and heated at 100 °C overnight. The reaction was cooled and partitioned between methylene chloride and 1 N HCl. The aqueous extract was extracted three times with methylene chloride/methanol (4:1).

The organic extracts were dried and evaporated to yield 1.61 g (99%) of relatively pure metabolite **15** ≡ **3**. For analysis, a sample was recrystallized from ethyl acetate to yield white crystals: mp 215 °C dec; IR (KBr) 3365 (OH), 2700–2560 (acid), 1720 (coumarin, acid), 1130 cm^{-1}; NMR (Me_2SO) δ 7.8–6.2 (m, 3 H, Ar), 3.94 (s, 3 H, OCH_3), 3.6 (s, 2 H, CH_2); UV max (CH_3OH) 225 nm (sh, ε 15000), 247 (3750), 257 (3800), 329 (14100); mass spectrum, *m/e* 250 (M^+), 232, 204 (base), 190, 161.

Anal. Calcd for $C_{12}H_{10}O_6$ (mol wt 250.21): C, 57.61; H, 4.03. Found: C, 57.53; H, 4.02.

This synthetic material was shown to be identical with the natural metabolite.

6-[(Carbomethoxy)methyl]-7-hydroxy-8-methoxycoumarin (16). A sample of 0.411 g (1.643 mmol) of the synthetic metabolite **15** in 15 mL of dry methanol was treated with 3 drops of concentrated sulfuric acid and heated under reflux for 1.5 h. The reaction was cooled and partitioned between water and methylene chloride. The aqueous phase was further extracted two times with methylene chloride/methanol (4:1). The organic extracts were dried and evaporated to afford 0.266 g (61%) of the methyl ester **16**, which was recrystallized from ethyl acetate to yield white needles: mp 138–139 °C; IR (KBr) 3290 (OH), 1740 (ester), 1720 (coumarin), 1605, 1150 cm^{-1}; NMR ($CDCl_3$) δ 7.8–6.2 (m, 3 H, Ar), 6.9 (br s, 1 H, OH), 4.08 (s, 3 H, OCH_3), 3.71 (s, 3 H, CO_2CH_3), 3.69 (s, 2 H, CH_2); UV max (CH_3OH) 204 nm (ε 44200), 225 (sh, 15200), 257 (4200), 327 (13600); mass spectrum, *m/e* 264 (M^+), 232, 205 (base), 204, 190, 176, 148, 133.

Anal. Calcd for $C_{13}H_{12}O_6$ (mol wt 246.23): C, 59.09; H, 4.58. Found: C, 59.08; H, 4.62.

6-(α-Bromoformylmethyl)-7-acetoxy-8-methoxycoumarin (19). A solution of 1.38 g (0.05 mol) of the aldehyde **13** in 25 mL of dry methylene chloride was treated dropwise over 5 min with 0.26 mL of bromine in 50 mL of the same solvent. The reaction was allowed to proceed for 1 h at 25 °C. The solvent was evaporated to afford 1.78 g (100%) of pure α-bromo aldehyde **19** as a light yellow oil of sufficient purity to be used directly in the next step: IR ($CHCl_3$) 2850 (CHO), 1765 (AcO), 1740 (CHO), 1190, 1120 cm^{-1}; NMR ($CDCl_3$) δ 9.5 (d, 1 H, CHO), 7.64 (d, 1 H, C(4) H), 7.31 (s, 1 H, C(5) H), 6.39 (d, 1 H, C(3) H), 5.37 (d, 1 H, CHBr), 4.06 (s, 3 H, OCH_3), 2.38 (s, 3 H, Ac); UV max (CH_3OH), 223 nm (sh, ε 14500), 238 (sh, (13000), 290 (10800), 322 (sh, 5500); mass spectrum, *m/e* 354/356 (M^+), 312/314, 294/296, 233 (base), 216.

6-(α-Bromocarboxymethyl)-7-acetoxy-8-methoxycoumarin (20). A solution of 1.78 g (0.05 mol) of the α-bromo aldehyde **19** in 50 mL of acetone at 0 °C was treated dropwise with 1.25 mL of Jones reagent over 1 min. After 0.5 h at 0 °C, the reaction was partitioned between methylene chloride and water. The organic phase was dried and evaporated to yield 1.812 g (98%) of the α-bromo acid **20** as a colorless oil of sufficient purity for use directly in the next step: IR ($CHCl_3$) 3500 (OH), 2700–2550 (CO_2H), 1740–1715 (br, acid, acetate, coumarin), 1400, 1190, 1160 cm^{-1}; NMR ($CDCl_3$) δ 7.69 (d, 1 H, C(4) H), 7.59 (s, 1 H, C(5) H), 6.43 (d, 1 H, C(3) H), 5.53 (5, 1 H, CHBr), 4.06 (s, 3 H, OCH_3), 2.40 (s, 3 H, Ac); UV max (CH_3OH) 242 nm (ε 11950), 288 (9000), 325 (sh, 3200), 365 (sh, 580); mass spectrum, *m/e* 328/330 (M^+ – CH_2CO), 310/312 (M^+ – HOAc), 249, 231 (base).

6-(α-Acetoxycarboxymethyl)-7-hydroxy-8-methoxycoumarin (21). A solution of 1.08 g (2.91 mmol) of the α-bromo acid **20** in 20 mL of tetrahydrofuran was treated with 20 mL of N hydrochloric acid. The reaction was heated at 70 °C for 7.5 h, cooled, and partitioned between methylene chloride and water. The organic phases were dried and evaporated to yield 0.844 g (94%) of the α-acetoxy acid **21** as a colorless oil. The compound was chromatographed over silica (EtOAc/HOAc, 9:1) to afford 0.597 g (67%) of pure product **21** isolated at R_f 0.55: IR (KBr) 3340–3100 (OH), 2680–2500 (CO_2H), 1740 (br, acetate, acid, coumarin), 1190, 1160 cm^{-1}; NMR (Me_2SO) δ 8.02 (d, 1 H, C(4) H), 7.61 (s, 1 H, C(5) H), 6.40 (d, 2 H, C(3) H), 5.65 (s, 1 H, CHOAc), 3.94 (s, 3 H, OCH_3), 2.26 (s, 3 H, Ac); UV (CH_3OH) 206 nm (ε 26100), 230 (sh, 13800), 289 (9900), 325 (sh, 4400); mass spectrum, *m/e* 290 (M^+ – H_2O), 266, 232 (base).

6-[(Methoxycarbonyl)methylene]-7-oxo-8-methoxycoumarin (23). A solution of 40 mg (0.130 mmol) of the α-acetoxy acid **21** in 5 mL of dry methanolic hydrogen chloride was heated under reflux for 5 h. The reaction was cooled and evaporated to yield 39 mg (100%) of the α-methoxy ester **23**. A sample was chromatographed over silica (EtOAc/hexane, 1:1) to yield pure **23** at R_f = 0.5: obtained as a white solid; mp 105–106 °C (EtOAc/pentane); IR (KBr) 3500 (OH), 1735–1718 (ester, coumarin) cm^{-1}; NMR (Me_2SO) δ 10.4 (br s, 1 H, OH), 7.97 (d, 1 H, C(4) H), 7.33 (s, 1 H, C(5) H), 6.25 (d, 1 H, C(3) H), 5.14 (s, 1 H, $CHOCH_3$), 3.83 (s, 3 H, OCH_3), 3.62 (s, 3 H, CO_2CH_3), 3.32 (s, 3 H, $CHOCH_3$); UV max (CH_3OH) 205 nm (ε 47980), 228 (sh, 19900), 295 (6480), 323 (17960), 380 (sh, 1030); mass spectrum, *m/e* 294 (M^+), 262 (M^+ – CH_3OH), 235 (base), 230, 220, 202.

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Registry No. 5, 93-35-6; **6**, 10387-49-2; **7**, 6748-68-1; **8**, 72939-36-7; **9**, 72939-37-8; **10**, 72939-38-9; **11**, 66510-31-4; **12**, 5307-54-0; **13**, 66510-36-9; **14**, 72939-39-0; **15**, 71942-06-8; **16**, 71942-08-0; **18**, 71942-11-5; **19**, 71942-09-1; **20**, 72939-40-3; **21**, 72939-41-4; allyl chloride, 107-05-1.

Synthesis of 4-Acyl-2-(acylamino)-Δ^2-1,3,4-thiadiazolines and 4-Acyl-2-amino-Δ^2-1,3,4-thiadiazolines by Acylation of Thiosemicarbazones[1]

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Acylation of aldehyde and ketone thiosemicarbazones (**2**) with acid anhydrides or acid chlorides gave 4-acyl-2-(acylamino)-Δ^2-1,3,4-thiadiazolines (**3**) in good yields. Treatment of **3** with hydrazine hydrate furnished the 2-amino derivatives (**4**). The 4-methylthiosemicarbazone of benzaldehyde underwent a similar cyclization with acetic anhydride to furnish the corresponding 2-(acetylmethylamino)thiadiazoline.

Acetylation of aldehyde thiosemicarbazones (**2**) followed by peracid oxidation has been reported as a route to 1,3,4-thiadiazoles.[2,3] The intermediate acylation products were considered to be the N^4,*S*-diacyl derivatives **1**. In a

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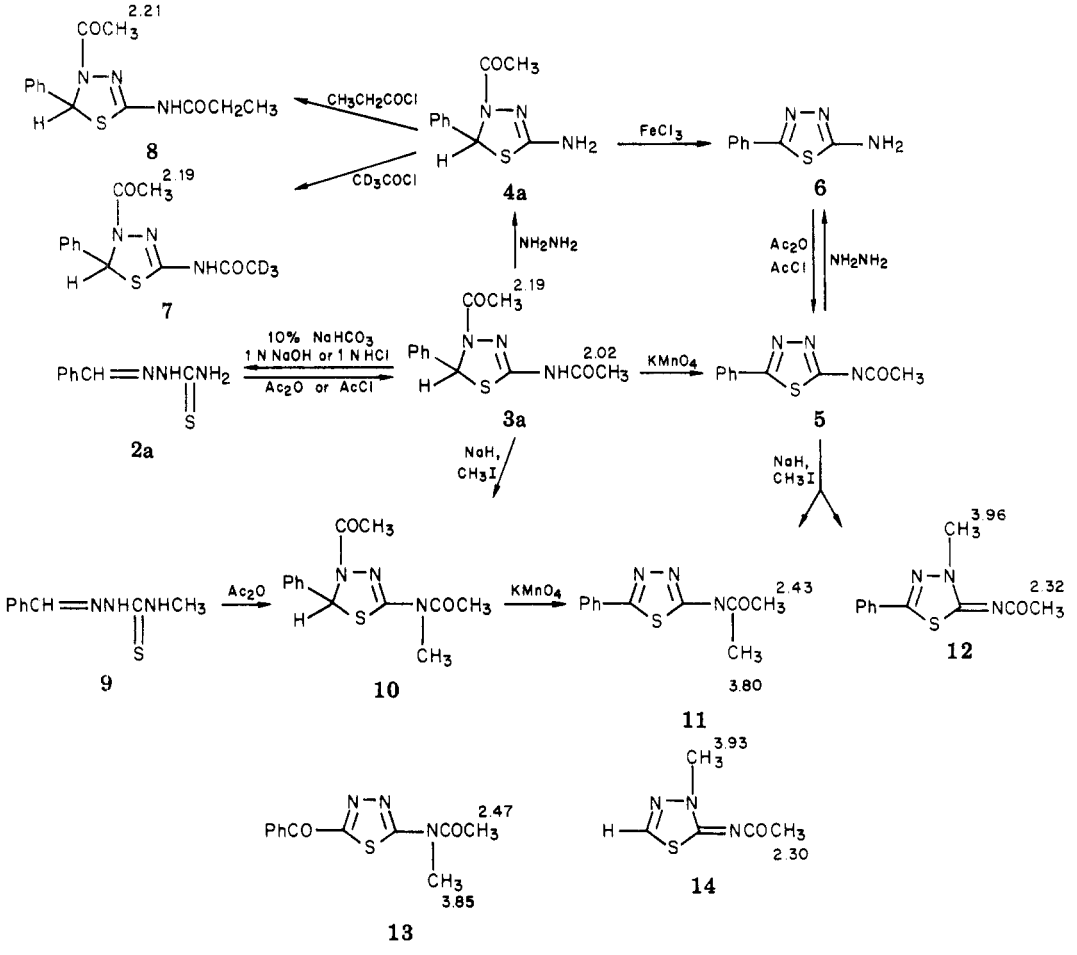
Table I. 5-Substituted 4-Acyl-2-(acylamino)-Δ^2-1,3,4-thiadiazolines (3)[a] and 4-Acyl-2-amino-Δ^2-1,3,4-thiadiazolines (4)[a]

			3[c]		4[c]	
compd	R_1	R_2	mp, °C	yield,[b] %	mp, °C	yield,[b] %
a	Ph	H	222-223[d]	84	219-221	77
b	p-NO_2Ph	H	210-211	57		
c	p-ClPh	H	229-233	68	141-143	83
d	p-CH_3OPh	H	168-169	76	149-150	64
e	p-Me_2NPh	H	222 dec	76	174 dec	74
f	2-pyridyl	H	206-208[e]	78	155-156	60
g	3-pyridyl	H	179-180[f]	66	170-172	58
h	4-pyridyl	H	220-222	54	193 dec	70
i	CH_3	H	164-165	45	144-145	37
j	H	H	237-239	30	215-216	63
k	CH_3	CH_3	195-196	86	153-154	62
l	Ph	CH_3	216-217	73	119-121	75

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds. [b] Isolated yields. [c] NMR data: see Tables II and III (Supplementary Material). [d] Lit.[2] mp 222-224 °C. [e] Lit.[2] mp 208-210 °C. [f] Lit.[2] mp 188-190 °C.

Scheme I



study of this reaction, we have found that the diacyl compounds are in fact the cyclized 4-acyl-2-(acylamino)thiadiazolines **3** and not the N^4,S-diacyl derivatives as thought previously.[2,3] (See Chart I.)

This paper describes details of structural determinations of compounds **3** and a general method for synthesis of these novel compounds from aldehyde and ketone thiosemicarbazones (**2**). The compounds prepared are listed in Table I.

Results and Discussion

Proof of the structure of the 1,3,4-thiadiazolines (**3**) is based upon physical and chemical evidence. The diacetyl derivative **3a** is used here as a representative. The NMR spectrum of **3a** showed a C-5 proton absorption at δ 6.80 with an upfield shift of 1.24 ppm from that of the methine proton in the open-chain thiosemicarbazone **2a**, in good agreement with other C-5 proton shifts reported for 1,3,4-thiadiazoline derivatives.[4] The aromatic proton

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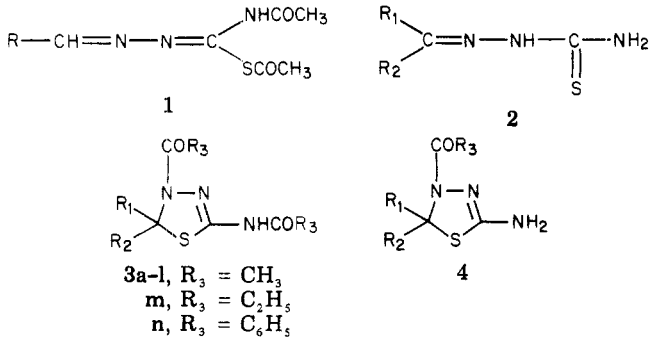
Chart I



signals of **3a** also differed from those of **2a**: the former appeared as a multiplet centered at δ 7.27 (5 H), while the latter consisted of two broad multiplets with centers at δ 7.36 (3 H) and 7.78 (2 H), due to the effect of the adjacent azomethine group. The NMR data for all other derivatives are listed in Table II (Supplementary Material).

Scheme I depicts the chemical evidence for the structure of **3a**.

3a was oxidized with potassium permanganate in acetic acid to 2-(acetamido)-5-phenyl-1,3,4-thiadiazole (**5**),[5] which was identical with the compound obtained by acetylation of 2-amino-5-phenyl-1,3,4-thiaziazole (**6**)[5] with acetic anhydride. The reverse reaction was accomplished by treating **5** with hydrazine hydrate. **3a** was also hydrolyzed to the starting thiosemicarbazone **2a** by treatment with 1 N hydrochloric acid, 1 N sodium hydroxide, or 10% sodium bicarbonate solution. On the other hand, treatment with hydrazine hydrate at room temperature furnished the 2-deacetylated derivative **4a**. The NMR data of this compound (Table III, Supplementary Material) were comparable with those of **3a**. Oxidation of **4a** with ferric chloride solution gave **6**. The reaction of **4a** with deuterioacetyl chloride gave 4-acetyl-2-(deuterioacetamido)-5-phenyl-Δ^2-1,3,4-thiadiazoline (**7**), whose mass spectrum showed a molecular ion, *m/e* 266.0928. Similarly, 4-acetyl-5-phenyl-2-(propionamido)-Δ^2-1,3,4-thiadiazoline (**8**) was obtained by reaction of **4a** with propionyl chloride or propionic anhydride. Chemical shift assignment of the two methyl group protons of **3a** was possible by examination of the spectra of **7** and **8**, whose acetyl protons appeared at δ 2.19 and 2.21, respectively. Thus, the δ 2.19 signal was assigned to the N-4 acetyl group, and the δ 2.02 singlet to the 2-acetamido group.

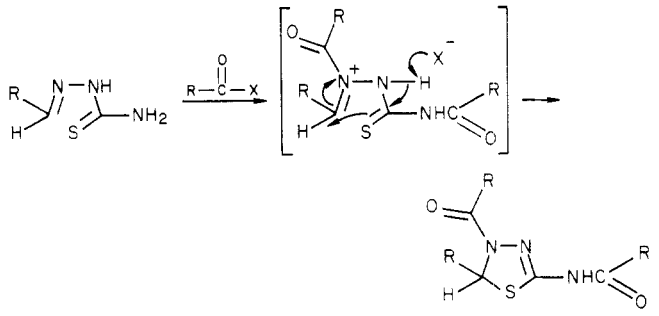
Methylation of **3a** with methyl iodide and sodium hydride gave exclusively **10**, which was identical with the compound obtained by the reaction of benzaldehyde 4-methylthiosemicarbazone (**9**)[6] with acetic anhydride. Like those of **3a**, the NMR absorptions of **10** for the protons at C-5 and in the aromatic region support the cyclic 1,3,4-thiadiazoline structure. Oxidation of **10** with potassium permanganate afforded 2-(acetylmethylamino)-5-phenyl-1,3,4-thiadiazole (**11**), which was identical with one of the two compounds obtained by methylation of **5** with methyl iodide and sodium hydride. The other methylation product was 2-(acetylimino)-3-methyl-5-phenyl-Δ^4-1,3,4-thiadiazoline (**12**). The δ values of the methyl and acetyl protons of **11** and **12** were in good agreement with reported values for **13** and **14**.[7]

On the basis of chemical evidence and these spectral data, the cyclized structures 2-(acetamido)-4-acetyl-5-phenyl-Δ^2-1,3,4-thiadiazoline, 4-acetyl-2-amino-5-phenyl-Δ^2-1,3,4-thiadiazoline, and 4-acetyl-2-(acetylmethylamino)-5-phenyl-Δ^2-1,3,4-thiadiazoline were assigned to compounds **3a**, **4a**, and **10**, respectively.

The reactions of various aldehyde and ketone thiosemicarbazones (**2b–2l**) with acetic anhydride gave thiadiazoline derivatives **3b–3l** in good yields. Physical data on these derivatives are listed in Table II. Treatment of the 2-(acetamido)-1,3,4-thiadiazolines (**3**) with hydrazine hydrate furnished the corresponding 2-amino derivatives (**4c–4l**), except in the case of **3b** in which the nitro group was reduced.

The reaction of **2a** with other acid chlorides and anhydrides followed a similar path. Propionic acid chloride and anhydride furnished the 4-propionyl-2-propionamido derivative **3m**, while the reaction with benzoyl chloride gave the 4-benzoyl-2-benzamido compound (**3n**). 2-Amino-5-phenyl-4-propionyl-Δ^2-1,3,4-thiadiazoline was prepared from **3m** by treatment with hydrazine hydrate and acetylation to give the corresponding 2-acetamido derivative.

The mechanism of formation of 1,3,4-thiadiazolines can be explained on the basis of the hard and soft acid and base principle.[8] The harder acylating reagent reacts with the harder nitrogen atom rather than the softer sulfur atom, and this acylation favors cyclization of thiosemicarbazones to 1,3,4-thiadiazolines.



Experimental Section

All melting points were determined by the capillary method and are uncorrected. NMR spectra were obtained on a JEOL PS-100 spectrometer using tetramethylsilane as an internal standard. The solvents used were $CDCl_3$ and Me_2SO-d_6 and all chemical shifts are given in δ (ppm) values. IR spectra were measured as KBr disks on a Hitachi EPI-G_2 spectrometer. UV spectra were obtained on a Hitachi Model 124 spectrometer. Mass spectra were recorded on a JEOL JMS-DU 300 spectrometer.

5-Substituted 2-(Acetamido)-4-acetyl-Δ^2-1,3,4-thiadiazolines (3a–l). **3b–l** were prepared by method A described below for **3a**. Melting points, yields, and NMR spectral date are shown in Table II. The starting thiosemicarbazones **2a–e**,[9] **2f–h**,[2] **2i**,[10] **2k**,[10] and **2l**[9] were prepared by literature methods.

2-(Acetamido)-4-acetyl-5-phenyl-Δ^2-1,3,4-thiadiazoline (3a). A. Acetylation with Acetic Anhydride. A mixture of **2a** (3 g, 16.8 mmol) and acetic anhydride (12 mL) was heated at 100 °C for 1 h. After the solution was cooled, the resulting precipitate was collected by filtration and recrystallized from ethanol to give 3.71 g (84%) of **3a**; IR (KBr) 3230, 1700, 1630, 1610 cm^{-1}.

B. Acetylation with Acetyl Chloride. Acetyl chloride (1.76 g, 22.4 mmol) was added dropwise at 0 °C to a stirred solution of **2a** (1 g, 5.6 mmol) in pyridine (9 mL) and acetone (5 mL). After being stirred at room temperature for 2 h, the mixture was poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 0.825 g (56%) of **3a**. The

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IR and NMR spectral data of this compound are identical with those of **3a** prepared by method **A**.

2-(Acetamido)-4-acetyl-Δ^2-1,3,4-thiadiazoline (3j). A mixture of formalin (1 g, 33 mmol), thiosemicarbazide (3 g, 33 mmol), and ethanol (10 mL) was heated at 100 °C for 1 h. A precipitate formed, was dried, and was heated with acetic anhydride (10 mL) at 100 °C for 1.5 h. The resulting solid was collected by filtration and recrystallized from ethanol to give colorless needles (0.93 g, 30%): mp 237–239 °C; IR (KBr) 3160, 1690, 1650, 1615 cm^{-1}.

5-Substituted 4-Acetyl-2-amino-Δ^2-1,3,4-thiadiazolines (4a, 4c–l). **4c–l** were prepared by the method described for **4a**. Melting points, yields, and NMR spectral data are shown in Table III.

4-Acetyl-2-amino-5-phenyl-Δ^2-1,3,4-thiadiazoline (4a). A mixture of **3a** (3 g, 11.25 mmol) and 36 mL of hydrazine hydrate (85%) was stirred at room temperature for 3 h. The resulting precipitate was collected by filtration and recrystallized from water to give 1.93 g (77%) of **4a**; IR (KBr) 3180, 1630, 1600 cm^{-1}.

Oxidation of 4a with $FeCl_3$. **4a** (0.1 g, 0.5 mmol) was added to a solution of $FeCl_3 \cdot 6H_2O$ (0.2 g, 0.7 mmol) in H_2O (3 mL) and the solution was heated at 100 °C for 3 h. After insoluble salts were removed by filtration, the hot solution was left to stand at room temperature. The resulting solid was collected by filtration and recrystallized from ethanol to give 56 mg of 2-amino-5-phenyl-1,3,4-thiadiazole (**6**, 70%), mp 221–222 °C.

2-(Acetamido)-5-phenyl-1,3,4-thiadiazole (5). A. Oxidation of 3a with Potassium Permanganate. Potassium permanganate (1.5 g, 10 mmol) was added portionwise at 10–15 °C to a suspension of **3a** (1 g, 4 mmol) in acetic acid (24 mL). After the mixture was stirred for 1 h, water (12 mL) was added and the mixture was treated with 30% H_2O_2 under ice cooling and left to stand at 0 °C for 15 h. The resulting crystals were collected by filtration and washed with ethanol to give 700 mg (70%) of **5**; mp 278–280 °C; IR (KBr) 1685 cm^{-1}; NMR (Me_2SO-d_6) δ 2.19 (3 H, s, CH_3), 7.50–7.90 (5 H, m, C_6H_5).

B. Acetylation of 6 with Acetic Anhydride. A mixture of **6** (100 mg, 0.6 mmol), acetic anhydride (1.2 mL), and pyridine (1 mL) was refluxed for 2 h. After the solution was cooled, the resulting crystals were collected by filtration and washed with methanol to give 100 mg (80%) of **5**. The IR and NMR spectral data of this compound are identical with those of **5** prepared by method A.

4-Acetyl-2-(deuterioacetamido)-5-phenyl-Δ^2-1,3,4-thiadiazoline (7). Deuterioacetyl chloride (152 mg, 0.18 mmol) was added dropwise at 0 °C to a stirring mixture of 4-acetyl-2-amino-5-phenyl-Δ^2-1,3,4-thiadiazoline (**4a**) (200 mg, 0.09 mmol), pyridine (1.8 mL), and acetone (1 mL). After being stirred at room temperature for 1 h, the mixture was poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 193 mg (80%) of **7**: mp 214–215.5 °C; NMR (Me_2SO-d_6) δ 2.19 (3 H, s, CH_3), 6.84 (1 H, s, C_5-H), 7.20–7.50 (5 H, m, C_6H_5), 10–12 (1 H, br, NH); mass spectrum m/e 266.0928 (calcd for $C_{12}H_{10}N_3O_2D_3S$, 266.09631) 266 (54.3, M^+), 224 (100), 180 (221), 147 (23.7), 121 (55.3), 104 (33.5), 88 (25.9), 77 (58.2), 46 (29.3). Anal. Calcd for $C_{12}H_{10}N_3O_2SD_3$: C, 54.12; N, 15.78. Found; C, 54.02; N, 15.82.

4-Acetyl-5-phenyl-2-(propionamido)-Δ^2-1,3,4-thiadiazoline (8). Propionyl chloride (126 mg, 1.4 mmol) was added dropwise to a solution of **4a** (300 mg, 1.4 mmol) in pyridine (2.7 mL) and acetone (1.4 mL) under water cooling. After being stirred at room temperature for 1 h, the mixture was poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 195 mg (51.7%) of **8** as colorless needles: mp 203–203.5 °C; NMR (Me_2SO-d_6) δ 0.98 (3 H, t, CH_2CH_3), 2.21 (3 H, s, $COCH_3$), 2.34 (2 H, q, CH_2CH_3), 6.82 (1 H, s, C5-H), 7.30 (5 H, m, C_6H_5), 11.70 (1 H, br, NH). Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 55.92; H, 5.53; N, 14.99.

4-Acetyl-2-(acetylmethylamino)-5-phenyl-Δ^2-1,3,4-thiadiazoline (10). A. Cyclization of Benzaldehyde 4-Methylthiosemicarbazone (9) with Acetic Anhydride. Benzaldehyde 4-methylthiosemicarbazone (**9**) (1 g, 5.2 mmol) was heated with acetic anhydride (4 mL) at 100 °C for 2 h. The reaction mixture was cooled and diluted with water. The resulting precipitate was recrystallized from ethanol to give 12 g (84%) of **10**: mp 185–186 °C; IR (KBr) 1675, 1641 cm^{-1}; NMR ($CDCl_3$) δ 2.23 (3 H, s, $COCH_3$), 2.25 (3 H, s, $COCH_3$), 3.32 (3 H, s, NCH_3), 6.77 (1 H, s, C5-H), 7.00–7.50 (5 H, m, C_6H_5). Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.12; H, 5.44; N, 15.00.

B. Methylation of 3a with Methyl Iodide and NaH. **3a** (603 mg, 2.3 mmol) was added to a stirring suspension of NaH (110 mg, 4.6 mmol, 50% dispersion in mineral oil) in THF at 100 °C and the mixture was stirred at room temperature for 1 h. Methyl iodide (1.63 g, 11.5 mmol) was added and the mixture was stirred at room temperature overnight and then poured into ice–water. The mixture was extracted with chloroform. The chloroform extract was washed with water and dried over Na_2SO_4. The residue obtained after removal of the solvent was recrystallized from ethanol to give 525 mg (82.7%) of **10**: mp 178–180 °C. The IR spectrum of the product was identical with that of **10** prepared by method A.

2-(Acetylmethylamino)-5-phenyl-Δ^2-1,3,4-thiadiazole (11). A. Oxidation of 10 with Potassium Permanganate. Potassium permanganate (270 mg, 1.7 mmol) was added portionwise to a stirring suspension of **10** (200 mg, 0.7 mmol) in acetic acid (5 mL) at 10–15 °C. After being stirred for 2 h, the mixture was diluted with water, treated with 30% H_2O_2 in an ice–water bath, and left to stand overnight. The resulting precipitate was collected by filtration and recrystallized from methanol to give 100 mg (59.4%) of **11**: mp 191–192 °C; UV (EtOH) λ_{max} (ϵ) 291.5 nm (16420); IR (KBr) 1670 cm^{-1}; NMR ($CDCl_3$) δ 2.43 (3 H, s, $COCH_3$), 3.80 (3 H, s, NCH_3). Anal. Calcd for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.72; H, 4.89; N, 18.15.

B. Methylation of 2-(Acetamido)-5-phenyl-1,3,4-thiadiazole (5). **5** (612 mg, 2.8 mmol) was added to a stirring suspension of NaH (67 mg, 2.8 mmol) in THF at 0 °C, and the mixture was stirred at room temperature for 1 h. Methyl iodide (2 g, 14 mmol) was added and sitrring at room temperature was continued overnight. The mixture was extracted with chloroform. The extract was washed with water, dried over Na_2SO_4, and evaporated to give a residue which was chromatographed on silica gel column, elution with chloroform/acetone (30:1) to give 247 mg (37.6%) of **12** [mp 144–144.5 °C; UV (EtOH) λ_{max} (ϵ) 313 nm (16960); IR (KBr) 1600 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (3 H, s, $COCH_3$), 3.96 (3 H, s, NCH_3). Anal. Calcd for $C_{11}H_{11}N_3OS$: C, 56.63; H, 4.75; N, 18.01. Found: C, 56.48; H, 4.67; N, 17.77] and 193 mg of colorless needles (mp 191–192 °C). The IR and NMR spectra of this compound were identical with those of **11** prepared by method A.

5-Phenyl-4-propionyl-2-(propionylamino)-Δ^2-1,3,4-thiadiazoline (3m). A. With Propionic Anhydride. A mixture of **2a** (3 g, 16.8 mmol) and propionic anhydride (12 mL) was heated at 100 °C for 1 h. After the solution was cooled, the resulting precipitate was collected by filtration and recrystallized from ethanol to give 3.29 g (67.5%) of **3m**: mp 154–156 °C; IR (KBr) 3160, 1700, 1628, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (3 H, t, CH_2CH_3), 1.16 (3 H, t, CH_2CH_3), 2.28 (2 H, q, CH_2CH_3), 2.64 (2 H, q, CH_2CH_3), 6.84 (1 H, s, C5-H), 7.28 (5 H, s, C_6H_5), 9.36 (1 H, s, NH). Anal. Calcd for $C_{14}H_{17}N_3O_2S$: C, 57.71; H, 5.88; N, 14.42. Found: C, 57.34; H, 5.99; N, 14.61.

B. With Propionyl Chloride. Propionyl chloride (2.20 g, 24 mmol) was added dropwise at 0 °C to a stirred solution of **2a** (1 g, 5.6 mmol) in pyridine (9 mL) and acetone (5 mL). After being stirred at room temperature for 20 h, the mixture was poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 1 g (62%) of colorless needles. The IR and NMR spectra of this compound were identical with those of **3m** prepared by method A.

2-Amino-5-phenyl-4-propionyl-Δ^2-1,3,4-thiadiazoline (4m). A mixture of **3m** (3 g, 10 mmol) and hydrazine hydrate (85%, 36 mL) was stirred at room temperature for 2 h. The resulting precipitate was collected by filtration and recrystallized from water to give 1.83 g (75.4%) of colorless crystals: mp 121–122 °C; IR (KBr) 3180, 1620, 1600 cm^{-1}; NMR ($CDCl_3$) δ 1.10 (3 H, t, CH_2CH_3), 2.58 (2 H, q, CH_2CH_3), 4.58 (2 H, s, NH_2), 7.04 (1 H, s, C5-H), 7.28 (5 H, s, C_6H_5). Anal. Calcd for $C_{11}H_{13}N_3OS$: C, 56.15; H, 5.57; N, 17.86. Found: C, 56.00; H, 5.60; N, 17.58.

2-(Acetylamino)-5-phenyl-4-propionyl-Δ^2-1,3,4-thiadiazoline. A. With Acetic Anhydride. A mixture of **4m** (0.5 g, 2.1 mmol) and acetic anhydride (2 mL) was stirred at 100 °C for 1 h under nitrogen atmosphere. The mixture was poured into water to give a colorless solid. Recrystallization from ethanol gave 361 mg (61.3%) of colorless crystals: mp 182–183 °C; IR (KBr) 3160,

1700, 1640, 1595 cm^{-1}; NMR (Me_2SO-d_6) δ 1.18 (3 H, t, CH_2CH_3), 2.20 (3 H, s, CH_3), 2.70 (2 H, q, CH_2CH_3), 6.95 (1 H, s, C5-H), 7.42 (5 H, s, C_6H_5). Anal. Calcd for $C_{13}H_{15}N_3O_2S$: C, 56.30; H, 5.45; N, 15.15. Found: C, 56.33; H, 5.53; N, 15.16.

B. With Acetyl Chloride. Acetyl chloride (0.5 g, 6.3 mmol) was added to a mixture of **4m** (0.5 g, 2.1 mmol), pyridine (4.5 mL), and acetone (2.5 mL) at 0 °C. After being stirred at room temperature for 2 h, the mixture was poured into ice–water. The resulting precipitate was collected by filtration and recrystallized from ethanol to give 108 mg (18.3%) of colorless crystals. The IR and NMR spectra of this compound were identical with those of the compound prepared by method A.

2-(Benzamido)-4-benzoyl-phenyl-Δ^2-1,3,4-thiadiazoline (3n). Benzoyl chloride (6.27 g, 44.6 mmol) was added dropwise to a stirring mixture of **2a** (2 g, 11.2 mmol), pyridine (1.8 mL), and tetrahydrofuran (20 mL). After the solution was refluxed for 6 h, the resulting precipitate was collected by filtration and recrystallized from ethanol to give 3.11 g (72%) of **3n**: mp 198–199 °C; IR (KBr) 3150, 1665, 1615 cm^{-1}; NMR (Me_2SO-d_6) δ 7.15 (1 H, s, C_5-H), 7.42 (5 H, s, C_6H_5), 7.20–8.10 (10 H, m, C_6H_5), 12.06 (1 H, s, NH). Anal. Calcd for $C_{22}H_{17}O_2N_3S$: C, 68.20; H, 4.42; N, 10.85. Found: C, 68.36; H, 4.38; N, 10.82.

Registry No. 2a, 1627-73-2; **2b**, 5470-48-4; **2c**, 5706-80-9; **2d**, 4334-74-1; **2e**, 2929-81-9; **2f**, 3608-75-1; **2g**, 555-90-8; **2h**, 1200-00-6; **2i**, 2302-95-6; **2k**, 1752-30-3; **2l**, 2302-93-4; **3a**, 62236-01-5; **3b**, 62236-05-9; **3c**, 62236-06-0; **3d**, 62236-07-1; **3e**, 62236-08-2; **3f**, 62236-02-6; **3g**, 62236-02-6; **3h**, 62236-04-8; **3i**, 72938-21-7; **3j**, 72926-22-8; **3k**, 72926-23-9; **3l**, 72926-24-0; **3m**, 72926-25-1; **3n**, 72926-26-2; **4a**, 62236-09-3; **4c**, 72926-27-3; **4d**, 72938-22-8; **4e**, 72926-28-4; **4f**, 72926-29-5; **4g**, 72926-30-8; **4h**, 72926-31-9; **4i**, 72926-03-5; **4j**, 72926-04-6; **4k**, 72926-05-7; **4l**, 72926-06-8; **4m**, 72926-07-9; **5**, 28898-88-6; **6**, 2002-03-1; **7**, 72926-08-0; **8**, 72926-09-1; **9**, 2613-12-9; **10**, 72926-10-4; **11**, 14537-59-8; **12**, 3357-38-8; acetic anhydride, 108-24-7; acetyl chloride, 75-36-5; formalin, 50-00-0; thiosemicarbazide, 79-19-6; propionyl chloride, 79-03-8; methyl iodide, 74-88-4; propionic anhydride, 123-62-6; 2-(acetylamino)-5-phenyl-4-propionyl-Δ^2-1,3,4-thiadiazoline, 72926-11-5; benzoyl chloride, 98-88-4.

Supplementary Material Available: NMR data for compounds **3** and **4** (2 pages). Ordering information is given on any current masthead page.

Synthesis of 4-Thioxo-2-azetidinones

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4-Thioxo-2-azetidinones, which are C- and N-substituted imides of monothionomalonic acid, have been prepared by a thermal rearrangement of 4-(2-methoxycarbonylethylsulfinyl)-2-azetidinones through the intermediacy of β-lactam 4-sulfenic acids. The 4-sulfinyl-2-azetidinones have been obtained by total synthesis, or from penicillin sulfoxides. The former approach, which allows the choice of variegated arrays of substituents, was employed in the synthesis of (±)-1-(1-(methoxycarbonyl)-2-methylprop-1-enyl)-3-phthalimido-4-thioxo-2-azetidinone (**8**) (a didehydrovaline derivative), (±)-1-(1-(*tert*-butoxycarbonyl)-2-*tert*-butoxyethyl)-3-phthalimido-4-thioxo-2-azetidinone (**19**) (a serine derivative), and 1,3,3-triphenyl-4-thioxo-2-azetidinone (**20**). Compound **27**, which is the levorotatory enantiomer of the racemic **8**, has been obtained by the degradation of methyl 6-(β-phthalimido)penicillanate sulfoxide (**21**).

4-Thioxo-2-azetidinones are formally derived from the imide of monothionomalonic acid. This class of compounds was unknown until 1976 when the syntheses of a few C- and N-substituted thiomalonimides were independently reported from this[1] and two other laboratories.[2,3] In the present paper we describe in detail a general method for the preparation of these compounds by total synthesis as well as by the degradation of sulfoxides of phthalimidopenicillanates.[4] The former approach provides an access to thioxoazetidinones bearing a varied array of substituents, and may be valuable for the synthesis of more elaborate systems including nuclear analogues of β-lactam antibiotics.[6] Some of the properties and reactions of 4-thioxo-2-azetidinones are described in the accompanying paper.[7]

Within the framework of a project on the synthesis of β-lactams structurally related to penicillins,[8] we were interested in the generation of the β-lactam sulfenic acid **6**. A plausible route to this acid was based on the thermal elimination of methyl acrylate from the β-lactam sulfoxide **5**. The (methoxycarbonyl)ethyl group in **5** was chosen since the enhanced acidity of its two α-hydrogen atoms, which are β to the sulfinyl group, was expected to facilitate the formation of the sulfenic acid **6**.[9,10] Indeed thermolysis of **5** in the presence of dihydropyran as a trapping agent and an aluminum halide as catalyst[11] afforded the dihydropyranyl derivative **7** as the major product, thus indicating the intermediacy of the sulfenic acid **6**. It was noticed, however, that **7** was accompanied by traces of a product, exhibiting in its IR spectrum an absorption band

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