$ (63 mg, 0.3 mmol), and then 2,4,6-collidine (48 mg, 0.4 mmol) was added after 5 min under ice-cooling. After being stirred for 0.5 h at the same temperature, the reaction mixture was diluted with CH_2Cl_2 , washed successively with 0.5N HCl, water, 5% NaHCO_3 and water, dried over Na_2SO_4 and concentrated. The residue was fractionated by preparative TLC using benzene–AcOEt (1:1) to give **18** (23 mg, 25%), **20** (27 mg, 33%), and **19** (24 mg, 27%), respectively, in order of increasing *R_f*.

1-Acetyl-2-methoxycarbonyl-3-(1-methoxy-2-*p*-nitrobenzyloxycarbonylaminoethylthio)-5,5-dimethyl-2-pyrroline (6**)**—A solution of **5** (78 mg, 0.17 mmol), MeI (50 mg, 0.35 mmol) and AgBF_4 (39 mg, 0.20 mmol) in nitromethane (1.5 ml) was stirred for 3.5 h at room temperature under argon. The resulting precipitates were filtered off and the filtrate was concentrated. The residue was washed with benzene to give a mixture¹⁸⁾ of 1-acetyl-2-methoxycarbonyl-5,5-dimethyl-3-[(2-*p*-nitrobenzyloxycarbonylaminoethyl)methoxysulfonio]-2-pyrroline tetrafluoroborate (**25**) and the starting material (**5**) (115 mg) as a viscous oil in the ratio of ca. 7:3 as judged from the NMR spectrum. $^1\text{H-NMR}$ ($\text{CDCl}_3 + \text{DMSO-}d_6$) δ : 1.67 (6H, s, $2 \times \text{CH}_3$), 2.26 (3H, s, $\text{CH}_3\text{CO-}$), 3.06 (2H, s, $\text{C}_4\text{-H}_2$), 3.5—4.1 (4H, m, N- CH_2 and S- CH_2), 3.90 and 4.00 (each 3H, each s, CO_2CH_3 and OCH_3), 5.16 (2H, s, $\text{NCO}_2\text{CH}_2\text{Ar}$), 6.56 (1H, br s, NH), 7.50 (2H, d, $J=9$ Hz, aromatic-H), 8.17 (2H, d, $J=9$ Hz, aromatic-H).

DBU (54 mg, 0.36 mmol) was added to a solution of the above mixture (115 mg) in CDCl_3 (1.5 ml) and $\text{DMSO-}d_6$ (3 drops),¹⁸⁾ and then occasionally shaken for 15 min at room temperature in an NMR tube. The reaction mixture was diluted with AcOEt, washed with 0.5N HCl and water, dried over MgSO_4 and concentrated. The residue was fractionated by preparative TLC using benzene–AcOEt (1:1) to give **5** (50 mg, 47%),¹⁹⁾ **4** (14 mg, 26%),¹⁹⁾ and **6** (2 mg, 3%),¹⁹⁾ in order of increasing *R_f*. Data for compound **6**: IR (CHCl_3): 1715, 1640 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.53 (6H, s, $2 \times \text{CH}_3$), 2.11 (3H, s, $\text{CH}_3\text{CO-}$), 2.60 and 2.92 (2H, ABq, $J=16$ Hz, $\text{C}_4\text{-H}_2$), 3.2—3.8 (2H, m, N- CH_2), 3.43 (3H, s, OCH_3), 3.83 (3H, s, CO_2CH_3), 4.44 (1H, dd, $J=6, 8$ Hz, S-CH- OCH_3), 5.17 (2H, s, $\text{NCO}_2\text{CH}_2\text{Ar}$), 5.9 (1H, br s, NH), 7.48 (2H, d, $J=9$ Hz, aromatic-H), 8.17 (2H, d, $J=9$ Hz, aromatic-H). FD-MS m/e : 481 (M^+).

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References and Notes

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