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NOVEL REARRANGEMENTS OF A 8a*H*-PYRIDO[1,2-*d*]THIENO-[2',3'-*b*][1,4]THIAZEPINE DERIVATIVE [1]

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Abstract – The reaction of 5-ethoxycarbonyl-3-[1-(4-methylpyridinio)]-4-phenythiopene-2-thiolate with dimethyl acetylenedicarboxylate in refluxing chloroform or tetrahydrofuran afforded the corresponding 10*H*-pyrrolo[1,2-*d*]-thieno[2',3'-*b*][1,4]thiazocines or the 6,8-dithia-2-azatetracyclo[7.3.2.0^{2,10}.0^{3,7}]-tetradeca-$\Delta^{3,7}$,4,11,13-tetraene derivative. Also, the thermal conversion from the former product to dimethyl (*Z*)- and (*E*)-2-[thieno[2',3':2,3][1,4]thiazino-[4,5-*a*]pyrrol-8-ylidene]succinates was confirmed.

In our recent paper[2] we reported the formation of an interesting byproduct, dimethyl 2-[thieno[2',3':2,3][1,4]thiazino[4,5-*a*]pyrrol-8-ylidene]succinate such as **C** (see Figure 1), in the one-pot synthesis of thieno[3,2-*d*]thiazole derivatives by the reactions of some 3-(1-pyridinio)thiophene-2-thiolates with dimethyl acetylenedicarboxylate (DMAD) in refluxing xylene. We were particularly interested in the presence of the pyrrole ring in this byproduct because a ring contraction rearrangement from the pyridine ring to the pyrrole one is involved in this reaction and we already observed the formation of similar ring transformation products, e.g., 5-thia-2,3-diazatricyclo[4.3.2.0^{2,7}]undeca-3,8,10-triene derivatives such as **F** in the reactions of pyridinium 1-(arylthiocarbonyl)aminides with DMAD.[3] From these observations we first assumed the following rough mechanistic sequence: 8a*H*-pyrido[1,2-*d*]thieno[2',3'-*b*][1,4]thiazepine (**A**) → 6,8-dithia-2-azatetracyclo[7.3.2.0^{2,10}.0^{3,7}]-tetradeca-$\Delta^{3,7}$,4,11,13-tetraene (**B**) → 8*H*-thieno[2',3':2,3][1,4]thiazino[4,5-*a*]pyrrole (**C**) and examined the isolation or the detection of the intermediates such as **B** or its thiophene-free analogue in the reactions of various pyridinium 1-(2-thioxo)ethylides and 3-(1-pyridinio)thiophene-2-thiolates with DMAD (**2**) under milder conditions. Almost all reactions which we reinvestigated under this assumption afforded

only already established products such as thiazepines (**A**) or their intramolecular Diels-Alder type adducts (**D**). However, the reaction of one substrate, 5-ethoxycarbonyl-3-[1-(4-methylpyridinio)]-4-phenylthiophene-2-thiolate, with **2** gave unexpected 10*H*-pyrrolo[1,2-*d*]thieno[2',3'-*b*][1,4]thiazocines (**E**) together with the expected 6,8-dithia-2-azatetracyclo[7.3.2.$0^{2,10}$.$0^{3,7}$]tetradeca-$\Delta^{3,7}$,4,11,13-tetraene (**B**). In this communication we report novel rearrangement reactions from the 8a*H*-pyrido[1,2-*d*]thieno[2',3'-*b*][1,4]thiazepine derivative to the corresponding rearranged products **B** and **E** and the thermal transformation from **E** to the corresponding dimethyl 8*H*-pyrrolo[2,1-*c*]thieno[2',3'-*b*][1,4]thiazin-8-ylidenesuccinate (**C**).

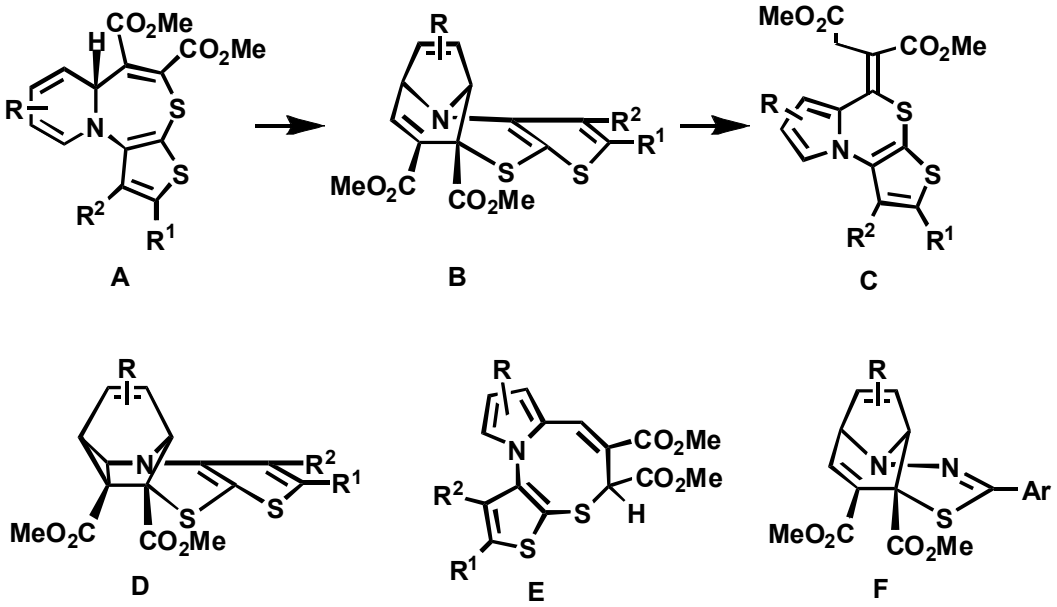
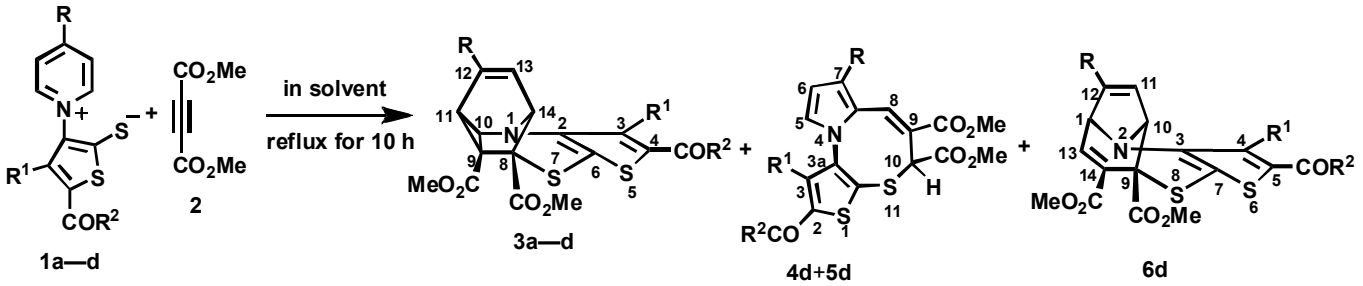


Figure 1

As described above, the reactions of almost all pyridinium 1-(2-thioxo)ethylides and 3-(1-pyridinio)thiophen-2-thiolates with **2** under various reaction conditions afforded only the corresponding type **A** and/or **D** adducts, but not the type **B** product. For example, the reactions of 3-(1-pyridinio)thiophene-2-thiolates (**1a–c**), which formed the corresponding type **C** products in refluxing xylene,[2] with **2** in refluxing chloroform or tetrahydrofuran (THF) afforded only intramolecular Diels-Alder type adducts **3a–c**[4] and any other significant products could not be obtained (Scheme 1). So, we focused our attention on some other substrates whose yields for adducts such as **3** in our previous reactions which were carried out in refluxing chloroform were very low.[5] After some elaboration we found that one substrate among them, 5-ethoxycarbonyl-3-[1-(4-methylpyridinio)]-4-phenyl-thiophene-2-thiolate (**1d**), smoothly reacted with **2** in refluxing chloroform for 10 h to produce the unexpected 2-ethyl 9,10-dimethyl 7-methyl-3-phenyl-10*H*-pyrrolo[1,2-*d*]thieno[2',3'-*b*][1,4]thiazocine-2,9,10-tricarboxylates (**4d**+**5d**)[6] as a diastereomeric mixture[7] in a 85% yield, while similar reactions of **1d**



1,3—6	R	R^1	R^2
a	H	Me	Me
b	H	Me	Ph
c	H	Ph	Me
d	Me	Ph	OEt

React.	Solvent	Products (%)
1a+2	$CHCl_3$ or THF	**3a** (65 or 48%)
1b+2	$CHCl_3$ or THF	**3b** (74 or 61%)
1c+2	$CHCl_3$ or THF	**3c** (28 or 78%)
1d+2	$CHCl_3$	**4d**+**5d** (85%)[a]
1d+2	THF	**6d** (38%)
1d+2	CH_2Cl_2	**4d**+**5d** (60%)[a], **6d** (30%)[b]
1d+2	C_6H_6	**3d** (13%), **4d**+**5d** (56%)[a], **6d** (11%)[b]

a) The ratio of **4d** : **5d** was *ca*. 85:15. b) These yields were determined by the integral ratios of the proton signals in the ^{1}H-NMR spectrum.

Scheme 1

in refluxing THF gave the expected adduct **6d**[8] in a 38% yield. On the other hand, the reactions of **1d** with **2** in refluxing methylene chloride or benzene afforded the mixtures of **4d**+**5d** (60%) and **6d** (30%) or **3d** (13%), **4d**+**5d** (56%) and **6d** (11%) respectively. Our attempts to separate the mixture of **4d**+**5d** by column chromatography were unsuccessful. This and the fact that the mixtures of **4d**+**5d** obtained under different conditions had almost the same isomeric ratio (*ca*. 85:15) strongly suggests the presence of an equilibrium between them. The structures of products **3a–d** could be determined by comparison with some data of known compounds and an authentic sample (**3d**)[5] and the structure of **6d** was also decided by the similarity of the chemical shifts and the coupling constants for the skeletal protons in the ^{1}H-NMR spectrum with those of dimethyl 4-aryl-5-thia-2,3-diazatricyclo[4.3.2.0^{2,7}]undeca-3,8,10-triene-6,11-dicarboxylate derivatives.[3] On the other hand, we could recognize that mixture **4d**+**5d** is a 1:1 adduct between pyridinium betaine (**1d**) and **2** from its elementary analysis and has a trisubstituted aromatic pyrrole structure and each

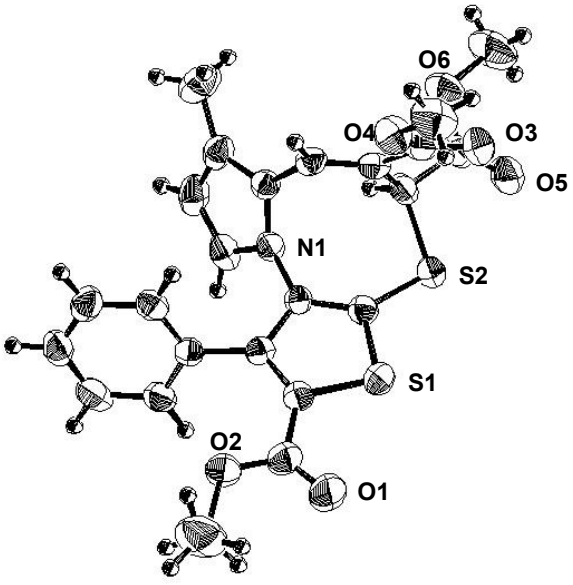
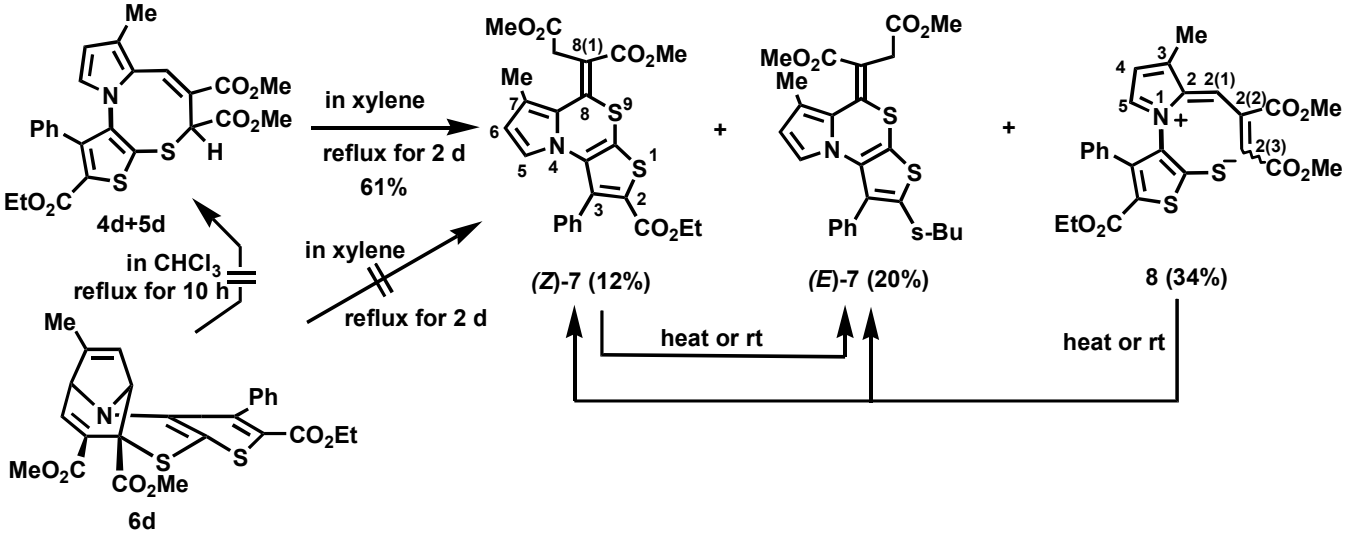


Figure 2. ORTEP drawing of **4d**

one uncoupled vinyl and methine proton from its ^{1}H-NMR spectral analysis, but further information for these structures was not obtained. Eventually, the X-ray analysis of the crystals obtained from the recrystallization of **4d**+**5d** made the structure for the major product **4d** clear.[9] The ORTEP drawing for **4d** is shown in Figure 2.[10]

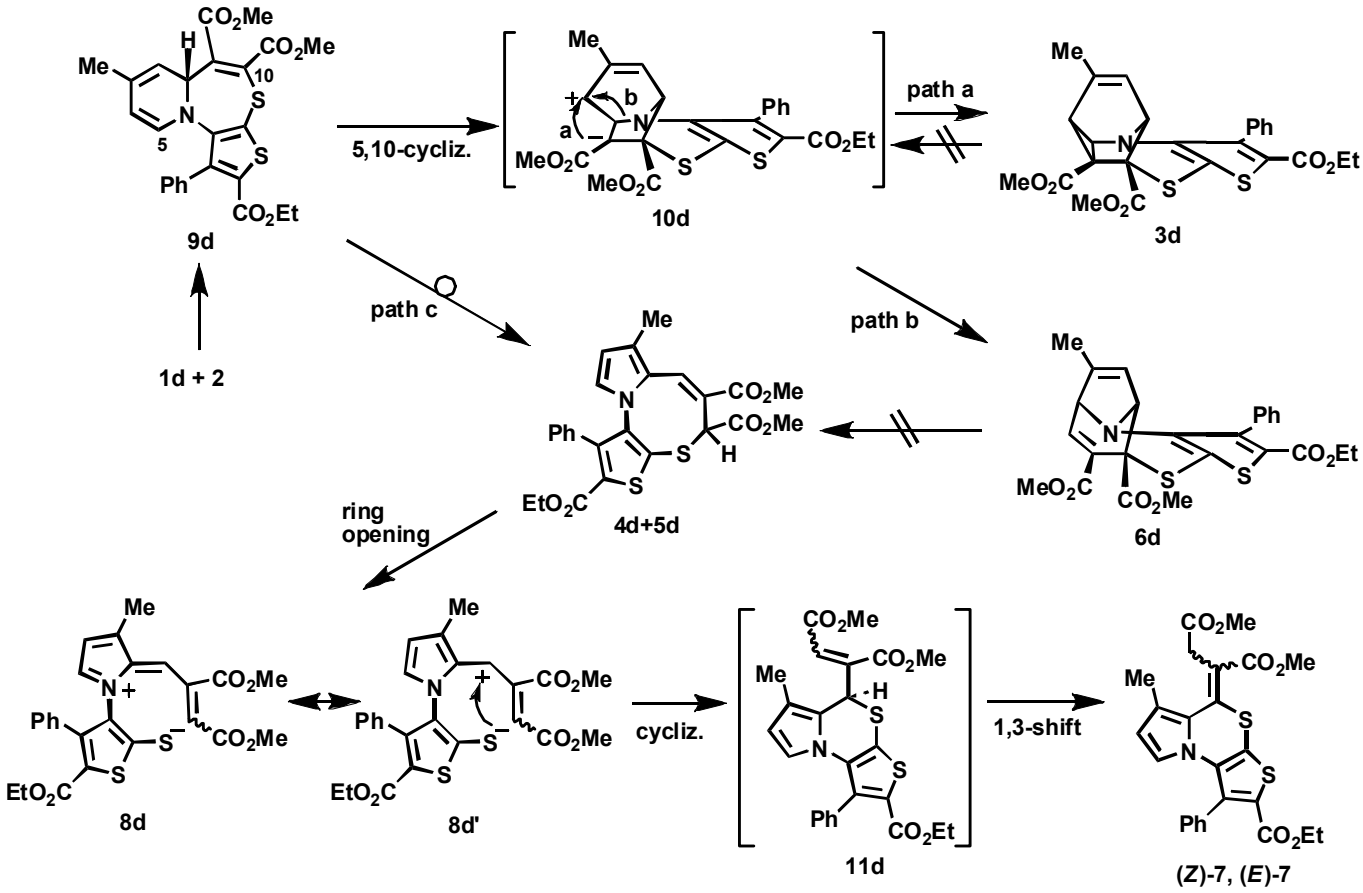
We next examined the formation of a dimethyl 8*H*-pyrrolo[2,1-*c*]thieno[2',3'-*b*][1,4]thiazin-8-ylidenesuccinate derivative such as **C**. Contrary to our first assumption, compound **6d** did not give the corresponding 1,4-thiazine derivative **7** in refluxing xylene for 2 d and also was not converted to 1,4-thiazocines **4d**+**5d** in refluxing chloroform for 10 h. On the other hand, mixture **4d**+**5d** in boiling xylene for 2 d provided the expected products **7**[11] in 12 and 20% yield respectively as the (*Z*)- and (*E*)-isomers in relation to the 8-exo methylene group, together with pyrrolium betaine **8** (34%)[12] (Scheme 2). Interestingly, product **8** gradually changed to (*Z*)-**7** and (*E*)-**7** during the separation and purification processes. Furthermore, (*Z*)-**7** was also unstable and isomerized to (*E*)-**7** even while being kept at room temperature.



Scheme 2

The structures of (*Z*)-**7** and (*E*)-**7** were determined by comparison of their ^{1}H-NMR spectra with known compounds,[2] and the distinction between the *Z*- and *E*-isomers was assumed by considering their stability and the presence of the geminal coupling constant of the methylene group attached at the 8(1)-position of (*Z*)-**7**. This structural assumption for isomers was also confirmed by their X-ray analyses and the ORTEP drawings[10] for compound (*Z*)-**7** and (*E*)-**7** are shown in Figures 3 and 4.[13] Similarly, the structure of **8** was assigned by the presence of a trisubstituted pyrrole ring and the 2 vinyl protons in its ^{1}H-NMR spectral analysis and by the intermediacy as a precursor to final products (*Z*)-**7** and (*E*)-**7**.

Possible mechanisms for these reactions are shown in Scheme 3. In particular, the transformation from [1,4]thiazocines **4d**+**5d** to final products (*Z*)-**7** and (*E*)-**7** can be readily interpreted by adding another



Scheme 3

intermediate, 8-[1,2-bis(methoxycarbonyl)vinyl-8*H*-pyrrolo[2,1-*c*]thieno[2',3'-*b*][1,4]thiazine (**11d**), which is formed from the cyclization in another resonance structure **8d'** of pyrrolium betaine **8d**. However, the reaction mechanism from thiazepine **9d**[14] to **4d**+**5d** is unclear[15] because the promising route from **6d**, which has a 1,4-dihydropyrrole ring in that skeleton, to **4d**+**5d** was refused. The reason why different products **3d**, **4d**+**5d**, and **6d** are formed from the same substrate **1d** and reagent **2** dependent upon the conditions employed is unclear, but the temperature dependency for the formation of **3d** in benzene[5] or type **F** compounds in chloroform[3] strongly suggests larger contribution of the reaction temperature than the solvent effect. The scope and limitation for these rearrangements are now in progress.

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3. A. Kakehi, S. Ito, F. Ishida, and Y. Tominaga, *J. Org. Chem*., 1997, **62**, 7788.

4. **3a**, colorless needles, mp195−196 °C. IR (KBr): 1628, 1713, 1730 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 2.40 (3H, s, 3-Me), 2.45 (3H, s, Ac), 2.77 (1H, ddd, *J* = 7.1, 5.9, 2.2 Hz, 11-H), 3.56 (1H, dd, *J* = 7.1, 1.4 (W-shaped coupling with the 10-H) Hz, 11-H), 3.72 and 3.74 (each 3H, s, CO_2Me), 4.16 (1H, dd, *J* = 6.6, 1.4 (W-shaped coupling with the 14-H), 1.2 Hz, 7-H), 6.09 (1H, ddd, *J* = 8.3, 6.6, 2.2 Hz, 13-H), 6.29 (1H, ddd, *J* = 8.3, 5.9, 1.2 Hz, 12-H). *Anal.* Calcd for $C_{18}H_{17}NO_5S_2$: Calcd C, 55.23; H, 4.38; N, 3.58. Found C, 55.18; H, 4.41; N, 3.50. **3b**, colorless needles, mp 152−154 °C. IR (KBr): 1630, 1721, 1742 cm^{-1}. *Anal.* Calcd for $C_{23}H_{19}NO_5S_2$: Calcd C, 60.91; H, 4.22; N, 3.09. Found C, 60.81; H, 4.36; N, 3.05. **3c**, colorless needles, mp178−181 °C. IR (KBr): 1636, 1725, 1742 cm^{-1}. *Anal.* Calcd for $C_{23}H_{19}NO_5S_2$: Calcd C, 60.91; H, 4.22; N, 3.09. Found C, 60.96; H, 4.26; N, 3.00.
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6. **4d**+**5d**, pale yellow prisms, mp 129−132 °C. IR (KBr): 1653, 1699, 1734 cm^{-1}. *Anal.* Calcd for $C_{25}H_{23}NO_6S_2$: Calcd C, 60.35; H, 4.66; N, 2.82. Found C, 60.29; H, 4.75; N, 2.78. ^{1}H-NMR δ ($CDCl_3$) **4d**: 1.16 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathit{H_3}$), 2.07 (3H, s, 7-Me), 3.75 and 3.80 (each 3H, s, CO_2Me), 4.10−4.20 (2H, m, $OC\mathit{H_2}CH_3$), 5.35 (1H, s, 10-H), 5.78 (1H, d, *J* = 2.8 Hz, 6-H), 6.14 (1H, d, *J* = 2.8 Hz, 5-H), 6.88−6.94 (2H, m, Ph-H), 7.15−7.22 (2H, m, Ph-H), 7.23−7.28 (1H, m, Ph-H), 7.92 (1H, s, 8-H). **5d**: 1.16 (3H, t, *J* = 7.1 Hz), 1.98 (3H, s, 7-Me), 3.49 and 3.86 (each 3H, s, CO_2Me), 4.10−4.20 (2H, m, $OC\mathit{H_2}CH_3$), 5.21 (1H, s, 10-H), 5.61 (1H, d, *J* = 2.8 Hz, 6-H), 6.07 (1H, d, *J* = 2.8 Hz, 5-H), 6.88−6.94 (2H, m, Ph-H), 7.15−7.22 (2H, m, Ph-H), 7.23−7.28 (1H, m, Ph-H), 7.87 (1H, s, 8-H).
7. This molecule has only one asymmetric carbon (C(10)) and usually exists as a pair of enantiomers. However, this rigid tricyclic structure, which is further promoted by the 3-phenyl group, strongly prevents the rotation of the C(3a)-N(4) bond and leads to an additional asymmetry.
8. **6d**, colorless needles, mp 156−158 °C. IR (KBr): 1437, 1719 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 1.14 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathit{H_3}$), 1.68 (3H, s, 12-Me), 3.21 (1H, d, *J* = 4.6 Hz, 1-H), 3.69 and 3.79 (each 3H, s, CO_2Me), 4.12 and 4.14 (each 1H, q, *J* = 7.1 Hz, $OC\mathit{H_2}CH_3$), 4.23 (1H, d, *J* = 2.0 Hz, 10-H), 5.64 (1H, br s, 11-H), 7.33−7.42 (5H, m, Ph-H), 7.44 (1H, d, *J* = 4.6 Hz, 13-H). ^{13}C-NMR δ ($CDCl_3$): 14.10, 15.05, 47.01, 52.00, 53.27, 60.75, 64.82, 66.64, 122.24, 125.53, 126.88, 127.76, 127.91, 128.24, 129.41, 134.14, 139.24, 142.49, 145.36, 151.44, 161.23, 164.16, 168.61. *Anal.* Calcd for $C_{25}H_{23}NO_6S_2$: Calcd C, 60.35; H, 4.66; N, 2.82. Found C, 60.28; H, 4.81; N, 2.73.
9. Crystal data of **4d**: $C_{25}H_{23}NO_6S_2$; M = 497.58; monoclinic, space group $P2_1/n$ (#14), Z = 4 with a = 12.02 (2) Å, b = 12.38 (3) Å, c = 16.42 (2) Å, β = 95.99° (13); V = 2430.1 (72) $Å^3$, and $D_{calc.}$ = 1.360 g/cm^3. All calculations were performed using CrystalStructure.[16] The structure was solved by a

direct method (SIR92).[17] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and R_w-factors after full-matrix least-squares refinements were 0.063 and 0.045 for 3175 (I>2.00s(I)) observed reflections, respectively.

10. C. K. Johnson, "ORTEO II, Report ORNL-5138," Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
11. (*Z*)-**7** (this compound could not be obtained in a pure state because of the ready transformation to (*E*)-7 isomer), pale yellow prisms. ^{1}H-NMR δ ($CDCl_3$): 1.15 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathit{H_3}$), 1.96 (3H, s, 7-Me), 3.51 (1H, br d, *J* = 18.8 Hz), 3.69 (1H, br d, *J* = 18.8 Hz), 3.69 and 3.87 (each 3H, s, CO_2Me), 4.14 and 4.16 (each 1H, q, *J* = 7.1 Hz, $OC\mathit{H_2}CH_3$), 5.94 (1H, d, *J* = 2.9 Hz, 6-H), 6.11 (1H, d, *J* = 2.9 Hz, 5-H), 7.41−7.50 (5H, m, Ph-H). (*E*)-**7**, pale yellow prisms, mp 181−182 °C. IR (KBr): 1414, 1688, 1746 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$): 1.14 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathit{H_3}$), 1.92 (3H, s, 7-Me), 3.71 and 3.76 (each 3H, s, CO_2Me), 3.76 (2H, s, CH_2), 4.15 (2H, q, *J* = 7.1 Hz, $OC\mathit{H_2}CH_3$), 5.89 (1H, d, *J* = 2.9 Hz, 6-H), 6.07 (1H, d, *J* = 2.9 Hz, 5-H), 7.31−7.49 (5H, m, Ph-H).
12. **8** (this compound could not be obtained in a pure state because of the transformation to (*Z*)-**7** and (*E*)-**7** isomers), colorless powder. ^{1}H-NMR δ ($CDCl_3$): 1.12 (3H, t, *J* = 7.1 Hz, $OCH_2C\mathit{H_3}$), 1.95 (3H, s, 3-Me), 3.60 and 3.73 (each 3H, s, CO_2Me), 4.12 and 4.13 (each 1H, q, *J* = 7.1 Hz, $OC\mathit{H_2}CH_3$), 5.74 (1H, d, *J* = 2.9 Hz, 4-H), 5.97 (1H, d, *J* = 2.9 Hz, 5-H), 6.45 and 6.50 (each 1H, s, vinyl-H), 7.35−7.53 (5H, br s, Ph-H).
13. Crystal data of (*Z*)-**7**: $C_{25}H_{23}NO_6S_2$; M = 497.58; monoclinic, space group $P2_1/c$ (#14), Z = 4 with a = 9.83 (3) Å, b = 10.22 (4) Å, c = 24.60 (2) Å, β = 96.03° (16); V = 2455.9 (126) Å^3, and $D_{calc.}$ = 1.346 g/cm^3. All calculations were performed using CrystalStructure.[16] The structure was solved by a direct method (SIR92).[17] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and R_w-factors after full-matrix least-squares refinements were 0.118 and 0.090 for 2704 (I>2.00s(I)) observed reflections, respectively. Crystal data of (*E*)-**7**: $C_{25}H_{23}NO_6S_2$; M = 497.58; triclinic, space group *P*-1 (#2), Z = 2 with a = 10.26 (3) Å, b = 12.64 (2) Å, c = 10.113 (18) Å, α = 113.26 (12); β = 98.6° (2); γ = 85.21 (19); V = 1190.9 (40) Å^3,

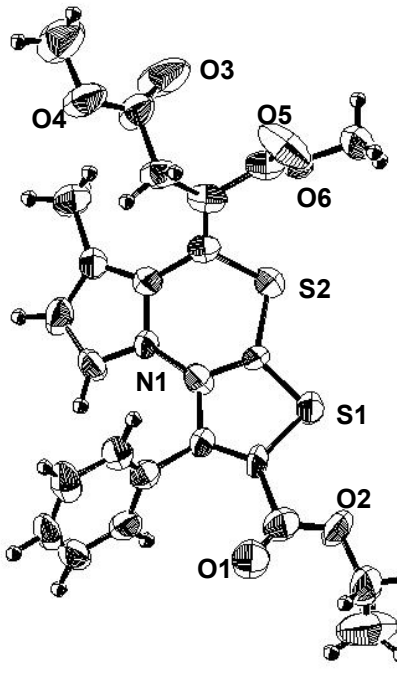

Figure 3. ORTEP drawing of (*Z*)-**7**

and $D_{calc.}$= 1.388 g/cm^3. All calculations were performed using CrystalStructure.[16] The structure was solved by a direct method (SIR92).[17] The non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were attached at the idealized position and not refined. The final R- and R_w-factors after full-matrix least-squares refinements were 0.063 and 0.041 for 2632 (I>2.00s(I)) observed reflections, respectively.

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15. The transformation from thiazepine **9d** to the corresponding thiazocines **4d**+**5d** was confirmed in $CDCl_3$ at 50−55 ^oC for 5 h, while that from adduct **3d** to thiazepine **9d** could not be detected under the same conditions even for 3 d.
16. CrystalStructure 3.8: Crystal Structure Analysis Package, Rigaku and Rigaku/MSC (2000−2006). 9009 New Trails Dr. The Woodlands TX 77381 USA.
17. SIR92: A. Altmare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. Burla, G. Polridori, and M. Camalli, *J. Appl. Cryst*., 1994, **27**, 435.

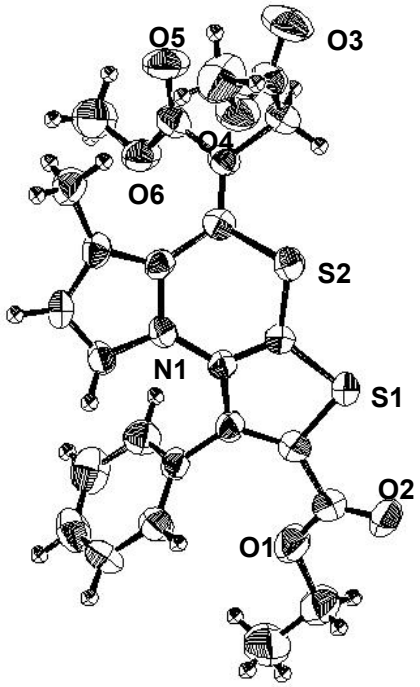

Figure 4. ORTEP drawing of (*E*)-**7**